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# Have We Entered the Stem Cell Era?

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## Treatments for cancer, blood diseases, and even HIV are finally realizing some of the potential for stem-cell medicine.

by Jeanne Lenzer

Stem cells placed in a scaffolding generate a brand new rat heart outside the body.

Image: The University of Minnesota

Wearing white jeans and a navy shirt bejeweled with glittering stars, 15-year-old Paizley Carwell-Bowen lounges in the living room of her family's North Hollywood apartment. She seems like a typical bubbly teenager —she chats and giggles with a girlfriend, she dreams of being a pop star—but she has a troubled past. "Sometimes I'd see the devil," she says.

Paizley's disturbing visions started after she had a stroke at age 6. The stroke was just one complication of sickle-cell anemia, the hereditary disease that has haunted her since infancy. Most common among people of African descent, the disorder causes oxygen-carrying red blood cells, which are normally flexible and round, to become rigid and take on a crescent (or sickle) shape. Sickle cells have trouble squeezing through fine blood vessels to deliver oxygen to the body's tissues and organs. Instead they clump and choke off blood flow, causing intense pain as bits of lung, bone, brain, and kidney succumb to a lack of oxygen. Those with the disease die slowly, over years.

Paizley was so sick that doctors told her parents she might not live to be 18. Her early stroke left her left leg partially paralyzed. The pain would upend her days and nights. Her hip joints began to erode. She missed so much school due to hospitalizations that by age 11 she had been held back two grades. Then things got even worse. Her doctors tried to prevent another stroke by giving her blood transfusions every three weeks to dilute her sickle cells with normal red blood cells. The scheme worked for a number of years, but Paizley's immune system learned to identify proteins on the transfused blood cells and began to attack them. Her own body was working at full speed to destroy the blood that was intended to save her life.

After a while it was virtually impossible to find blood for transfusion that could slip past Paizley's ever-alert immune system. The prognosis was grim. "We were running out of options," says Hisham Abdel-Azim, one of her doctors at Children's Hospital of Los Angeles. He and his colleagues ultimately told Paizley and her parents that there was only one hope left: a risky stem cell transplant. Using powerful chemotherapy drugs, they would wipe out the bone marrow that produced the faulty sickle cells. Then they would transfuse donor bone marrow rich in the highly prized stem cells that are capable of generating new, normal blood. The family took the gamble.

Now, almost four years later, it is hard to imagine that Paizley is the same person. And in a critical way, she isn't. Although she was born with sickle-cell genes, she no longer has sickle-cell disease. The healthy blood that flows through her veins is not her own; it is that of a 45-year-old woman who donated her marrow. Her body was rebuilt with that stranger's stem cells, and Paizley now sleeps at night pain-free. She does not need blood transfusions. She no longer worries about having another stroke or dying young. She attends school uninterrupted. The devil is at bay.

***WAITING FOR MIRACLES***

Paizley's recovery highlights just one minuscule part of the potential of stem cells, the immortal progenitor cells that endlessly divide, generating new tissue throughout a person's life. The stem cells used to treat Paizley, specific to the blood, came from the bone marrow of a healthy adult donor. But even more far-ranging treatments may be possible with embryonic stem cells, the blank-slate cells that give rise to all organs and tissue types and that (theoretically) can repair all forms of organic damage and disease. These endlessly malleable cells were first isolated from embryos by University of Wisconsin scientists in 1998. Since then, they have been touted as the cure for nearly every disease, and even as the antidote to aging and death.

The early concept about how to harness these cells was simplicity itself: Harvest the unformed cells from embryos and inject them into needy recipients. The stem cells would then start rebuilding damaged hearts, pushing cancer to remission, or healing injured spinal cords. Multiple sclerosis, lupus, arthritis, even psychiatric illnesses would all be swept away under the tidal wave of the stem cell cure.

Given the grandeur of the vision, is it any wonder that when research stalled, frustration grew? As the paralyzed lived out their lives in wheelchairs, as loved ones faded into the netherworld of Alzheimer's, as cancer and heart disease struck with impunity, calls for cures grew louder: Where are our stem cell therapies? Why have we had to wait so long?

