

AFGHAN WOMEN'S TRIUMPH • BIN LADEN'S MONEY

U.S. News & WORLD REPORT

DECEMBER 3, 2001

www.usnews.com

EXCLUSIVE

THE FIRST HUMAN CLONE



The Inside Story:

How American scientists made history
by creating lifesaving embryo cells



A phase-contrast micrograph of the first human embryo cells created in a laboratory

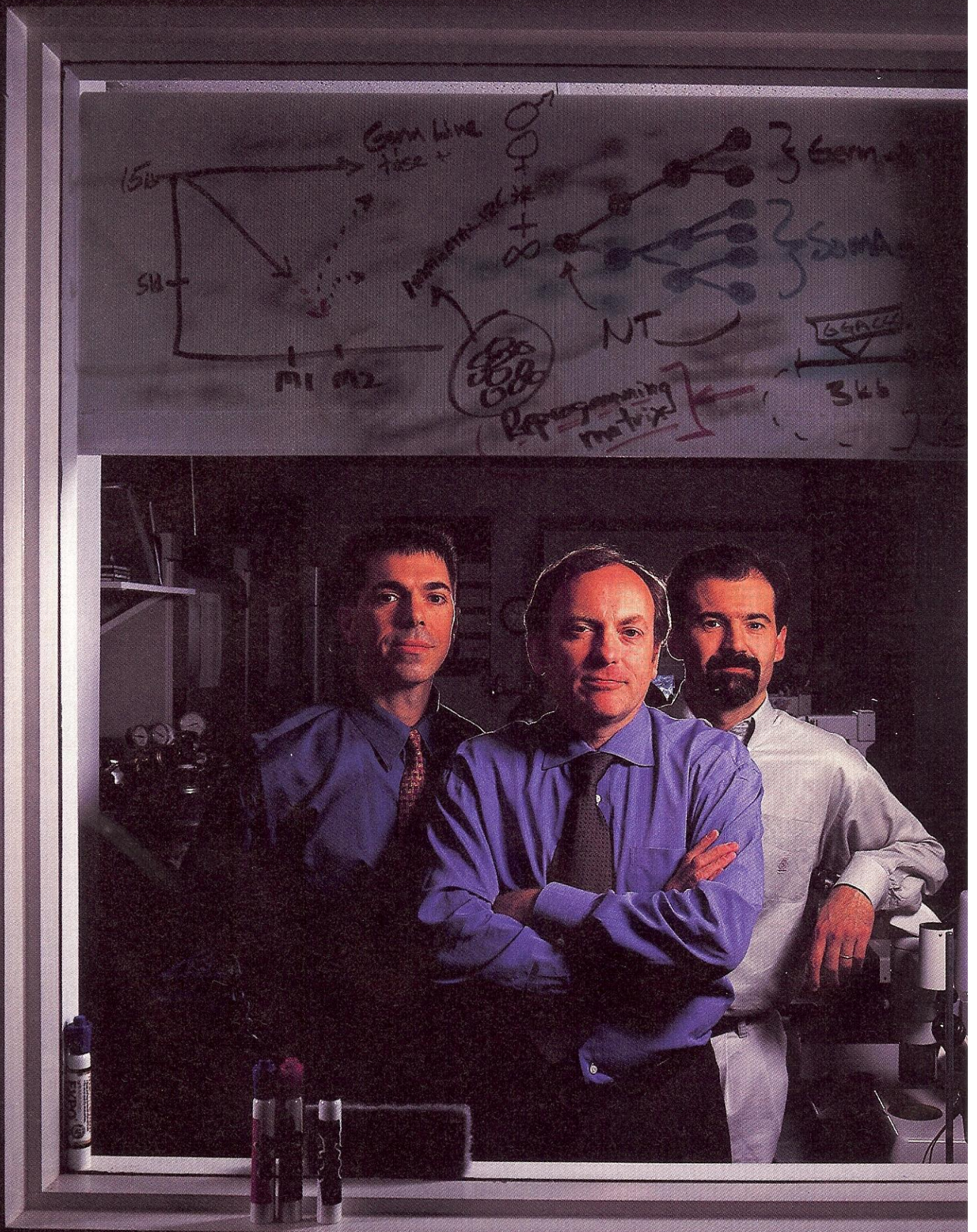
The First Clone

COURTESY JOSE CIBELLI—ACT



The first cloned human embryo would sit on the head of a pin.

