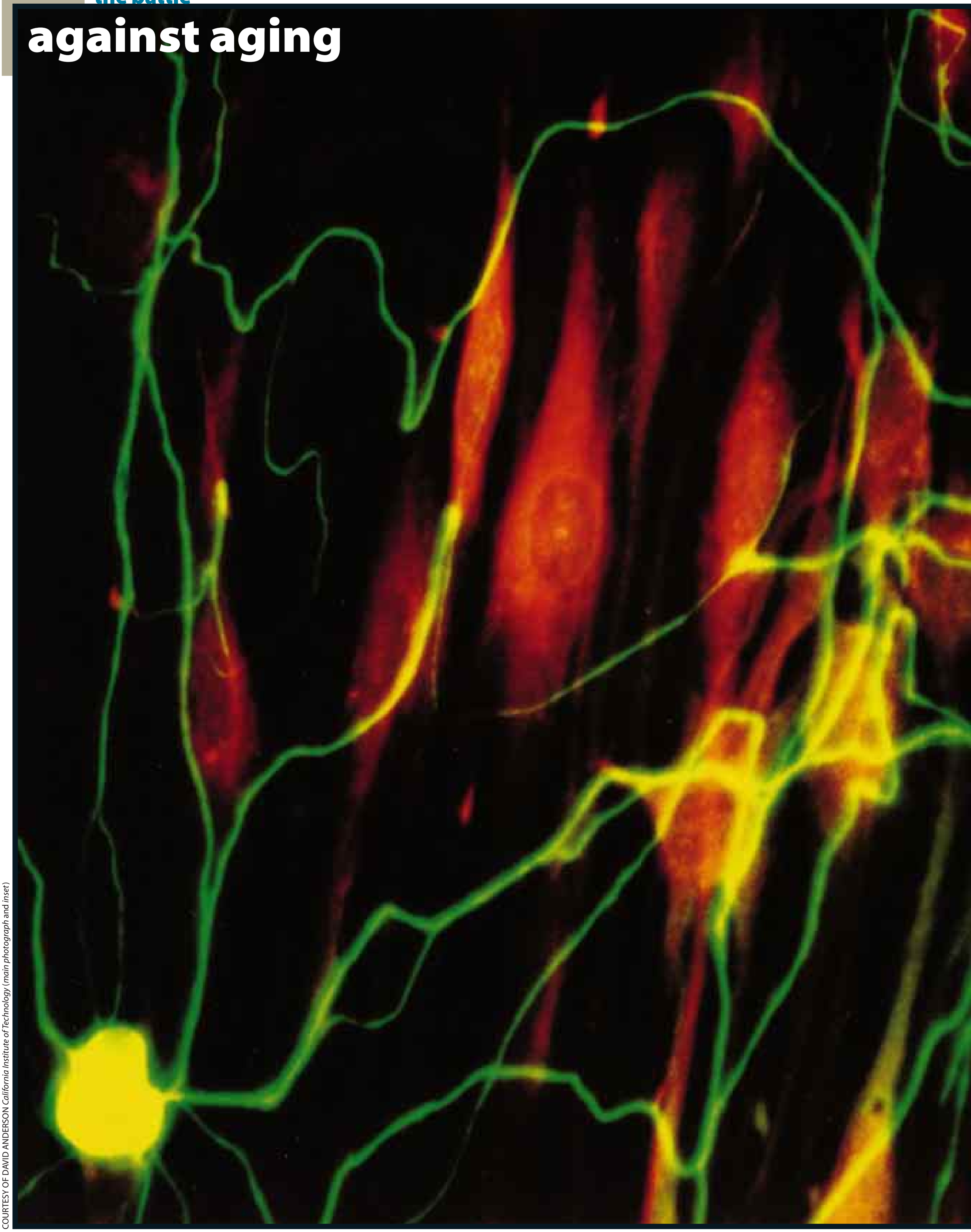