For a long time, the answer appeared to be political, a by-product of the controversy over abortion. The most potent of the stem cells are the most undifferentiated ones, so immature that they are neither skin nor nerve, heart cell nor muscle; they are derived from the embryo in the earliest stages of life. The mother of all stem cells is the zygote, the single cell formed by the fusion of an egg and sperm. Within about five days, the zygote evolves into a blastocyst, a clump of about 150 cells that contains a handful of "pluripotent" cells imbued with the capacity to transform into every type of tissue except placenta. It is at this stage, when the fertilized egg is smaller than the period at the end of this sentence, that researchers extract the inner part of the blastocyst, from which embryonic stem cells are derived.

Once extracted, these flexible human cells are placed on top of a layer of embryonic mouse cells. Under the right conditions, colonies of human cells grow out from the edge. Researchers remove these mechanically and, with some luck, can nurture them into an embryonic stem cell line that lives in perpetuity in the laboratory.

But until recently there was no way to produce those cells without sacrificing an embryo, an act that is considered tantamount to murder by some critics. Moreover, because foreign stem cells would be rejected by the body, much like a foreign heart or kidneys, scientists had proposed literally cloning the patients, in essence creating a duplicate from which cells could be culled in embryonic form. Even though such clones would be just a collection of cells, the concept unleashed a firestorm of criticism, leaving some researchers fearing for their lives.

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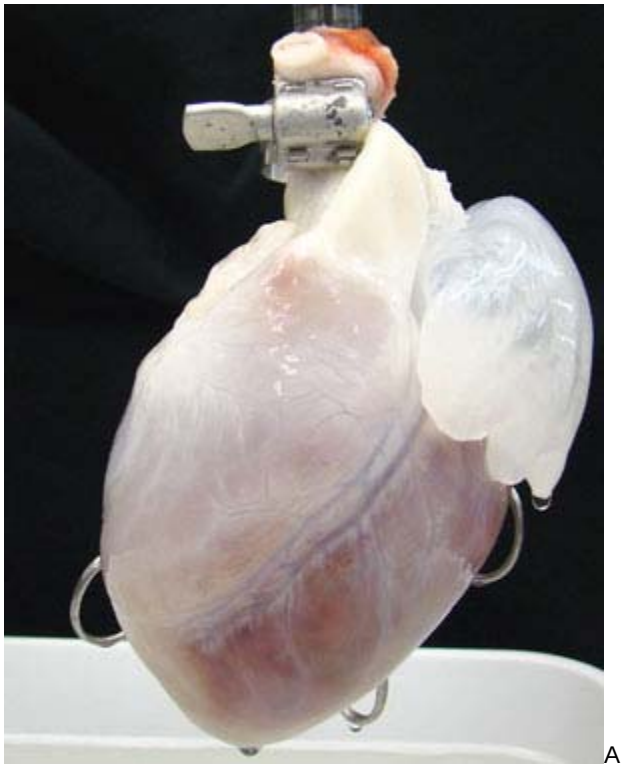
A pig heart, drained of its cells, stops beating. When repopulated with stem cells, it begins to beat again.

The University of Minnesota

The upshot was that embryonic stem cell research appeared stuck in neutral. During the eight years of the George W. Bush administration, it was limited to a few cell lines, some of them sickly, and was barred from federal funding—the only source of money plentiful enough to push such cutting-edge biology into high gear. Year after year, progress was glacial.

And then, even with the restrictions in place, the breakthroughs began. One of the greatest came in November 2007, when scientists in Japan and the United States reported that they could make adult skin cells from mice revert to the embryonic state. This feat was later achieved in humans as well. The reverted cells, called induced pluripotent cells, appear to be capable of transforming into a wide range of cells. No embryos are involved, and because the cells come from a person's own body, the pitfall of rejection is eliminated.

