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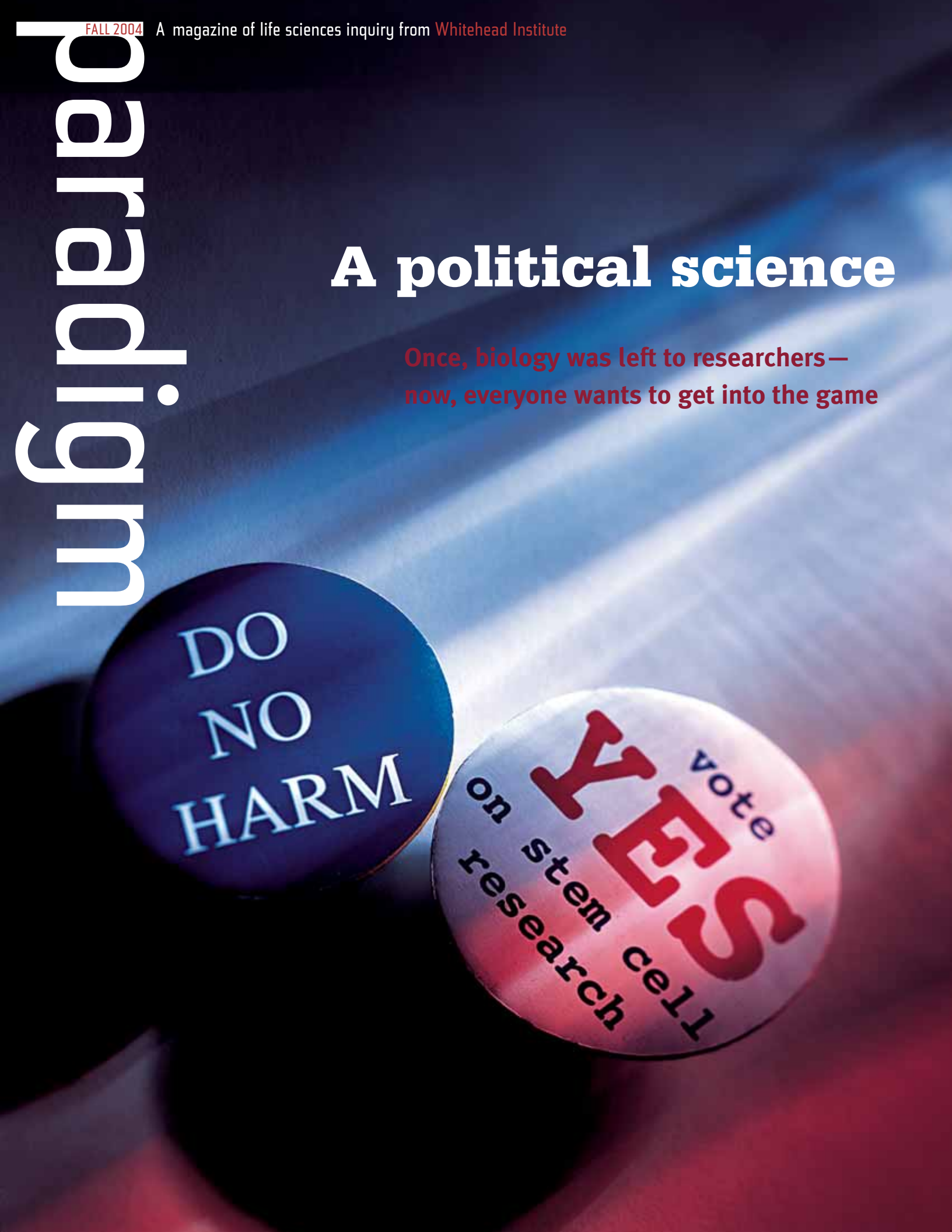
parad!gm

A political science

Once, biology was left to researchers—now, everyone wants to get into the game



Life, death, and stem cells

Both sides of the debate on therapeutic cloning are fighting for life and against death. It's probably the only thing they have in common.

BY DAVID CAMERON

Your doctor has some bad news. Turns out your heart isn't working right. In fact, due to deterioration in the muscle tissue, it's only operating at 10 percent capacity. That explains your chest pains, difficulty breathing, and inability to exert yourself without getting winded. Unfortunately, you know what the diagnosis means: getting on a donor list, staying at home, and waiting for the hospital beeper to go off if a donor organ becomes available. And even if that does happen—and the chances are slim—you'll always be wondering how long the transplant will last, worrying that your immune system will wise up to this foreign mass of muscle and attack it with everything it's got.