Scientists have finally cloned a human embryo. The breakthrough promises cures for terrible diseases. Here's the inside story:



The cloning troika (from left): Robert Lanza, Michael West, and Jose Cibelli

BY JOANNIE FISCHER

Physically, Judson Somerville didn't feel a thing. When he took the cigar-cutter-like tool and clipped a chunk of skin cells from his right calf last April, there was no pain. The 40-year-old Texas physician has been using a wheelchair for years, paralyzed from the chest down, the result of a terrible cycling accident. But emotionally, that was another story. Cutting the skin from his calf, Somerville says, he felt the thrill of being a sort of astronaut, a pioneer. By donating his skin cells, Somerville was volunteering for nothing less than service on the frontier of human cloning.

Somerville did not make the decision lightly. As a conservative

Republican, a longtime contributor to President Bush, Somerville knows how controversial cloning is for many of his political compatriots. But he is also a devout Episcopalian. After consulting with his church leaders, Somerville concluded that being one of the first humans to be cloned—not to produce a baby, which he would never do, but to create healthy new cells for ailing patients—would be one of the best things he could do for his fellow man. His decision wasn't completely selfless, however. Neurons derived from his own cloned embryo could end Somerville's paralysis. "My 14-year-old daughter doesn't want me getting her wedding gown caught up in my wheelchair," he says, laughing. "So when the day comes, she's counting on me walking her down the aisle."

Now, Somerville may be a step closer to that walk, and humanity is moving into uncharted medical and ethical territory. Since the 1997 announcement of the cloned sheep Dolly, scientists around the world have been trying to duplicate and advance the work in a variety of species from mice to monkeys. Some have succeeded, but many more have been thwarted in their efforts. A few researchers had even set out to clone humans, without success. But this week, scientists at Advanced Cell Technology, a small biotech start-up company in Worcester, Mass., are announcing that they have done just that—successfully engineered the world's first cloned human embryo.

ACT is the only laboratory on U.S. soil that has acknowledged working on human therapeutic cloning. But other than being called to testify before Congress on these issues, the company's leadership and its scientists have not publicly elaborated on their human-cloning efforts—until now. Over the past 18 months, *U.S. News* has reported from inside the ACT laboratory, with exclusive access to the cloning scientists and their laboratory work. In a highly technical paper in the *Jour-*

nal of Regenerative Medicine, the scientists now describe their laboratory success—the transfer of human DNA into human eggs and the growth of those eggs into six-cell embryos. What that scientific paper doesn't describe, and what *U.S. News* documents here, is what went on in the hearts and minds of the people behind this achievement and the many setbacks and adjustments that preceded the final success.

The accomplishment presents huge challenges to every premise of scientific, religious, and legal thought. Given the intensity of last summer's national debate over human embryonic stem cell research, ACT's work is sure to become a lightning rod for conservative critics when the issue is taken up again in the months ahead. It will be condemned as an ethical abomination akin to playing God and described as the creation of embryos for spare parts. It will also be hailed as the hugest medical breakthrough of the past half century—an accomplishment that could cure many diseases of aging and provides hope for people like Somerville.

