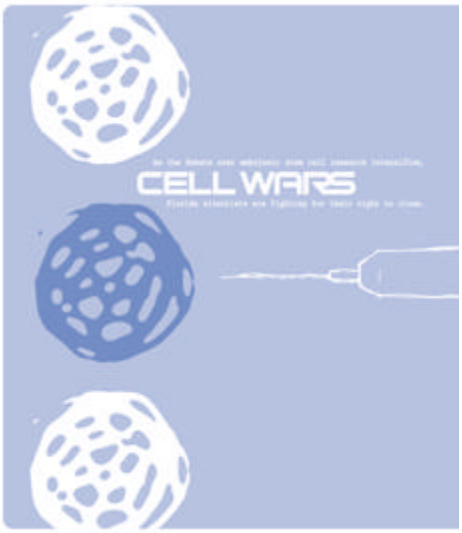
April 9, 2003

Cell wars

As the debate over embryonic stem cell research intensifies, Florida scientists are fighting for their right to clone.

by Colleen Dougher



Fourteen years ago, when Ellen Ullman's chubby 1-year-old son began to slim down, she figured he was just losing his baby fat. But soon, his thirst became insatiable, his wet diapers grew heavier, and he began acting lethargic. By the time she brought Zachary to see his doctor, his breathing had gotten labored, too. Ullman told the doctor that she thought Zachary might have diabetes. He told her that any connection between drinking and urinating too much and diabetes was just an old wives' tale.

As it turned out, she was right on the mark, and Zachary, who was experiencing diabetic ketoacidosis, was completely dehydrated. When the boy was rushed to Miami Children's Hospital, "they could barely get an IV into his little collapsed veins," his mother recalls. "It was horrible."

For days, Ullman, who was pregnant at the time, felt as if people were talking to her through a cloud. Needless to say, she was overwhelmed. "I had to learn how to give injections," she says. "And I was really needlephobic."

Ullman considered herself a hippie of sorts, was a member of La Leche League and was accustomed to breast-feeding her son on demand. Now, nursing could take place only at mealtimes, which had to be perfectly timed and measured.

Zachary remained in the hospital for about a week before being sent home. With no nurse to help her, Ullman would have to give her son his shots. She wasn't feeling quite ready for this and, before leaving the hospital, asked a social worker to put her in touch with another parent of a diabetic for support.

That's how she met Barbara Singer, a founding member of the

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Diabetes Research Institute Foundation who'd lost a daughter to diabetes. Ullman stresses that diabetes is far more than an inconvenience that necessitates injections and laying off sugar. It's an insidious, debilitating and destructive disease that can result in blindness, kidney failure and heart disease, and it needs to be cured.

Zachary is 15 now, and Ullman continues to support the institute's efforts to find a cure. And she believes that the best chance of finding a cure for diabetes — as well as Alzheimer's, Parkinson's and other life-threatening diseases — lies within adult and embryonic stem cells.

Embryonic stem cells are important, because they can continuously regenerate and are capable of evolving into any of the approximately 220 cell types that are found in the human body. Researchers and their advocates believe that stem cells can be used to replace damaged organs and that this science might revolutionize modern medicine.

But Ullman and others like her worry about the future of such research, given the controversy surrounding the use of embryonic stem cells, which are generally removed from 4-to-5-day-old embryos. During this period, called the blastocyst stage, these cells have not begun to specialize, or differentiate. To access a cluster of cells, the embryo, which is about the size of the head of a pin, must be destroyed — a fact that infuriates people who see these cells as future human beings and has caused widespread debate, a number of lawsuits, congressional hearings and controversial legislation.

In November 1998, University of Wisconsin developmental biologist James Thomson became the first person to cultivate human embryonic stem cells. Before doing so, he'd consulted bioethicists, read numerous studies and weighed the pros and cons of the research. Considering its potential and the source of the cells — eggs fertilized in vitro at fertilization clinics, then donated for research by individuals who no longer needed them — Thomson had decided to forge ahead. "I could not see that throwing them out was better," he told *Time* magazine.