But your doctor has another idea. He will

collect cells from the surface of your skin and put them in a dish. You'll go home, with orders to stay in bed and rest. About six weeks later, you will arrive at the hospital and be wheeled into the operating room. The last thing you'll remember is the anesthesiologist placing a mask on your face and asking you to count backward from 10. When you wake up in recovery, groggy and achy, your doctor will say that you're going to be fine. Even as the two of you speak, your heart muscle will be renewing itself. Tissue will have been engrafted into your heart—tissue created from your very own DNA. No red flags to alert your immune system. In a few weeks, you'll be completely restored.

For now, the above scenario is speculative fiction—highly controversial speculative fiction. Politicians, lawyers, ethicists, religious leaders, United Nations delegates, and scientists are embroiled in a debate over whether the process used to "heal your heart" is morally flawed.

For that new heart tissue to be created, researchers would need to remove the nucleus from one of your skin cells and implant it into a donor egg cell from which the nucleus had been removed. They would coax the egg cell to divide into a blastocyst, a mass of about 100 cells. In the center of that mass they'd find the payload—embryonic stem cells, microscopic dots with nothing but pure potential. The cells are able to form any type of cell in the human body, including those from which scientists could conceivably grow your heart tissue. Or liver tissue. Or pancreatic tissue. Or brain tissue. Or spinal cord tissue. And so on. To do that, they would need to destroy the cloned blastocyst, and that's where it gets messy.

If, rather than harvesting it for stem cells, scientists instead placed that blastocyst, grown from your skin cells, inside a human uterus, it would have the potential to develop into a fetus. Nine months later, if all went well, a baby would be delivered. But not just any baby. It would be a carbon copy of you, cell for cell. It would be your clone, the "twin" you never had.

Just the prospect of creating a human being in this way is an ethical minefield in and of itself. But so is destroying the blastocyst. And so is creating it in the first place. To make matters worse, for researchers today to learn how to create "your" heart muscle tomorrow, they need to experiment on

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human embryonic stem cells. Until now, scientists in the field have used leftover blastocysts that stock the freezers of fertility clinics for their studies. These blastocysts are fertilized embryos that have the potential to develop into healthy babies.

Welcome to the ethical bouillabaisse known as embryonic stem cell research, where issues related to religion, abortion, cloning, and human disease are dumped together into a single scientific stew. Rarely has an issue of basic science been so hotly debated on every imaginable front, from family dinner tables to political platforms.

The Bush administration remains firmly behind the stem cell research policy announced in 2001, which restricted federally funded embryonic stem cell research to existing stem cell lines. But last May, Nancy Reagan, Republican icon and wife of the late President Ronald Reagan, asked the sitting president to change his policy on embryonic stem cell research, calling it the best hope for people with Alzheimer's disease, the illness that plagued her husband in his final years. And in July, the Reagans' son, Ron, carried the same message to the Democratic National Convention.

But behind all the political sparring, where is the science? Critics claim that embryonic stem cell advocates are inflating their case; advocates say it is the most exciting development in biology in decades. Still, fundamental questions remain: How advanced is the research? Can therapeutic cloning actually work, delivering on its promise to cure the incurable? And what of the arguments both camps cite to prove their points? Do the current findings somehow manage to achieve a weird combination of ambiguity and promise in such a way that both sides can claim science is on their side?

THE MONSTER IN THE GONAD

In 1953, cancer researcher Leroy Stevens discovered teeth and hair in mouse testicles, and the field of stem cell biology was born. A major tobacco company had awarded a grant to Jackson Laboratory in Bar Harbor, Maine, where Stevens was a scientist, for a study the company hoped would prove that the paper in cigarettes—not tobacco—caused cancer. After exposing mice to large amounts of cigarette ingredients, Stevens noticed that a few were developing gigantic scrotums. When he dissected the scrotums, he was taken aback by what he found inside: a hodgepodge of random tissue, including cartilage, teeth, and hair.

This particular type of tumor is called a teratoma, taken from the Greek word "teraton," which means monster. It's a tumor that originates from a germ cell (precursors for both egg and sperm cells), hence its ability to form such a bizarre array of tissue. Stevens quickly abandoned his tobacco research and spent the next few decades studying these teratomas, trying to get at their cellular roots.