The story of ACT's breakthrough is largely the story of three men, from very different backgrounds, who came together to stake their scientific careers on this controversial enterprise. Here's how, against the odds, they pushed the world into the age of cloning:

The instigator

Jose Cibelli's ambitions started out simply enough. Raised on the Pampas of Argentina, the talented young researcher just wanted "to do something for the farmers." So after obtaining his degree in veterinary medicine, he married his high school sweetheart and headed to the University of Massachusetts-Amherst to get his Ph.D. There he quickly became a star student in the lab of James Robl, who was doing work on so-called transgenic animals—cattle, for example, with improved genetic properties



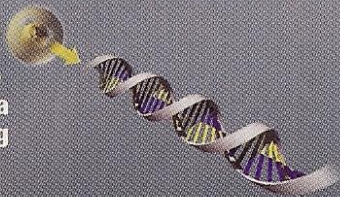
Judson Somerville
Shown with his wife, Melanie,
he donated cells for the first
cloning experiments.

The art of cloning

The idea behind cloning is simple: Remove DNA from an egg and replace it with the DNA from a body cell. But actually getting that process to work is still as much a guessing game as an exact science, dependent on timing as well as technique. Here are some of the main challenges.

THE STEPS

1 Remove DNA from a human egg



2 Deliver new genes into the egg



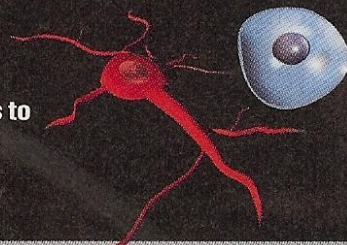
3 Trick the egg into action



4 Collect stem cells



5 Get the stem cells to specialize



THE CHALLENGES

(A) A human egg is very fragile. It can take hundreds of tries to extract the 2 meters of chromosomes with a microscopic needle without destroying the egg.

(B) There is a tiny window of time—just a few hours—during which an egg can be prepared for cloning. Then the egg loses its ability to repair and regenerate DNA.

(C) If one too many drops of cellular material are accidentally removed along with the DNA, the egg can be rendered useless.

(A) No one knows which body cells are the most amenable to cloning. The easiest cells to get from donors—skin cells—are not ideal because they are very large and hard to work with.

(B) Some scientists use an electric current to fuse an entire body cell into the egg cell, but the line between too little and too much current is perilously thin.

(C) Other scientists take the genes out of the body cell and inject them into the egg, but the chromosomes are often damaged by the process.

(A) No sperm is involved in cloning. So scientists must find another way to make the egg think it has been fertilized.

(B) Some scientists use an electric current to make the egg grow. Others use a mixture of chemicals. But it is all too easy to kill the egg with either method.

(C) There appears to be only about a four-hour period during which an egg will respond to activation signals. Prodding the egg before or after that doesn't work.

(A) Dozens of nutrient mixtures have been developed to help embryonic cells proliferate, but no one yet knows which is best.

(B) Biologists disagree about how much oxygen the growing cells should be exposed to in order to develop the healthiest stem cells.

(C) Stem cells must be separated from the other cells without damage and kept alive until they become a self-sustaining colony.

(A) Any one of thousands of different "growth factors" may be involved in spurring a stem cell to become a brain cell or a blood cell.

(B) Even if the right chemicals are found, the stem cells may not respond unless the chemicals interact with the cells' DNA in precisely the right sequence.

(C) The body has over 200 types of specialized cells, and the recipe for growing certain types may remain a mystery for years.

MILESTONES IN CLONING



February 1997
The first cloning of a mammal, Dolly the sheep, from an adult body cell is announced.

March 1997
President Clinton bans federal funding of human-cloning research.

1998-2000
Researchers clone mice, calves, goats, and pigs. A bull is "recloned" from a cloned bull.

April 2000
Scientists find that cloning can restore body cells to a youthful state.

October 2001
The first cloned human embryos are created at Advanced Cell Technology's lab in Worcester, Mass.

Source: Jose Cibelli, Advanced Cell Technology

ROD LITTLE—USN&WR

years a creationist, and he trained as a paleontologist with the goal of proving the Bible's account of God's design. But as he studied the fossil record, instead of finding God's divine plan, he found an endless account of disease and suffering. Out of that bleak vision he developed a new spiritual fervor: "If God is about love and life," he says now, "then we should do everything we can to end suffering and death."