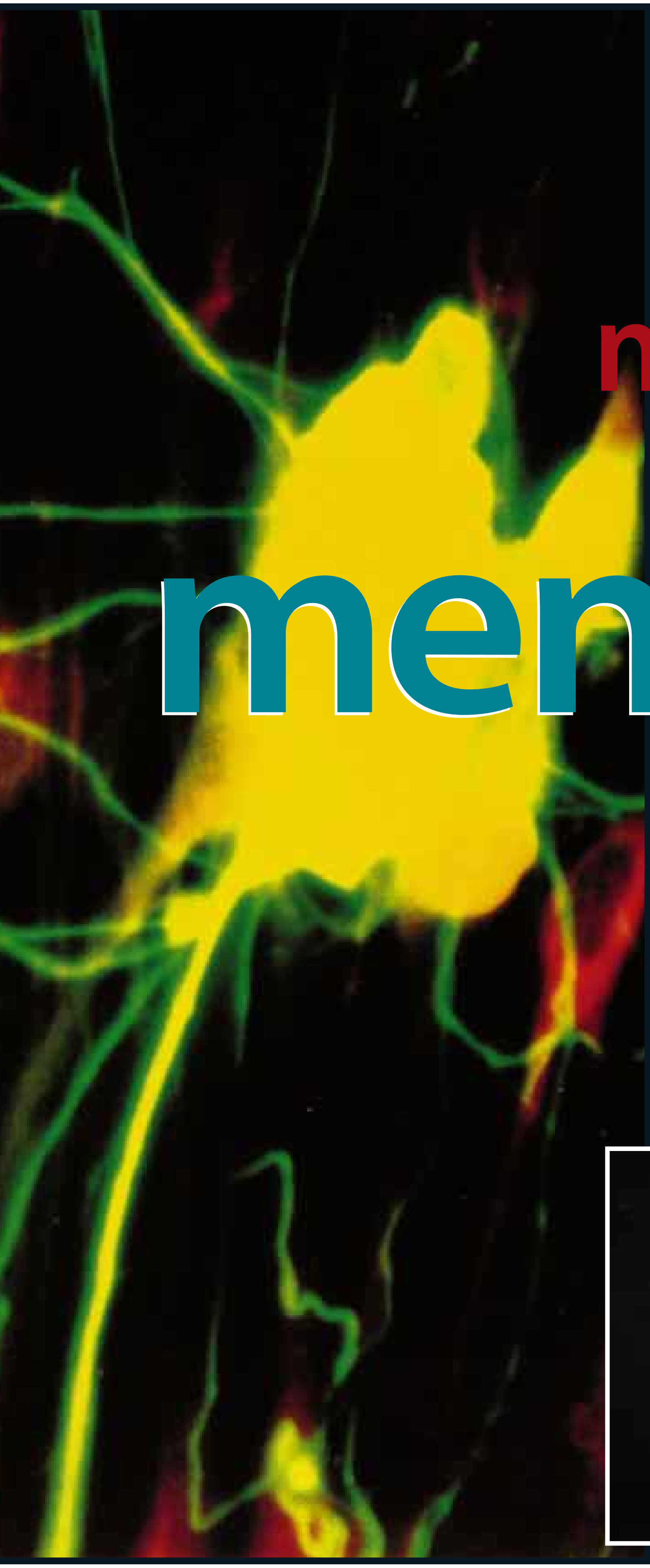
the battle against aging