In 2008 a group of medical researchers led by Robert Lanza at Advanced Cell Technology in Worcester, Massachusetts, reported another leap: They discovered a way to avoid destroying the embryo by deriving an entire stem cell line from a single embryonic cell. The cell, taken from the embryo between the zygote and blastocyst stages, can be collected without damaging the embryo, and yet it is still versatile enough to give rise to whole classes of tissue types. Some of these harvested cells produce blood, for instance, and others neuronal tissue or muscles or retinal cells.

Now stem cells are being combined with gene and immune therapies, compounding the pace of progress. For instance, researchers at the Salk Institute in California have taken skin cells from a patient with the genetic disease Fanconi's anemia, often associated with leukemia. The cells were reverted to the embryonic state and then retrofitted with healthy genes lacking the Fanconi mutation. In lab tests the refurbished cells cured the disease in mice and in human blood. The researchers have not yet injected the cells back into the patient but say this is "proof of principle that this technology could be used to cure a disease."

While stem cell science is in fast-forward, the political climate is changing as well. Under the auspices of President Obama, the National Institutes of Health has loosened its guidelines so that new, hardier, and more experimentally useful embryonic stem cell lines can be studied and deployed. Fresh research funding appears poised to give an extra jolt to the revitalized field.

Stem cell treatments are already a reality for diseases of the blood, such as leukemia and sickle-cell anemia (like Paizley's),

and for tissue repair of the skin and the cornea. Projects that loom ahead include treatments for Parkinson's, Alzheimer's, and even paralysis.

Funded by the U.S. Army, tissue engineers have begun developing designs for replacement organs—kidneys, hearts, and lungs. The Army hopes the effort will make it possible to regenerate arms and legs lost by soldiers in war. Even autoimmune diseases, in which the body attacks itself, promise to recede in the face of coming stem cell treatments as defective immune cells are replaced with healthy ones. As if all this were not enough, Japanese scientists have announced an emerging capability to regenerate organs in place, inside the body itself. Their proof of concept, published this past August, enlists stem cells to regenerate teeth in mice.

Many researchers have found it hard to check their euphoria. There was a thrilling moment in 2007 when stem cells cured an HIV patient who received a bone marrow transplant to treat his leukemia. Aiming to treat the HIV as well, the hematologist chose a donor with a rare genetic mutation that makes cells immune to HIV. As hoped, the donor's stem cells took over, treating the leukemia and apparently banishing the HIV.

But in medicine, dramatic cures are rarely as simple as they may seem. Bone marrow transplants can cause deadly immune reactions, turning the decision to proceed into a perilous judgment call; HIV patients are better served with today's drug cocktails unless they need the transplant for another disease, experts say. In short, stem cell therapies remain uncertain and risky, hampered by unforeseen complexities. Stem cell clinics in India and Mexico may proclaim that they can heal everything from autism to cancer, but clients who spend millions of dollars there may be buying snake oil. The reality, say leading stem cell researchers, is that every disease and disorder needs its own special formula, including just the right promoter chemicals given at just the right dose, and just the right kind of stem cells introduced at just the right stage.

Where the promise is great, the risk is great as well. "Embryonic stem cells represent the good, the bad, and the ugly," says Doris Taylor, director of the Center for Cardiovascular Repair at the University of Minnesota. "When they are good, they can be grown to large number in the lab and used to give rise to tissues, organs, or body parts. When they are bad, they don't know when to stop growing and give rise to tumors. The ugly—well, we don't understand all the cues, so we can't control the outcome, and we aren't ready to use them without more research in the lab." The potential can become reality only through costly research and the words that every patient dreads: more waiting.

***LET THE TRIALS BEGIN***

With most stem cell therapies so new or experimental, the best place to access them is in a clinical trial—but you might want to hold back unless you are close to death. That was the grim dilemma facing Deanna Graham, whose joints began to swell and hurt in the fall of 2007, about the same time the 49-year-old accountant noticed the wrinkles on her fingers disappearing as if she were aging in reverse. Within a few months, her fingers began to turn cold and changed color from a dusky red to a deathly white. Then she began to have kidney problems, high blood pressure, and difficulty breathing. Her joints became so painful that, she says, "I was walking like Quasimodo." Just months after Graham's symptoms appeared, her doctors made a diagnosis of a systemic form of scleroderma, an autoimmune disease in which the body overproduces collagen, the fibrous supporting structure of the body. The disorder causes the skin to become thick and hard. If it affects internal organs, too, the patient is said to have systemic sclerosis, an often-fatal condition with no known cure.