So in his early 20s, West knew his holy grail: to conquer aging and death—a goal

so stunning in its scope that many colleagues over the years have discounted him as a quixotic dreamer. "When I talk about ending aging, I'm not talking about some vain fountain of youth," he explains. "I'm talking about ending the suffering of aging: macular degeneration, cancer, Alzheimer's, heart disease."

After getting his Ph.D. in biology, West enrolled in medical school but was too impatient with the establishment to finish. Instead, he reincorporated his late father's truck-leasing business as a biotech

firm called Geron (Greek for "old man"), committed to ending the ravages of aging. Enchanted by findings that each body cell has an ever shortening fuse called a telomere that signals a cell to age and die, West poured all his energies into finding a way to keep extending the fuse to give a cell endless life. It took seven years, but his company did eventually identify telomerase, the enzyme that replenishes telomeres. (And he ended up marrying the Geron scientist who cloned the gene for telomerase.)

Telomerase alone proved not to be enough to reverse aging, and West became fascinated with work on newly discovered stem cells. West immediately recognized that stem cells had the potential to rejuvenate aging bodies, and he quickly began funding scientists who ended up isolating the first human stem cells.

But as Geron grew, its board became more and more uneasy with West's controversial interests, and West despaired at the company's lack of support for his vision. In early 1998, he left the company he had founded and lost access to the intellectual property he had created on telomerase and human stem cells.

It wasn't long, though, before West caught wind of Cibelli's cloning feats, and he immediately seized on the concept as one far superior to producing "generic" stem cells. (Generic stem cells, derived from human embryos, are the kind that President Bush agonized so publicly over last sum-

mer before deciding to fund limited research on the cells.) But, West wondered, why would you treat patients with cells from an embryo donated from an in vitro fertilization clinic—with another person's cells—when you could give patients their very own cells? In a flash, West was in talks with Advanced Cell Technology—at that time an agricultural genetics company—and within the year became CEO, then owner of the venture.

Both Cibelli and West knew from the start that they would need to race to form useful therapies before controversy overshadowed their efforts. Because no new treatments can be given to humans without first being tested in animals, Cibelli and West needed someone with connec-

tions in the research world who could get those studies up and running right away. As it turned out, that person was working just a mile or so down the road.

The activist

Robert Lanza is the living embodiment of the character played by Matt Damon in the movie *Good Will Hunting*. Growing up underprivileged in Stoughton, Mass., south of Boston, the young preteen caught the attention of Harvard Medical School researchers when he showed up on the university steps having successfully altered the genetics of chickens in his basement. Over the next decade, he was to be "discovered" and taken under the wing of scientific giants such as psychologist B. F. Skinner, immunologist Jonas Salk, and heart transplant pioneer Christiaan Barnard. His mentors described him as a "genius," a "renegade" thinker, even likening him to Einstein.