COURTESY OF DAVID ANDERSON *California Institute of Technology* (*main photograph and inset*)



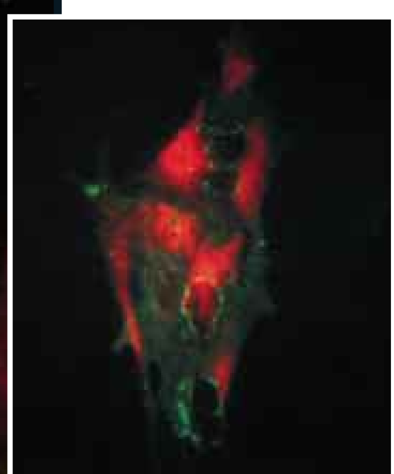
STEM CELLS MIGHT ROUTINELY REPAIR OUR WORN-OUT TISSUE, IF SOCIETY ACCEPTS THIS APPROACH

mother nature's menders

BY MIKE MAY

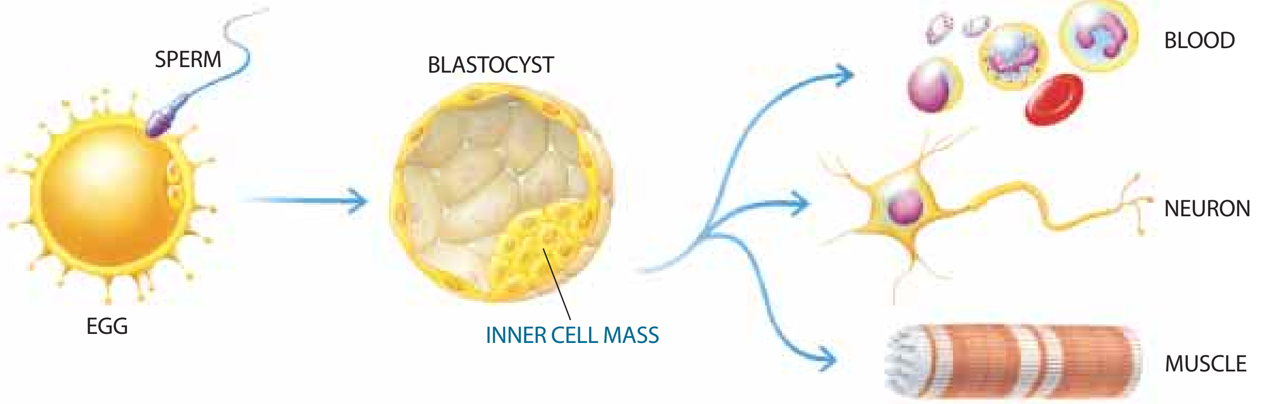
In the 1970s *The Six Million Dollar Man* television program opened each week by showing a terrible accident that turned astronaut Steve Austin into "a man barely alive." Then we heard: "Gentlemen, we can rebuild him. We have the technology." The idea intrigued us but seemed centuries away. It's not. An explosion of work surrounding stem cells, which can differentiate into many other cell types, raises hope for medical repairs beyond our imagination—mending a damaged heart, fixing a failing liver, improving a forgetful brain and, most exciting, significantly extending life. Instead of using bionic parts, like the ones that made Steve Austin stronger and faster, this technology could provide us with longer and healthier lives by enabling us to control our natural repair mechanisms.

This emerging field takes advantage of a cell that may



TWO FROM ONE: Neural stem cells (*inset*) can give rise to differing cell types: neurons (*yellow*), which are wired to their neighbors, and glia (*red*), nucleated structures in the background.

origin of a stem cell



SPECIALIZATION: Some scientists consider a stem cell to arise when a sperm fertilizes an egg (*left*). Others think it originates in the inner cell mass of the blastocyst, a hollow sphere that emerges after several cell divisions (*center*). Either way, stem cells can differentiate into unique cell types, such as muscle, blood and nerve tissue (*right*).

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emerge from the moment of conception. When a sperm cell works its way into an egg during fertilization, some scientists consider the result to be a stem cell. Other researchers consider stem cells to appear after several cell divisions that turn a fertilized egg into a hollow sphere of cells called a blastocyst. That sphere includes a region called the inner cell mass, consisting of a group of stem cells. Wherever stem cells first arise, they can branch out in many directions. A stem cell holds all the information it needs to make bone, blood, brain—any part of a human body. It can also copy itself to maintain a stock of stem cells.

Many of us imagine that a human body builds up most of its cells and tissues early in life, and then everything begins to fall apart, cell by cell. New findings prove otherwise. Stem cells busily work away throughout our lives, acting like an army of housekeepers, cleaning up a little mess here and repairing some damage there. In some cases, a group of these cells work together to perform gargantuan tasks. For example, the stem cells located in bone marrow must replace more than one billion red blood cells every day. Such rebuilding might be going on constantly all over the body. Stem cells also seem to make new cells continuously for bone, liver, heart, muscle and even the brain, where scientists long thought that we were incapable of generating new cells.