Eventually he came across what he called a "pluripotent embryonic stem cell," that is, a cell that can give rise to a variety of tissues. Stevens' work was limited in that the cell lines he discovered always maintained the potential to form these monster-like cancers.

Nearly 30 years after Stevens' initial discovery, scientists in the United States and the United Kingdom isolated embryonic stem cells from a mouse blastocyst, a find that energized the field. Still, research in the area remained safely cloistered in the walls of academic study. Then, in 1998, two groups independently announced that they had isolated human embryonic stem cells. One group from the Wisconsin Regional Primate Research Center had used leftover blastocysts from a fertility clinic. The second team, from Johns Hopkins University School of Medicine, harvested their stem cells from aborted fetuses.

For researchers, this was a watershed discovery. For opponents of embryonic stem cell research, it was a call to arms. The ethical and political question of "should we find therapies this way?" came head to head with the scientific question "can we find therapies this way?" The stew began to bubble.

OF CLONED MICE AND MEN

Whitehead Institute's Rudolf Jaenisch knows a thing or two about mice. Years ago he was among the first scientists to incorporate foreign DNA into a mouse's genome in such a way that the new genetic information could be passed down to subsequent generations. Called "transgenics," this procedure is now commonplace in labs around the world. For well over a decade, Jaenisch, who also is

a professor of biology at MIT, has cloned thousands of mice, trying to decipher all the factors involved in what he calls "reprogramming"—the process by which the host egg cell reactivates the entire genome of the donor nucleus. While much of the basic biology of how cloning works remains a mystery, one thing is clear to Jaenisch: There is no such thing as a normal clone.

"The vast majority of cloned embryos die in utero," he says. "Others are stillbirths." The slim percentage that grow to adulthood "are ridden with all sorts of genetic-related health conditions. They're obese; they die young. I suspect many have neurological damage which is hard for us to detect. Out of all the animals ever cloned, I'm not sure whether any normal clone has yet been produced."

The problem, Jaenisch says, is that it's impossible for an egg cell to reactivate every single gene in the donor nucleus. Something inevitably goes wrong. "This isn't a technical issue," he maintains. "It's not like the early days of in vitro fertilization, where we simply needed to improve the techniques. This is a principal biological issue." For this reason, he and most other scientists in the field believe that human reproductive cloning should be universally—and permanently—banned. "Human reproductive cloning would be the conscious and willful creation of a grossly malformed person. The very thought of doing it is reprehensible."

While the fetus created from a cloned blastocyst is not normal, the embryonic stem cells derived from it are. In 2002, Jaenisch collaborated with George Daley, then a Whitehead Fellow, on a study of a mouse that had no functional immune system due to a genetic defect—for all intents and purposes, a "bubble boy." The team removed a cell from the tip of the mouse's tail, extracted the nucleus, and placed it into a de-nucleated egg cell. It became a blastocyst from which they culled embryonic stem cells. The stem cells, because they were taken from the diseased mouse, contained that same genetic flaw. The scientists corrected the defect in the stem cells and grew them into mature blood stem cells, which they then injected into the mouse. It was, essentially, the same kind of procedure used in the hypothetical repair of your damaged heart. And it had the same outcome: The mouse was cured.

This study, published in the journal *Cell*, was "the first proof-of-principle experiment proving that therapeutic cloning can work," says Jaenisch.

Last summer, Mayo Clinic scientists reported in the *American Journal of Physiology* that they used embryonic stem cells to repair damaged heart tissue in rats.

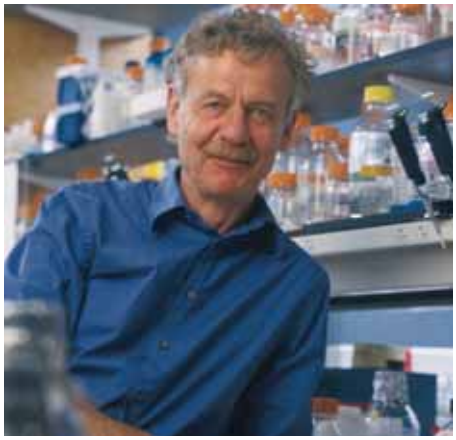
Obviously, neither mice nor rats are men. Still, "Human cells are no more complex than mouse cells," says Lawrence Goldstein, a professor of cellular and molecular medicine at the University of California, San Diego. "It's like a Cadillac versus a Volkswagen. The parts don't necessarily go in the same places, but the principles are the same."