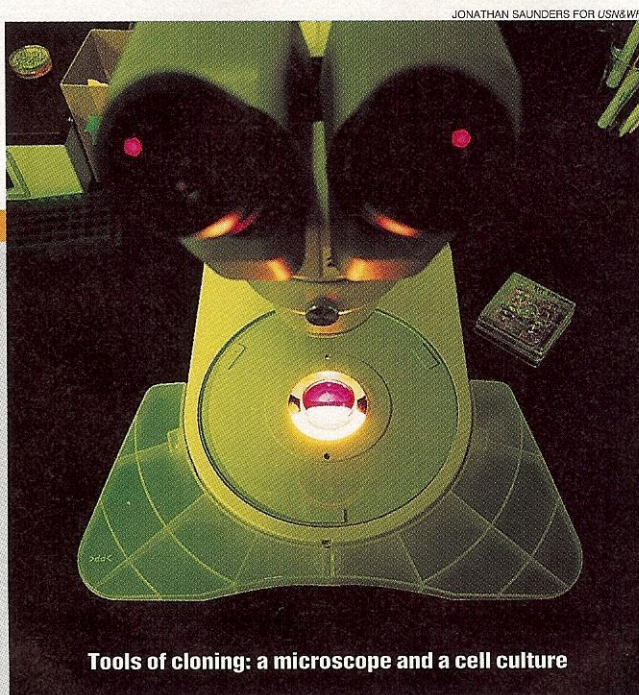
With a gift for enticing the

CURES WITHOUT QUALMS

Seeking a road beyond cloning

As if creating a human embryo by cloning weren't mind-boggling enough, Advanced Cell Technology researcher Jose Cibelli has also demonstrated another way to engineer an embryo, one that might raise fewer ethical qualms. During his cloning work, he coaxed a human egg to begin dividing and developing into an embryo *without* the addition of sperm or DNA of any kind—a process known as parthenogenesis, from the Greek for "virgin birth."

As eggs form, they normally shuck half their chromosomes. An egg can't start dividing and forming an embryo until a sperm cell replaces the missing chromosomes. But Cibelli tricked eggs into keeping copies of their chromosomes, so they could be



Tools of cloning: a microscope and a cell culture

spurred to develop. Parthenogenesis has never been reported with human eggs before, although it has been done with animals such as mice. And although certain lizards, for example, naturally reproduce through parthenogenesis, a human embryo cannot fully develop without genes from two parents. Because it is harder to view as a potential human life, a parthenogenetic embryo might be a more acceptable source of stem cells, the versatile cells that promise to pro-

vide replacement tissue for ailing patients.

Perfect match. Yet for now, parthenogenetic embryos could supply perfectly matched stem cells only to women of childbearing age, because only they could provide the eggs that would generate the cells. Ultimately, Cibelli thinks men who produce viable sperm could also be helped: An egg's DNA could be replaced with genes from sperm, and the egg could then be activated to become a "parthenote."

Advanced Cell Technolo-

gy has a patent on file for yet another technique that could ease ethical concerns, though its therapeutic promise is far less certain. The jellylike material inside an egg contains thousands of proteins that make the parents' old DNA young again, ready to develop into an embryo. By dropping bits of that material into a body cell, scientists might be able to take the cell back in time to an embryonic and moldable state without actually creating an embryo.

But the true revolution will come, says Cibelli, when scientists finally understand how an egg works its rejuvenating magic. At that point, they will be able to synthetically reprogram patients' cells, converting them directly into stem cells. "The ultimate goal is to move beyond cloning," Cibelli says. "It's a transitional step that will teach us how the egg works so that we can eventually stop using eggs." In other words, the only way out of cloning is through it. —J.F.