In 1999, the journal *Science* named stem cell research the scientific breakthrough of the year. But given an existing ban on federal funding for research involving human embryos, Thomson — to avoid endangering his university's federal support — set up an off-campus lab, and the debate over whether the ban should continue began to heat up.

"The image of researchers dissecting tiny human beings should not be allowed to dominate the discussion," wrote Dr. Ronald Green, the director of the Ethics Institute at Dartmouth College and a former member of the National Institutes of Health's Human Embryo Research Panel, in an essay published in 2001. "The public had to understand that the key issue was whether spare embryos would be used for valuable research that could save human lives or

would merely be thrown away."

On Aug. 9, 2001, after much deliberation, President George W. Bush announced a compromise. He approved the use of federal funding for embryonic stem cell research, but only for 64 extant cell lines taken from embryos that had already been destroyed. These cell lines had been derived from leftover embryos at in vitro fertilization clinics, but many scientists believe that the future of this research lies in preserving the right to obtain these cells through procedures they refer to as "somatic cell nuclear transfer" and "therapeutic cloning."

But last year, a bill that would ban cloning in Florida passed the state House, though the Senate didn't consider it. And recently, two cloning-related bills were introduced in the U.S. Senate. One of these, the Human Cloning Prohibition Act of 2003, would ban all cloning, forbid importation of cloned embryos and punish violators with a $1 million fine. The other, the Human Cloning Ban and Stem Cell Research Protection Act of 2003, would ban reproductive cloning but allow therapeutic cloning, which the Coalition for the Advancement of Medical Research defines as "the transplanting of one's own DNA into an unfertilized egg in order to grow stem cells that cure devastating diseases."

Dr. W. Dalton Dietrich, scientific director of the Miami Project to Cure Paralysis, has conducted research using embryonic stem cells. He says that when most people hear the word *cloning*, they think of babies, when, in fact, cloning is "just a procedure."

Therapeutic cloning "is not producing organs," he argues. "It's not producing babies. It's producing cells that can one day be transplanted back into the heart, into the kidney, into the brain and into the spinal cord, to replace the cells that are dysfunctional or have been damaged by disease." And since a patient's own DNA would be used, he says, the body's immune system would be less likely to reject the new cells.

Opponents of the procedure, many of them churchgoers and right-to-lifers, contend that the distinct terms *reproductive cloning* and *therapeutic cloning* are misleading, since both produce human embryos. The former procedure, they argue, produces embryos that result in babies, whereas the latter results in embryos that can be dissected for the purpose of obtaining stem cells. They argue that, regardless of their research potential, embryos have rights.

"My biggest question when it comes to embryonic stem cells," Ullman says, "is: Why are those frozen eight cells in vitro more important than my living, breathing child suffering today? And if people use the 'Choose life' [slogan], well then choose *my* child's life, and choose every other person who's living."

According to the National Institutes of Health, stem cells in a developing fetus give rise to the multiple specialized cells that make up the heart, lungs, skin and other organs and tissue. Stem cells

are also found in some adult tissue, such as bone marrow, muscle and the brain. Adult stem cells replace cells lost through normal wear and tear, injury or disease. Scientists believe that these cells could be used not only for treating diseases but for screening new drugs and understanding birth defects.

Yet researchers must first understand the fundamental properties of embryonic stem cells. They are trying to determine what causes the cells, when removed from a days-old embryo, to remain unspecialized and self-renewing for years. They also want to identify the signal that causes them to specialize.