Bodily Tune-ups

Stem cells serve as a natural defense against aging. As things wear out, these cells can repair some damage. As we get older, though, the failures in our bodies apparently overrun the stem cells. Consequently, we decline—getting slower, weaker, more forgetful. Nevertheless, many scientists believe that they could slow these processes with a stem cell tune-up. Moreover, a regular dose of jazzed-up stem cells might fight off degeneration and keep us living a longer and healthier life.

The inherent qualities of stem cells have drawn tremendous attention to them. To be sure, some scientists take the *Six Million Dollar Man* approach and try to fabricate new parts from exotic metals and space-age polymers. You can already get an artificial hip joint, an implantable device to help with hearing loss, and replacement valves for your heart. Some groups are even pursuing an electronic retina. But why rely on so many different parts—essentially a new fix for every problem—when you could use stem cells instead? Stem cells might be a cure-all of sorts, basically one-stop shopping for repairing anything that ails you.

Despite the recent interest in stem cells, they are not entirely new in medical therapies. Physicians have been extending human lives for years by including stem cells in some treatments. For example, some forms of cancer, such as childhood leukemia, require such a devastating dose of chemotherapy that it destroys a patient's bone marrow. A bone marrow transplant can restore a patient's blood-making capability, presumably because it provides a new supply of blood-making stem cells. When physicians started using bone marrow transplants, though, no one had seen a human stem cell. They just assumed that such cells existed.

In late 1998 all that changed. Two sets of researchers in the U.S.—John Gearhart's group at Johns Hopkins University and James Thomson's team at the University of Wisconsin–Madison—isolated human stem cells. These results shook up science and society, raising hope for therapeutic uses of stem cells as well as a range of ethical questions.

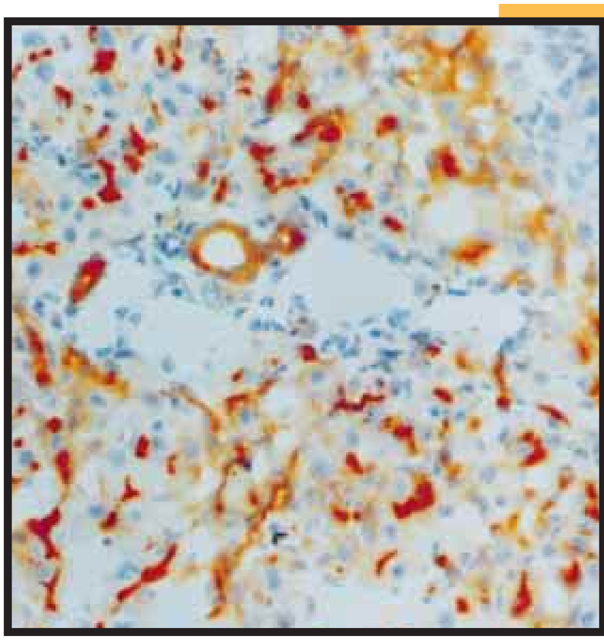
After the first reports, investigators launched a parade of promising animal experiments. Evan Snyder of Harvard Medical School has shown that neural stem cells seek out damaged areas of a mouse's cortex—the highest centers of the brain—and make new neurons there. He has very preliminary evidence that neural stem cells can do this in primates, too. "We're starting to move our way up the evolutionary ladder," Snyder says, "suggesting that this really may be a kind of intervention or kind of application that we could use." He also mentions evidence that neural stem cells could generate new neurons in other areas of the brain and even in the spinal cord. If human neural stem cells can go to damaged areas in the nervous system and create neurons there, such a technique might fend off Parkinson's disease, amyotrophic lateral sclerosis (better known as Lou Gehrig's disease) or old-age dementia.

Tissue Flipping

These findings seem to be cropping up in one organ after another. For instance, Bryon Petersen of the University of Florida says his work in rats showed that a cell that originated in the bone marrow could travel to the liver, incorporate into that organ and become a functioning liver cell. Presumably, that bone marrow cell was a blood-making stem cell. As Ronald McKay of the National Institute of Neurological Disorders and Strokes explains, "One really exciting thing that's going on in the field at the moment is, in fact, we're sort of discovering that the stem cells that have been defined in different tissues are actually capable of flipping from one tissue to another." McKay notes that researchers are not absolutely sure that the flipping really goes on in stem cells but adds that "there are cells that are capable of giving rise to the cells of another tissue: brain into blood, brain into muscle, pancreas into liver, muscle into blood."