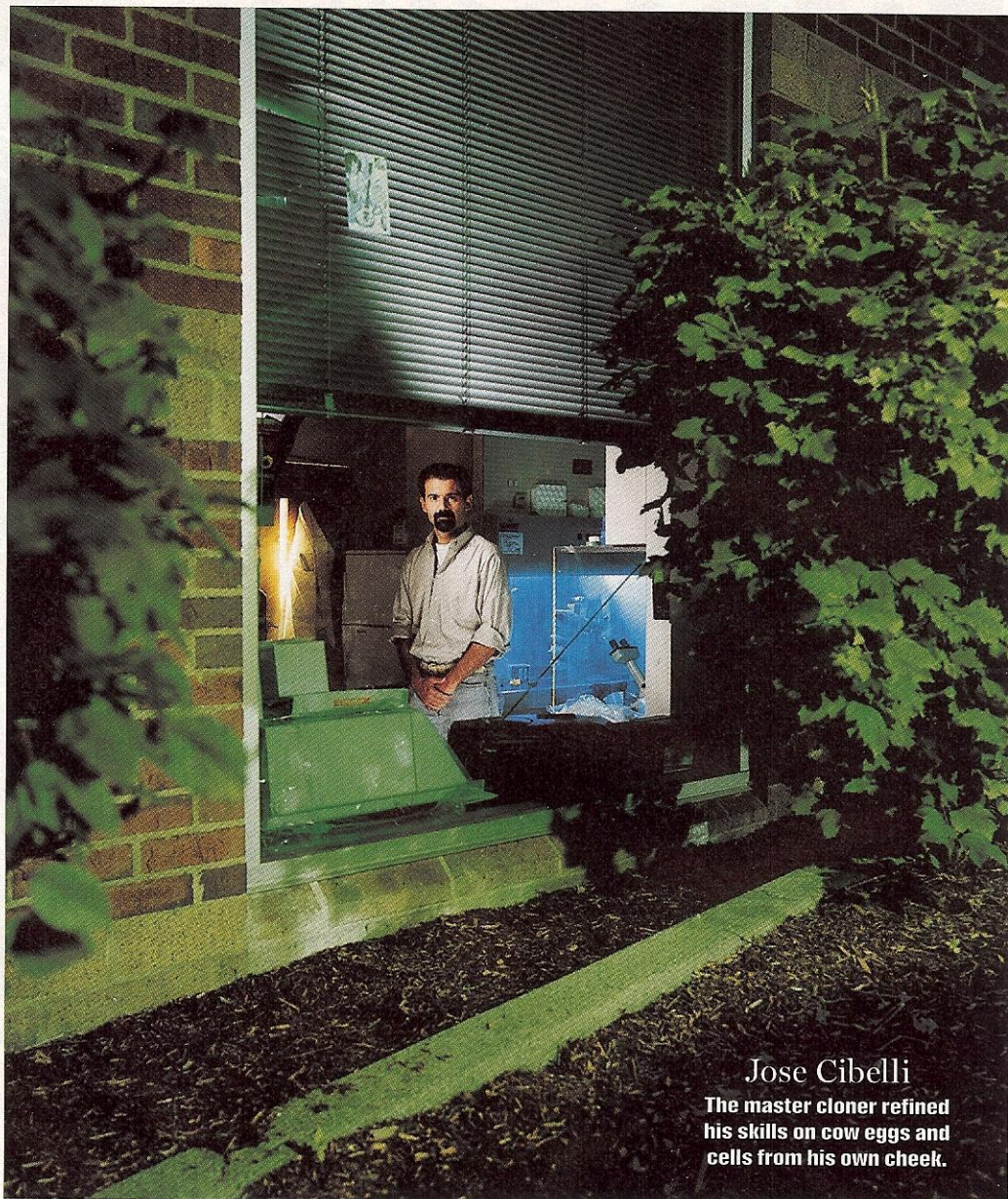
world's top minds, Lanza managed as a medical student to extract essays from the likes of C. Everett Koop, Boutros Boutros-Ghali, and Linus Pauling, which he compiled into a book sounding warning bells about the declining chances for health and survival of the species over the coming century.

Lanza focused his laserlike intellect on transplant medicine and tissue engineering. For 20 years, he worked to cure diseases such as diabetes and leukemia through infusions of new cells and organs from donors. "But for 20 years, I hit my head against the same thing over and over again—rejection, rejection, rejection," says Lanza. Using strong drugs to prevent patients' immune systems from attacking the foreign cells, Lanza says, the cure was often worse than the disease. "Even with the drugs, I watched too many children have first their fingers amputated, then their hands, then their arms." When Lanza discovered that it might be possible to clone a patient's own cells, he felt that he finally had the solution he'd spent decades searching for, and in March 1999 he signed on as Advanced Cell Technology's director of medical research.

With characteristic chutzpah, his first act upon joining the company was to persuade 67 Nobel laureates to sign a letter to then President Clinton in support of human embryonic stem cell research. Like his newfound colleagues West and Cibelli, Lanza knew that human therapeutic cloning would have to prove its ability to revolutionize medical care as fast as possible, before political and ethical controversies swamped the whole enterprise.

The controversy

In the spring of 1999, ACT's new troika sat down to discuss just how to venture into what's arguably the most controversial area in medicine today. "We knew that we would have to fend off attacks," recalls Lanza. "But we never imagined all the insanity that would come." Over the course of the next two years, the men would be called "mad scientists," "baby killers," and "monsters"; their names would be added



Jose Cibelli

The master cloner refined his skills on cow eggs and cells from his own cheek.