Until recently, scientists thought adult stem cells lacked what's scientifically known as "plasticity." It was thought, for example, that a blood-forming cell in bone marrow could not give rise to the cells of a different tissue, such as nerve cells in the brain. But experiments conducted over the past several years indicate that it may be possible for those cells to become neurons, liver cells, heart muscle or cells that could be made to produce insulin. Such discoveries, however, only fuel the fire for debate, prompting opponents of embryonic stem cell research to argue for abandoning it altogether and using adult stem cells found in placentas, umbilical cords and other parts of the body.

Mary Jo Iozzio, an associate professor of moral theology and chairwoman of the Barry University Council on Bioethics, approves of the research being done on the cell lines approved for federal funding. But she would like to see more research in nonhuman species and adult stem cells, which she sees as far less problematic, and not just because of the ethical issues.

"What we're learning is that embryonic stem cells are totipotent, and totipotency is just what it sounds like," she says. "They can become anything. The problem is that they can become anything. It's kind of like creating monsters. They are uncontrollable."

Dietrich admits that the inability to control stem cells once they're injected into the body is a problem. "They kind of turn into a cell that maybe we do not want those cells to turn into," he says. "So basically, what the scientists are trying to understand is how to control the differentiation process."

Ken Goodman, director of the bioethics program at the University of Miami, says both embryonic and adult stem cells must continue to be studied. "The question of what's the better path requires that we study the two paths," he says. "It may be at the end of the day that adult stem cells are easier to get, cheaper to acquire and, in fact, are just as good, in which case, thank goodness." But first, he says, both types of cells must be robustly researched.

Juan Dominguez-Bendala, a doctor in the Pancreatic Development and Stem Cell Laboratory of the Diabetes Research Institute, agrees. He notes that scientists in Minnesota isolated adult bone marrow-derived cells that appear to share the potency and

properties of embryonic stem cells. If those results can be reproduced, such cells could eventually offer an alternative to embryonic stem cells.

“We must be cautious about the hype surrounding many adult stem cell types,” Dominguez-Bendala warns. “Hands-on work on them shows that they are not even remotely comparable to embryonic stem cells in their clinical potential.”

In general, he says, adult stem cells don’t differentiate or proliferate as easily as their embryonic counterparts. They also tend to age quickly when cultured in vitro. “If you envision a therapeutic approach based on the rapid proliferation of stem cells to obtain large-enough amounts of tissue for transplantation,” he says, “adult stem cells don’t seem to be an appropriate choice.” This is why, he says, scientists continue to pursue the more controversial embryonic stem cell research, adding: “We are confident that as soon as novel therapies emerge, public opinion and federal regulations will be more favorable.”

Yet Dominguez-Bendala notes that only a handful of the 64 cell lines that qualify for federal research dollars have been extensively characterized, while the rest are largely useless due to poor manageability, limited undifferentiated proliferation or genetic abnormalities. He says access to the few good cell lines, especially given the NIH grants that help speed up this process, has not been as difficult as some people have suggested, but the real problems begin when someone tries to define intellectual property rights on research conducted using these cell lines.

Consider Thomson’s initial research. The University of Wisconsin, through the Wisconsin Alumni Research Foundation (WARF), which distributes cells to private and academic researchers, holds patents on five cell lines developed by Thomson, as well as the techniques he used to grow the cells. The foundation’s managing director, Carl Gulbrandsen, has argued that these patents help assure no private corporation dominates potential stem-cell therapies.

In 2001, however, the WARF found itself at odds with Geron Corp., the California-based company that partially funded Thomson’s work and holds licensing rights on six types of tissue that might be developed from his cells. Geron sought to add more tissue types to the licensing agreement, but the WARF was opposed, believing that such a move would preclude potentially valuable work by other researchers.

So the university’s patent agency filed a federal lawsuit against Geron, alleging that the corporation had no right to add cell types to its licensing agreement with the foundation, since the company’s option to do so expired on July 31, 2001, and negotiations for an extension had failed. Geron issued a statement claiming that it had exercised its rights under the option prior to the deadline.