Graham looked to the Internet for treatment options and came across Duke University oncologist Keith Sullivan, who was comparing standard chemotherapy and stem cell therapy as part of a large-scale clinical trial for scleroderma. The first group of volunteers received intensive chemotherapy, which wipes out the marrow that produces the immune cells responsible for the disease. The fix eliminated these immune cells but failed to replace them with healthy cells able to fight off infection. The second group received chemotherapy along with adult stem cells taken from their own bone marrow. Sullivan's hope was that after the chemo destroyed the original, defective immune cells, the reintroduced stem cells would settle in the bone marrow and turn out healthy immune cells—permanently.

Sullivan, who strives to be completely honest with his patients, gives clinical-trial volunteers a brochure explaining that the treatment "may be ineffective and could be more harmful than receiving no treatment at all." Graham decided to enroll anyway. A small and articulate woman, she explained her decision from a hospital bed at Duke University Medical Center. Facing a "50 percent chance of death" from scleroderma, she could not imagine not taking a chance.

That was a year ago, and Graham says she is now "doing great," though problems persist. Her hands still curl into claws and her knees and hips are still weak, she says, but "the list of healed areas is much longer. I feel hopeful, happy, and am much more active today." Other ongoing stem cell trials are targeting blood disorders like aplastic anemia, leukemia, lymphoma, and, of course, sickle-cell disease.

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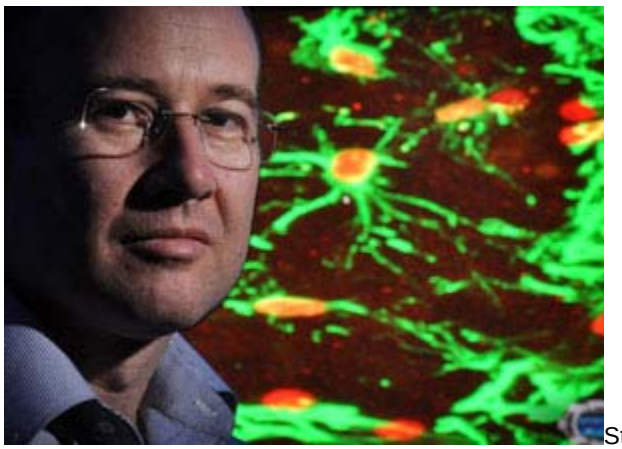 Stephen Davies of the University of Colorado is working with neural stem cells to heal spinal cord injuries.

Image: The University of Colorado

Tannishtha Reya, codirector of the Stem and Regenerative Medicine program at Duke, is particularly fascinated by the link between stem cells and cancer. She notes that stem cells normally divide and reproduce in a very regulated way, “but these signals get hijacked during cancer formation and may promote cancer growth.” Her research has recently shown that a signaling pathway dubbed “hedgehog” is important not only for normal development of stem cells but also for the growth of cancer cells in chronic myelogenous leukemia. When Reya and her colleagues blocked the hedgehog molecules in mice, they found they could slow the development of cancer even when it had become resistant to conventional therapy.

Stem cell research also shows great promise for healing wounds, regenerating damaged limbs, and replacing whole organs. Doris Taylor surprised the world in early 2008 with the first beating bioartificial heart. She and her team created it by dissolving all the cellular material in a rat heart, leaving behind only the extracellular matrix, a heart-shaped protein scaffolding. Then the team planted a mix of heart stem cells on that matrix. “You can grow heart cells in a dish but they won’t beat well enough to pump blood,” Taylor says. On the matrix, however, the cells beat effectively and even grew their own blood supply. “It’s gorgeous,” she marvels. “You can see the whole vascular tree, from arteries to the tiny veins that supply blood to every single heart cell.”