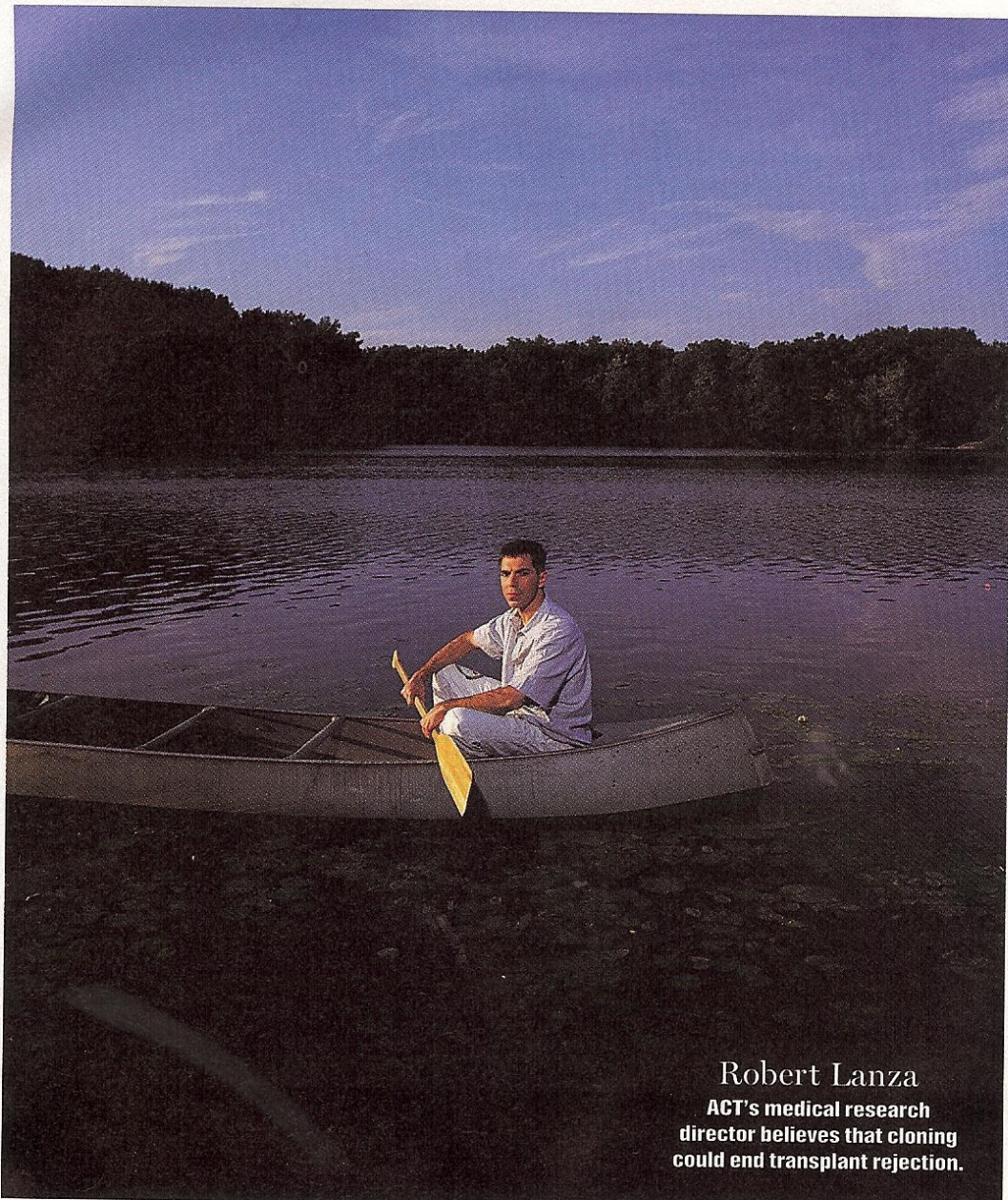
JONATHAN SAUNDERS FOR USN&WR

to antiabortion "assassination" lists on the Web; the FBI would warn them of threats on their lives, and conservatives would push a bill through the House of Representatives declaring them federal criminals deserving of 10 years in prison and a \$1 million fine.