Still, scientists must answer a crucial question: Do the new cells really work? In most cases, it's hard to tell. Just because a stem cell ends up in the brain and turns into what looks exactly like a neuron doesn't mean that it works properly. Still, McKay and his colleagues did show at least one case in which new neurons did work. First, they caused a Parkinson's-like disease in rats by killing neurons that communicate through a neurotransmitter called dopamine. Then they obtained neural stem cells from rat embryos and injected the cells into the Parkinsonian adult rats. In less than three months the normal movement in most of the treated rats improved by about 75 percent.

Over this incredibly promising work looms a controversy that threatens some stem cell research. It all revolves around one word: embryo. In essence, scientists talk about two general classes of stem cells, ones that come from embryos and ones from adults. Some people would never condone using embryos in any way because of ethical beliefs. If you can get stem cells from adults, though, surely this entire problem can be resolved by forgoing the use of embryonic stem cells. But, as Thomson explains, "the embryonic stem cells have the potential to form anything. It's not clear what the developmental potential is of some of these other stem cells." In other words, an embryonic stem cell can do it all—make any cell needed—and adult stem cells might be limited to making a few kinds of cells. Furthermore, adult stem cells could be partially worn out, so that they would not offer the full rejuvenating benefits of embryonic ones.



A NEW IDENTITY: Stem cells in bone marrow transplanted from one rat to another developed into cells that produced a functional enzyme (*red-orange areas*) in the liver of the recipient animal.

BRYON PETERSEN *University of Florida*

Despite all the potential benefits of using embryonic stem cells, working with them remains off-limits for researchers receiving federal funding for their studies, as all powerful laboratories do. A ban put in place by the U.S. Congress on the use of federal money means that research is confined to the narrow universe of just a few private biotechnology companies—Geron Corporation and Advanced Cell Technology being the leaders. Progress in the field is slower than it might be without the prohibition. But the funding environment may change.

In November 1998 President Bill Clinton asked the National Bioethics Advisory Commission to investigate the medical and ethical issues behind embryonic stem cells. Its report concluded: "[T]he Commission believes that federal funding for the use and derivation of [embryonic stem] cells should be limited to two sources of such material: cadaveric fetal tissue [from naturally aborted fetuses] and embryos remaining after infertility treatments." The report thus encouraged federal funding for certain approaches to stem cell research. Then, in December 1999, the National Institutes of Health, the primary source of U.S. biomedical funding, published a draft for guidelines on stem cell research, which went out for public comment. These documents suggest that the outlook for at least limited federal support has become less bleak.

But the National Bioethics Advisory

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Commission did not endorse an approach called nuclear transfer, which Michael West of Advanced Cell Technology champions. In his technique, researchers remove the nucleus from a cow's egg, implant a human cell—say, a skin cell—inside it and allow it to grow embryonic stem cells. With this system, West and his colleagues might be able to use skin cells—obtained by merely scraping a toothpick across the inside of your cheek—to make embryonic stem cells just for you. That could be important because your immune system might fight off stem cells from anyone else, seeing them as foreign invaders, like a virus. In addition, cow's eggs come cheaply and in large numbers. Still, combining human and cow cells started more than a little disgruntled mooing, because some people see it as a dangerous mixing of species. West defends his approach, saying, "We take the [cow] egg and remove its DNA, so there's no more mixing of species than there is when you drink cow's milk."