But figuring out which "parts" go where requires a steep learning curve.

"We know a tremendous amount about mouse embryonic stem cells and how to culture and differentiate them," says Daley, now a professor at Harvard Medical School. "But for now, our understanding of how to do the same in human embryonic stem cells is much more primitive. There are issues of cell viability and engraftability that have yet to be explored in greater detail. I'm sure there are challenges that we don't even know yet."

Still, researchers have begun to see some success in creating mature tissue from human embryonic stem cells. So far, they've derived heart cells called cardiomyocytes, blood precursors (which can become either red or white

SOURCES: GEORGE DALEY AND KONRAD HOCHEDLINGER GRAPHIC: CHRISTINA ULLMAN



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blood cells), and certain classes of neurons. Goldstein is using human embryonic stem cells to create Alzheimer's cells. "Our goal is to make human embryonic stem cells that carry the mutations that cause hereditary Alzheimer's disease and use those cells to test hypotheses that we've gotten from animal models of the disease," says Goldstein. Using funding from Howard Hughes Medical Institute allows him to take advantage of human embryonic stem cells outside the limited number approved for federal funding in 2001 by President Bush.

But what about human therapeutic cloning, performing in a person the same kind of procedure Jaenisch and Daley performed in a mouse?

The first—and so far only—breakthrough here occurred earlier this year when Woo Suk Hwang and Shin Yong Moon of Seoul National University reported in the journal *Science* that they had successfully cloned a human blastocyst and removed viable embryonic stem cells from it. Notes Jaenisch, "This paper proves that human therapeutic cloning is possible."

The American Medical Association, the National Academy of Sciences, and such publications as the *New England Journal of Medicine* have issued statements supporting this work, creating the impression that all scientists stand united against those trying to prevent embryonic stem cell research on moral and religious grounds.

But first impressions can be deceiving.

"Human reproductive cloning would be the conscious and willful creation of a grossly malformed person," declares Whitehead Founding Member Rudolf Jaenisch. "The very thought of doing it is reprehensible."

A DISSENTING VOICE

James Sherley is blunt. "I do not subscribe to the majority view at all," the MIT associate professor says. "I'm just one of many scientists who feels this way. Ask yourself, 'What are we destroying?' It really is nonsensical to debate the whole question of when life begins. We know that embryos are alive. With therapeutic cloning, we're talking about destroying one human being for another human being's gain. That's something that we as a society must not do."

This argument essentially is the same as the one posed by the anti-therapeutic-cloning, anti-embryonic-stem-cell research faction: Whether the blastocyst is cloned or taken from a fertility clinic, they claim, acquiring embryonic stem cells destroys a human life. (Jaenisch counters by pointing out that a cloned blastocyst has little, if any, chance of ever developing into a normal baby.)

But Sherley has another problem with this area of research, one that his fellow critics seldom, if ever, mention.

A researcher at MIT's Biological Engineering Division, Sherley works with adult stem cells. Unlike embryonic stem cells, adult stem cells are generally thought to become only the type of tissue from which they've been taken. A familiar example: bone marrow transplants in which the adult stem cells from the donor marrow help the cancer patient. Ideally, a person's own adult stem cells could be used in treatment. A cancer patient could have adult stem cells taken from his blood samples, multiplied in a dish, and administered without any danger of rejection.

Adult stem cell researchers have hit two significant roadblocks: These cells are hard to identify and difficult to grow.

But according to Sherley, embryonic stem cell researchers soon will face the same obstacles.

"You have to ask, 'What do you need in order to produce tissue for long-term replacement therapy?' The answer is, 'You need adult stem cells,'" Sherley says. "If these embryonic stem cell therapies will be successful, they must produce adult stem cells. So these researchers will soon have the same problems that we have. They'll have to figure out ways to locate and then multiply the adult stem cells from the tissue cultures that they created using embryonic stem cells."

Sherley says that mature tissue alone won't suffice for long-term replacement therapy. Even with bone marrow transplants, if the marrow doesn't contain adult stem cells, the procedure fails.