Taylor believes that an artificial pacemaker coupled with a biosynthetic heart could allow doctors to create made-to-order, rejection-free human heart implants—a salvation for the thousands of people in the United States who die each year while awaiting traditional heart transplants. She and her colleagues are also working on biosynthetic livers, kidneys, lungs, and pancreases.

Thinking on a grand scale, last year the U.S. Department of Defense established the Armed Forces Institute of Regenerative Medicine with the goal of creating an entire warehouse of spare body parts. One Army grantee, tissue engineer Stephen Badylak of the University of Pittsburgh, has developed what some call “pixie dust,” a therapeutic powder made of extracellular matrix that activates adult stem cells already living in the body. When applied to the wound of a patient whose fingertip was accidentally amputated, the fingertip—nail and all—grew back. Badylak says his powder provides a scaffold that recruits the patient’s own stem cells to lay down the new cells needed to regrow a fingertip. He also treated two soldiers who lost entire fingers in combat and whose wounds had completely scarred over. To help them heal, he reopened the scar tissue and applied his powder. It worked there, too, Badylak reports: Volunteers had an average of nine millimeters (about one-third of an inch) of soft tissue growth, enough to let them turn a key, work a zipper, or use a fork. This approach could someday be used to regrow an entire limb. Badylak says his stem cell stimulator is currently being applied, with great success, to heal injured hearts, thoracic wounds, and the outer lining of the brain.

> Before treatment it would have been difficult to predict that Paizley would do brilliantly while Hina would endure a rocky course.

At Advanced Cell Technology, Lanza uses stem cells to prevent or treat blindness. He has thus far derived stem cells from retinal cells and transplanted them into mice with Stargardt disease (a form of blindness caused by early-onset macular degeneration) and rats with full-blown macular degeneration, achieving near-normal function in the former and “100 percent

improvement" in the latter.

Lanza is also working with hemangioblasts, intermediate cells derived from embryos that can make all blood and vascular cell types. He and his colleagues have injected hemangioblasts into animals with obstructed blood flow to their limbs and eyes and observed robust new blood vessel growth. He believes hemangioblasts will someday be used to repair vascular injuries caused by heart attack and restore circulation in the legs of diabetics who might otherwise lose their toes, feet, or legs to gangrene. Already hemangioblasts have been used to generate functional human blood in the lab. "The beautiful thing," Lanza says, "is that if you have an embryonic stem cell line that is O negative, because it's immortal you could create an unlimited amount of universal blood that would match virtually everybody, so you wouldn't have to worry about matching blood types."

***THE LONG ROAD AHEAD***

Despite so much progress, serious obstacles remain. For instance, stem cells and the protein scaffolding are just two of the three essential elements needed for the regeneration of body parts. The third ingredient is the complex array of signaling molecules that regulate the growth and development of stem cells. These molecules tell the cells which side is right, which is left; where to morph into vessel or nerve, muscle or bone; and when to stop growing.

Faulty control signals may allow stem cells to run amok and proliferate wildly. If that happens at an early stage, the result can be a clump of undifferentiated cells that grow out of control: cancer. If the signaling error occurs before the cells have differentiated to become either bone or hair or skin, the result can be a teratoma, a tumor that contains a jumble of cell types. The specter of teratomas and cancer should make researchers and patients alike wary of embracing stem cell therapies before they are proven, Lanza says. "You don't want a bone or a tooth growing out of your eye."

Stephen Davies, a neuroscientist at the University of Colorado at Denver who studies nervous system regeneration using stem cells, is one of the key scientists working to overcome the obstacles in place. His corner office on the ninth floor of the Anschutz Medical Campus in Aurora, Colorado, offers an inspirational panorama of the Rocky Mountains in the distance. But Davies's attention is squarely on his work as he clicks his keyboards, calling up brilliantly colored slides that flash across two computer monitors. The images encapsulate the effort that consumes virtually all of his waking hours: coaxing stem cells to repair spinal cord injuries and reverse paralysis.