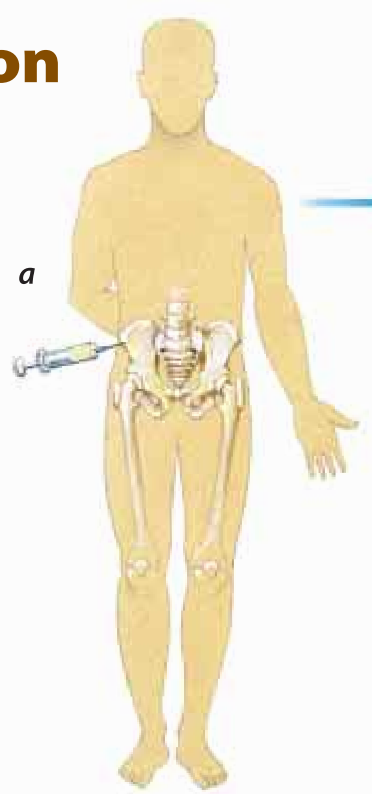
In any case, you need West's approach only if your body really is likely to reject foreign stem cells. West says your immune system would search out foreign cells with the efficiency of a hawk hunting a mouse. Thomson, one of the first to isolate human embryonic stem cells, agrees that the body would reject stem cells as it does some organ transplants: "Absolutely. Once they differentiate, they'll become adult cells like any other cell in the body," which would cause them to be rejected. But Thomson's opinion is not universal. One company, Osiris Therapeutics, has found through its studies that foreign stem cells are not cast out by the immune system. "It really doesn't seem to be the case. We don't quite know why that is," says Osiris scientist Mark Pittenger.

Luckily, investigators do agree on some topics. For example, most everyone thinks they could grow these cells in culture and keep them alive essentially forever. About his human embryonic cells, for instance, Thomson says, "We've kept them growing for well over a year. By any measure that we have, they appear to be immortal." And once researchers know how to culture whatever kind of cells they have, they can make incredibly large numbers of them. For example, a single human skin cell can spawn 170 trillion trillion trillion cells. Moreover, farming these cells in culture could reduce the concerns about using embryonic tissue. "One of the things I think people don't like about this is the idea of constantly going back to human embryos and doing the stuff over and over and over again," McKay says. "But technically, we can grow the cells, we can really grow them. I think this is going to be very efficient, so you needn't be concerned that this is going to be a big [embryo] harvesting industry. It's not going to be like that." The recently created WiCell Research Institute—with Thomson as its scientific di-

tissue rejuvenation

BIOENGINEERING: Companies have already begun to contemplate medical techniques that would use stem cells to reverse the effects of aging on flesh, blood and numerous organs. A sample of bone marrow containing stem cells could be extracted from the pelvis (*a*). The cells could then be grown in a culture (*b*) before being removed, inserted into a blood bag and reinjected into the body (*c*). (The solution would contain both stem cells and progenitor cells, products of stem cells primed to make certain tissue.) In the body, this mixture would home in on locations where they could help revive, say, a damaged liver or kidney. One company, Aastrom Biosciences, is developing a machine that will culture enough stem cells over a 12-day period to make medical uses practical (*photograph*).

a



EXTRACTION

b

CULTURING

AASTROM BIOSCIENCES

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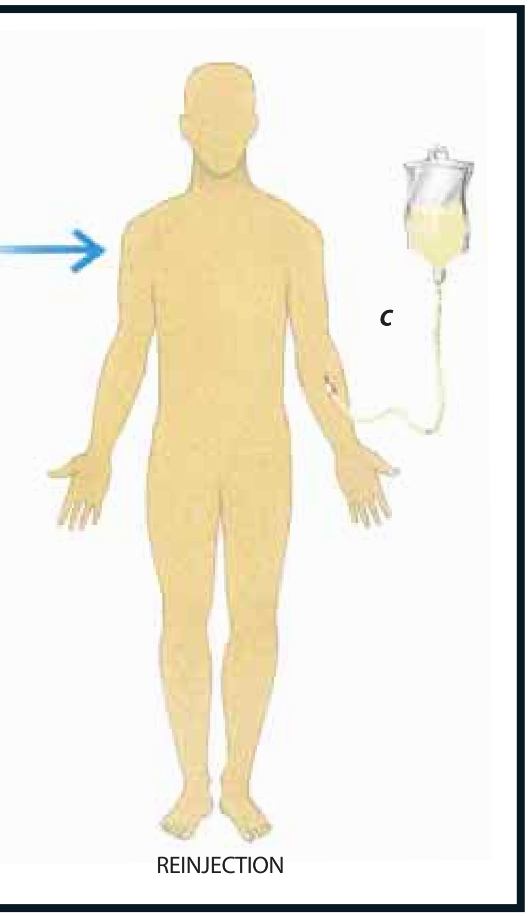
rector—plans to grow and sell human embryonic stem cells for research.