Five months later, the suit was resolved, with both parties entering

into a new licensing agreement that grants Geron specific rights to develop therapeutic and diagnostic products from certain embryonic stem cell-derived cells but allows a subsidiary of the WARF to distribute existing cell lines to academic and governmental researchers without royalties or fees.

Dominguez-Bendala says another commonly overlooked problem is that none of the cell lines that qualify for federal research is desirable for therapeutic application, since the standard process for establishing these cells, prior to Aug. 9, 2001, involved culturing the early embryo on a layer of feeder cells obtained from mice, posing the risk of transmission of animal diseases.

It's not that there aren't solutions to these problems. A few months ago, Dominguez-Bendala points out, a novel procedure for isolating these cells in feeders of human origin was reported by a Singapore-based team, and new cell lines obtained by this method would be suitable for transplantation. The trouble is that those cells don't qualify for federal funding. "In view of this, we believe that [Bush's] regulations should be revised to include cell lines with actual therapeutic value, even if they have been established after Aug. 9, 2001," Dominguez-Bendala argues.

Goodman, meanwhile, fails to understand why embryonic stem cell research is legal on cells obtained prior to that date but not on others. "If destroying blastocysts is wrong," Goodman asks, "then why did [Bush] permit any research at all? I just don't understand it. … I think we have a moral duty, and I think that actually failing to do the research is morally blameworthy."

Scientists argue that these limitations make doing their jobs difficult. Roger Pedersen, a top University of California researcher, departed for England last year, noting that "more stem cells are needed here" and blaming U.S. policy for delaying the benefits of research to patients with degenerative diseases. In November, it was reported that the NIH had spent about $19 million for ongoing human embryonic stem cell research, while England had set aside roughly $57 million and was trying to lure foreign researchers to relocate there.

"Some people feel strongly that they're being hampered by some of the guidelines and are going to other countries, I assume," Dietrich posits. "I've read about how they can go to a fertility clinic, for example, and get these eggs and generate new cell lines and then go from there."

It's not illegal to establish and research other stem cell lines, only to get federal funding for doing so. Private groups, such as the Michael J. Fox Foundation for Parkinson's Research and the Christopher Reeve Paralysis Foundation, have increased their support for stem cell research and donated millions to laboratories, some in Europe. Palm Beach County philanthropist Lois Pope gave a $100,000 grant to the University of Wisconsin's Thomson, who said he would use the money to study how to better understand and

culture embryonic stem cells.

Last year, an anonymous benefactor donated $12 million to Stanford University for a stem cell research center. In December, the university announced its intention to develop human embryonic stem cells through therapeutic cloning and to gear its research toward treating cancer.

Goodman believes it's a mistake not to regulate therapeutic cloning. "From my perspective, I believe the tools of applied ethics and human-subjects protection are adequate to prevent inappropriate research and applications. Look, if that's not the case, the entire human-subjects research enterprise is doomed," he argues. "You let your doctor prescribe drugs that are really dangerous. Society does that because there's oversight, education and accountability. Well, oversight, education and accountability is a good way to guide research, too — not a legislative ban on a particular form of science."

Ullman concurs, calling the Senate bill that would ban therapeutic cloning "the most ridiculous piece of legislation I have ever heard."

"There was one congressman who supported this legislation," she says. "And he does have a child with diabetes. And he said, 'Oh, it was such a difficult choice.' Yeah, well, he wanted to maintain his political career — that was the difficult choice, in my opinion."

If one thing has become clear about this debate, it's that the battle lines aren't always drawn where one might expect them to be. Mary Landrieu, a Democratic senator from Louisiana and an abortion-rights advocate, is a co-sponsor of the Senate bill that would ban both forms of cloning. However, the Human Cloning Ban and Stem Cell Research Protection Act, which would allow therapeutic cloning, was introduced by Sen. Orrin Hatch (R-Utah), a devout Mormon well-known for his staunch anti-abortion views. After considering the fate of thousands of embryos routinely destroyed at in vitro fertility clinics and the potential medical benefits of this research, Hatch said, he came to the conclusion that "the fertilized egg is a living human cell, but it has absolutely zero chance of becoming a living human being unless it is implanted in a womb." He was moved, he said, by his conversations with people suffering from Parkinson's, spinal-cord injury, cancer and juvenile diabetes who have placed their faith for a cure in stem cell research.