Davies is cautious in making claims about what stem cells can deliver, reiterating how much work he has yet to do. After other researchers reported that bone marrow stem cell therapy led to a modest but promising 5 percent improvement in the regeneration of sensory nerve fibers in rats with spinal cord injuries, he performed a critical reality check. He tested what happened to rats with untreated spinal cord injuries and discovered they also showed 5 percent nerve fiber growth. Many of his colleagues found the results demoralizing, but Davies did not give up. In one follow-up he transplanted adult neurons into the spinal cords of rats and found they could grow robustly, though often in the wrong direction.

That last discovery made Davies even more interested in experimenting with neural stem cells at an early stage of development. These progenitor cells, he hypothesized, might be undifferentiated enough to take cues from surrounding cells in the spinal cord so that they would develop properly. Davies began working with "glial-restricted precursors" (GRP), a type of stem cell that turns into specialized nerve tissue. Alas, GRP cells took cues from scar tissue at the site of spinal injuries, forming even more scar tissue. Hopes for these cells were dealt another serious blow when researchers showed that they coaxed the nerves to grow—but that they also grew new pain receptors, increasing patients' discomfort with no reduction in paralysis.

Despite these frustrations, Davies persisted, discovering that he could use GRP cells to generate astrocytes, the star-shaped structural cells that play a crucial role in nervous system function right along with neurons. Eventually he found that if he treated GRP cells with a special signaling molecule, they generated a type of astrocyte called GDA (glial-restricted precursor derived astrocyte). GDA cells could promote nerve growth while suppressing scar formation, allowing recovery to begin. In one recent study, paralyzed rats treated with GDA were able to walk across a ladder just as they had before their spinal cords were severed.

Human trials should follow soon. Small, early-phase studies of stem cell treatments for human spinal cord injury are now under way at sites around the world.

***KEEPING THE FAITH***

Even when all the kinks are addressed, stem cell therapies may heal some patients but not others with the same disease. Hina Patel is a slight girl of 17. Like Paizley Carwell-Bowen, Hina underwent transplantation at Children's Hospital of Los

Angeles to treat her sickle-cell disease. But nine months after the procedure, she languishes in an isolation room behind a plastic barrier. Her mother sits in a chair close by. Staff and visitors must don a gown, gloves, mask, and booties before entering her room in order to protect her weakened immune system from any infectious organisms they might carry.

Hina had developed the devastating immune reaction known as graft-versus-host disease, in which donor cells attack the walls of the gut, skin, lungs, liver, and sometimes—though rarely—even the patient's brain. Unlike a drug, which can be discontinued, the donor cells she received would go on day after day, month after month, launching attacks on her gut and causing intestinal bleeding. Over a period of several months, Hina required as many blood transfusions as she had during a lifetime of sickle-cell disease. She could not eat for more than a month, and at one point her weight dropped to a perilously low 75 pounds. Nonetheless, Hina, her family, and her doctors are optimistic that she will recover and do well.

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Before treatment it would have been impossible to predict that Paizley would do brilliantly while Hina would endure such a rocky course. The inability to predict who will flourish and who will not raises enormous conundrums. Although treatment for sickle-cell disease with marrow from related donors is now accepted as a standard of care, treatment with marrow taken from an unrelated donor is still evolving, reserved for only the most seriously sick patients. Such subtle distinctions can be lost on anxious parents eager to save their children.

Many patients may not really know what they are getting into when they agree to stem cell treatments beyond the very few that have been proved effective. The researchers themselves may not know the real risks, in part because there are data on so few patients and in part because doctors may be reluctant to report bad outcomes. In the medical community, there is a tendency not to publish negative results, and if such data are submitted, medical journals may be less likely to accept them for publication. As a result, researchers can end up repeating the same failed experiments, putting patients at unnecessary risk.