Although physicians already rely somewhat on stem cells—at least for bone marrow transplants—many more clinical applications might lie just over the horizon. Stem cells might be used to repopulate or replace cells devastated by disease. It might even be possible to take a stem cell, nudge it chemically toward making the kind of tissue desired and then control its environment in a way that causes it to build an entire organ. The organ could then be used in someone who needs a transplant, the pinnacle of so-called tissue engineering.

When could some of these stem cell techniques be available? "I think we're going to be moving into clinical trials with human neural stem cells of some type for some disease within two years," Snyder says. That means that stem cell–boosting treatments could be available in five to 10 years. Making entire organs from scratch, however, lies much further in the future. In theory, physicians could get so good at fixing organs with stem cell treatments that such organ fabrication might never be needed.



REINJECTION

Just Hit "Play"

Some companies are already counting on a market in stem cell medicine. For instance, Douglas Armstrong of Aastrom Biosciences describes a machine developed by his company that is primed with a sample of bone marrow or even blood from an umbilical cord, both of which contain stem cells. According to Armstrong, "The equipment operates much like a VCR with a videocassette. The user takes the cassette, pops it into the machine and the machine takes over. Twelve days later the cassette comes back out, goes on another machine and transfers the cell product to a blood bag that's ready for therapy."

The resulting blood bag would contain stem cells as well as so-called progenitor cells, which are products of stem cells that are primed to make specific tissues. A physician could simply inject stem and progenitor cells into the bloodstream, and many of them would home in on locations where they were needed.

Armstrong adds, "It's practical to think we may be entering a future period where all of us put aside a small amount of bone marrow or even our umbilical cord blood when we are born, and then samples of that are grown out into populations and we get infusions of those cells later in life that might, indeed, help us live much longer, healthier lives."

Many hurdles lie between ongoing research and turning stem cell techniques into therapies for humans. "These therapies are brand-new," Thomson says. "There are no precedents for them." Consequently, a researcher can't simply see what stem cell treatments do in rats and mice and then try the same thing in humans. In a hypothetical example, Thomson speculates that a newly discovered technique that cures diabetes in mice might not help human diabetics but instead leave them with a worse disease—pancreatic cancer, for example. In other words, a treatment for a serious but survivable disease could give patients a certain death sentence.

"So you want to make really sure what you're doing isn't worse than the disease you're trying to cure and that there's a lot of safety involved," Thomson continues. "Because the therapies are so new, going straight into humans would be a problem." Much more research on primates and then extensive clinical testing must be completed before new stem cell techniques become available as a routine form of treatment.

Scientists do know that stem cells promise entirely new views of how the human body works. "For me, the absolute true potential of these is more in how it's going to give us a clue to understand the human body," Thomson says. "So even if [stem cells] were never to be used for transplantation purposes, they give you this brand-new scientific model to study. If you're interested in heart disease, you can study populations of human heart cells in tissue culture for the first time on a regular basis.

"I think the transplantation stuff will be important," he goes on, "but someday we'll understand enough about the human body that these transplantation therapies won't be necessary, because it will be possible to cause specific cells to regenerate themselves in ways they don't naturally do, because we will understand how that development normally occurs."

We might never see science rebuild a man with Steve Austin–like techniques. Instead researchers may rebuild us by tweaking systems that our bodies possessed all along—stem cells, the ultimate medical weapons. Now we must wait to see if science and society can agree on ways to use these seemingly magical wonders of biology.

Mike May *lives and works as a freelance writer in Clinton, Conn.*

Further Information

Stem Cells: A New Lease on Life. Elaine Fuchs and Julia A. Segre in *Cell,* Vol. 100, No. 1, pages 143–155; January 7, 2000.

Stem Cells: A Primer. Available at www.nih.gov/news/stemcell/primer. htm