Certainly, many people who feel they would benefit from this research have expressed their views. Peggy Prichard Ross, who in October 2001 was diagnosed with an inoperable brain tumor, contributed an editorial about the politics of stem cell research last month to the *Tallahassee Democrat*. "In six months, there is a good chance I'll be dead," she wrote. "This doesn't bother me near as much as having a president who wants to jail scientists and doctors who are trying to find cures for people with my disease and other illnesses."

In the *Los Angeles Times*, Don Reed wrote of his son who is paralyzed because of a spinal cord injury and "suffers the agonies of the damned. All I can do is turn him over in the bed, and stretch his feet in the morning and fetch his catheterization kits when he needs to use the restroom. Yet anti-abortionists rave about the rights of near-invisible cells in a petri dish, calling them more important than healing my son."

Barry University's Iozzio doesn't want to be mistaken for someone who believes that an embryo is a child, but she argues that an embryo's potential to become a human being makes it special. "The reason research scientists want those embryos is because it's human genetic material," she says, "and I think research science tends to forget that the reason they're so valuable is because they are human."

Iozzio contends that research scientists deliberately avoid using the word *embryo* when describing therapeutic cloning, but cloning — "therapeutic" or otherwise — will always create an embryo. She admits that she rarely agrees with Bush but supports his decision to restrict federal funding to those 64 cell lines. "It makes sense to continue research on lines that can be perpetuated indefinitely," she says. Yet Iozzio is against using any of the 100,000 or more embryos worldwide that are currently stored in what she calls "frozen limbo."

"I argue against their use for research, because the reason they were created was for the hope that they could become children," she says. "So there is intentionality that needs to be considered here. I would argue that the respect owed to those embryos is to remove them certainly from cold storage and an ignominious life of existence, and they ought to be donated to infertile couples, or a fertile couple willing to accept the burden of another pregnancy, or a single woman desirous of having a child. These embryos ought to be adopted in the same way we adopt children that are already born. That's a greater respect of the embryo — to be adopted, rather than be subject to research. … In one scenario, they have the chance to become a living breathing child. In the other scenario, they may yield information and certainly will be destroyed."

Ullman acknowledges there is yet another option: One in which small clusters of cells are protected and people with diseases suffer. "I just can't imagine who, if there was potential out there to cure their child, how they could say that cells are more important than curing my child," she says.

"I think I'm just as stubborn as they are," she says of those who oppose stem cell research. "But I think I'm choosing life this way."

Goodman says that the people fighting to advance embryonic stem cell research and preserve the right to therapeutic cloning don't disrespect human life "but believe that we show it respect by reducing human suffering."

Before the anti-cloning bill was passed by the U.S. House of Representatives in February, Rep. Dave Weldon (R-Fla.), a co-sponsor of the bill, said that "the evidence isn't there" to support the medical potential of therapeutic cloning.

Goodman argues that the evidence is everywhere. "I see an aging population with Alzheimer's," he says. "I see Parkinson's, I see diabetes, I see heart disease. I see an entire field of reconstructive medicine that wants to rebuild organs after they're damaged by cancer. What about liver disease? How about pulmonology? How about rebuilding an immune system? So I don't know what would constitute adequate medical need to try to do this."

There are interesting arguments, Goodman says, for and against destroying a blastocyst: "There are also arguments for and against regulating the airline industry. There are arguments for and against environmental protection and for and against allowing police officers to take home their cars on the weekend. That there's an argument for and against doesn't mean there's a best answer that achieves broadly agreed-upon goals."

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