To assess risk, Thomas Adamkiewicz, codirector of the Hemoglobinopathy/Genomics Training Program at Morehouse School of Medicine in Atlanta, surveyed four medical centers and found that seven children with sickle-cell disease had been treated with umbilical cord blood from unrelated donors. Only four of the seven cases had been published, and the three unpublished cases had worse outcomes overall, including one death. "Doctors who want to treat patients with stem cells might look at the published data and conclude, 'Oh, this is good,'" Adamkiewicz says, "but when you see the results for all seven, it's not as rosy a picture."

This bias may come from good intentions: The most fervent believers in the stem cell future are often the scientists themselves. George Daley of Children's Hospital in Boston and the Harvard Stem Cell Institute, who studies stem cell development and differentiation, says that only well-conducted studies can tease out the good from the bad. But he also believes that medical researchers will overcome some of the thorny obstacles to safe and effective therapies—just as once seemingly insurmountable obstacles to kidney transplants were overcome —clearing the way for treatment of diseases such as Parkinson's, blindness, and immune disorders.

As his colleagues make strides over the coming years, Daley expects that stem cell trials for a wide swath of cancers and autoimmune diseases will come online. Organ replacement, limb regeneration, even rejuvenation might follow.

"The greatest risk is that we will overpromise what we can do with stem cells," Doris Taylor says. "Still, embryonic stem cells are a potent tool in the armamentarium against disease. Those cells know how to become virtually every organ tissue. From them we can learn how to build."

The few people who have already experienced the technology in action make a persuasive case for the power of the stem cell. Paizley, the teenager who was once nearly destroyed by sickle-cell disease, is now free of the illness that haunted her, free to attend school like all of her healthy friends. Flashing a broad smile, she says that if she does not make it as a singer, she just might study marine biology instead.

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**Can You Buy a Cure in China?**

If you spend a lot of time in the blogosphere, you might get the idea that stem cell cures for everything have already arrived. Broad claims of success have sparked the ire of scientists, who insist the complexities of stem cell therapies make such

success unlikely. Instead of genuine treatments, they contend, the miracle cures promoted online are actually scams aimed at people who are ill and desperate.

Hundreds of parents have flown to China and paid $20,000 to $30,000 for stem cell treatments for visually impaired infants born with optic nerve hypoplasia. A number have returned claiming “cures” based on small but real increases in their child’s vision or light perception. But failure to understand the natural course of a disorder—the outcome of the disease without any treatment at all—can mislead patients into crediting risky stem cell treatments that may actually offer no help. According to Mark Borchert, head of the vision center at Children’s Hospital of Los Angeles, up to half of all children under the age of 5 with optic nerve hypoplasia will improve without any treatment. Only controlled clinical trials will allow doctors to understand whether there is any overall net benefit—or net harm—involved.

One clinician who has not waited for controlled clinical studies is California osteopath David Steenblock, who offers stem cell therapy for more than 20 diseases, including Alzheimer’s, traumatic brain injury, Parkinson’s, arthritis, stroke, and heart disease. Steenblock’s method: extracting a patient’s bone marrow and injecting it right back in, stem cells and all. “The stem cells in your bone marrow are sitting there like they are in a safety-deposit box at your bank,” he says. “So we have to pull them out and say, ‘Hey, let’s use them!’ We spread them around, and voilà: You get better.”

George Daley of Children’s Hospital in Boston and the Harvard Stem Cell Institute doubts that Steenblock’s treatment can cure much. “I’d like to ask him on what, other than wishful thinking, does he base those claims? One single stem cell from the bone marrow is not going to be able to treat disorders as different as Alzheimer’s disease and rheumatoid arthritis,” he says. To counteract all the claims, Daley helped devise a set of guidelines issued by the International Society for Stem Cell Research in 2007. Those guidelines strongly discourage doctors from treating patients outside of clinical trials. “It’s gut wrenching,” Daley says of the letters and e-mail he receives virtually every day. “There are patients who are being given spinal injections of cells for anything from cerebral palsy to Alzheimer’s, and for many conditions there is absolutely no scientific evidence that this works.”