The solution, as he sees it, is to bypass altogether the moral quagmire of experimenting with human blastocysts and focus exclusively on adult stem cells. Besides, "I just can't accept that reproductive clones are unhealthy but stem cells from reproductive clones are fine," he says. "The data aren't convincing."

But many of his fellow scientists aren't persuaded. "The real issue," says Jaenisch, "is that so far, it's impossible to propagate and grow adult stem cells. And adult stem cells haven't been shown to have therapeutic value, except for blood cells."

What's more, Daley notes, not every tissue has adult stem cells. "For the pancreas, the heart, and much of the brain, there does not appear to be active regeneration from adult stem cells. For these tissues, embryonic stem cells are likely to be the best source of replacement cells."

As for the moral question regarding when life begins, "I just spent the other day working with a number of ethicists and philosophers discussing this very issue," says Goldstein, "and very smart, experienced people with different viewpoints confront the issue differently and arrive at different answers. This sort of debate is a standard thing to happen when we have new technologies that test our conceptions of who we are and what we're about."

TOWARD A PUBLIC-POLICY TRAIN WRECK

In 2002, Bernard Siegel was channel surfing when he stumbled on a press conference in which spokespersons for the UFO cult the Raelians announced that they had cloned the first human baby. Siegel, an attorney, decided that the manner in which the cult members were manipulating this alleged baby was evidence for a child abuse investigation. So, he filed for guardianship.

"Then came the media firestorm," he says. (Because of this case, the Raelians refused to do a DNA test on the child—who Siegel is certain does not exist.)

Even after the case was dropped, Siegel noticed how the Raelians had affected the world of stem cell research. Rael, their leader, had testified in a congressional hearing and appeared before the National Academy of Sciences to make his case in favor of human reproductive cloning. Conservatives seized on his testimony and used it as evidence that all forms of cloning—including therapeutic cloning—should be banned.

"There was no single, unified group of scientists that could answer to this," says Siegel. And so he founded the Genetics Policy Institute (GPI), a Coral Gables, Florida-based science advocacy group whose membership includes many top stem cell researchers.

This fall will mark the first real test of the group's effectiveness.

Toward the end of this year, delegates with the United Nations will renew a debate on two competing treaties that were tabled last year. The first, the Costa Rican treaty—which is supported by the U.S.—bans all forms of cloning, including therapeutic. The second, the Belgium treaty, would allow therapeutic cloning while banning the procedure for reproduction.

It is too early to tell how the vote will go. If delegates adopted the Costa Rican treaty, "it would cast a pall on the research, declaring it an affront to human dignity and morally reproachable," Siegel says. But what he fears most is that it would breathe life in the Brownback Bill, a bill authored by United States senator Sam Brownback (R-Kan.), that proposes to make the very process of nuclear transfer with human cells a criminal offense, punishable with mandatory jail time for any scientist who attempts it.

This fall, "we're heading straight toward a public-policy train wreck," says Siegel. Coming to a head are the U.N. vote, a U.S. presidential election in which embryonic stem cell research has been a key issue, and a California initiative that would provide up to $295 million annually for embryonic stem cell research. "These will all, in one fell swoop, influence the landscape of stem cell research," he says.

Meanwhile, both scientists and the public must be patient. It will be many years before we see whether therapeutic cloning will ever treat, for example, "your" heart muscle. And there still is the possibility that researchers will find ways to cure myriad diseases in mice and rats, yet never apply those techniques successfully in people. Until someone does, in fact, make the transition to humans, the debate will rage on, forcing scientists to work under a cloud of public controversy.

But researchers push forward, confident that this field eventually will deliver on some of its promises.

Goldstein, for one, is optimistic that his efforts one day will yield treatments to rid the body of cancer, diabetes, and other ailments. "Sure, it's possible for this to be a huge failure, but I don't see that," he predicts. "The science and the data are sound enough so that a guy like me, who's done this for 25 years and has a reasonably good scientific track record, is willing to put substantial resources and energy into this. I'm willing to take risks, but I wouldn't do this if I thought there was a high likelihood it would fail."

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"With therapeutic cloning, we're talking about destroying one human being for another human being's gain," maintains MIT biologist James Sherley. "That's something that we as a society must not do."

[*For more information about cloning, visit Whitehead's On Topic resource at* www.wi.mit.edu/news/ontopic/cloning.html.]