The source of the hysteria is a widespread misunderstanding of just what an early embryo is, according to West, Cibelli, and Lanza. "If you ask the average person, they will tell you it's a tiny little person with buggy eyes," says West. "But, in fact, these are just a few reproductive cells, not much different than eggs or sperm. They are the raw materials of life, but they are not a person."

Most scientists agree. During the first

14 days after an egg is fertilized, the group of cells is known as a "preimplantation embryo." In nature, the majority of these pass from the body without ever attaching to a woman's uterus and developing further. If one truly believed that these were individual human lives being lost, argues Ronald Green, director of the Ethics Institute at Dartmouth and chairman of ACT's bioethics committee, then this should be considered a huge public-health crisis, and there would be a massive medical campaign launched to save these "lives." Moreover, these preimplantation embryos often split off to become two or more entities or, conversely, two groups of the cells sometimes merge together. And currently, there are an estimated



Robert Lanza
ACT's medical research
director believes that cloning
could end transplant rejection.

JONATHAN SAUNDERS FOR USN&WR

1 million of these early embryos left over worldwide from in vitro fertilization procedures, poised to be discarded.

Religious leaders have changed their minds many times over the years about when life begins. Some religions say it begins at conception; some say after 40 days of development; others say at the "quickening," when fetal movement can be felt; and others say not until birth. An Episcopal bishop advised Judson Somerville that cloning his cells would not constitute creating a human being. "These are my cells being multiplied in a lab, not those of some other human being," concludes Somerville.

Still, the "pre-embryos," as many call them, if implanted into a woman's womb, do have the possibility of becoming a

human being, which makes some ethicists uneasy about the idea of creating them in the first place. "Many people do not consider embryos to be human beings, but they are also not just another cell or bit of tissue," social critic Francis Fukuyama wrote in a recent *Wall Street Journal* essay. "Research cloning would get us accustomed to the idea that human life in its early stages should be treated like any other pharmaceutical product." Yet, because of advances in science, we are fast approaching a point when any given cell has the potential to be developed into a human being, given the right chemical tinkering. "To commit ourselves morally to protecting every living cell in the body would be insane," counters Green. "Re-

search advances are making all cells 'embryonic,' " adds Lanza. "But if you consider those cells a human life, then 100 souls are lost every time I sneeze."

All three men are adamant that they are following the most moral path. "Three thousand Americans die every day of diseases that therapeutic cloning could treat," says Lanza. "It would be wrong of us to abandon those people because we're afraid of controversy." West is even more graphic about his beliefs. "I feel as if all my loved ones are trapped in a burning building, dying of diseases like diabetes and heart disease," he says. "I have the fire extinguisher—the therapeutic cloning technology—that can save them, but people are trying to take it out of my hands." And Cibelli is disgusted with the brouhaha. "Therapeutic cloning has to be done, and soon," he says. "Patients are all waiting for the public to get over the hype and fearfulness so that they have a chance to live."

All three are equally insistent that cloning for reproductive purposes is completely unethical, because the risks to both child and mother are too great. In fact, West considers the Raelian cult and other groups that claim to be working on cloning an actual human being to be his company's worst enemies: Any success could scare the public enough to sink ACT's efforts at providing new medical cures.

The effort

Because of the hostile climate, it took nearly two years for Cibelli to even begin the experiments. During that time, the partners searched for members to serve on an ethics board and debated how to best go about getting donors for both body cells and human eggs. Should they ask Christopher Reeve to donate his cells? Should Cibelli's willing wife donate her eggs? The questions and concerns seemed endless. One major turning point came in late September of 1999, when Cibelli met with Harvard professor Ann Kiessling, who agreed within five minutes to help set up a program to collect eggs from women. Another breakthrough came in mid-2000, when Dartmouth's Green