



[Features](#) - November 24, 2001

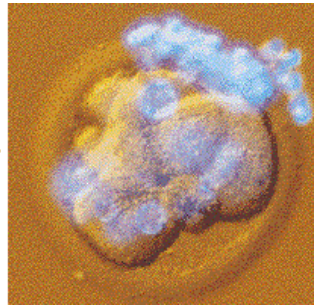
The First Human Cloned Embryo

Cloned early-stage human embryos, and human embryos generated only from eggs, in a process called parthenogenesis, now put therapeutic cloning within reach

EXCLUSIVE

The First Human Cloned Embryo

By Jose B. Cibelli, Robert P. Lanza and Michael D. West, with Carol Ezzell



Get the insight you need on today's science & technology

FREE newsletters & alerts from SciAm.com

SIGN UP NOW

THEY WERE SUCH TINY DOTS, YET THEY HELD SUCH immense promise. After months of trying, on October 13, 2001, we came into our laboratory at Advanced Cell Technology to see under the microscope what we'd been striving for, little balls of dividing cells not even visible to the naked eye. Insignificant as they appeared, the specks were precious because they were, to our knowledge, the first human embryos produced using the technique of nuclear transplantation, otherwise known as cloning.

With a little luck, we hoped to coax the early embryos to divide into hollow spheres of 100 or so cells called blastocysts. We intended to isolate human stem cells from the blastocysts to serve as the starter stock for growing replacement nerve, muscle and other tissues that might one day be used to treat patients with a variety of diseases. Unfortunately, only one of the embryos progressed to the six-cell stage, at which point it stopped dividing. In a similar experiment, however, we succeeded in prompting human eggs, on their own, with no sperm to fertilize them, to develop parthenogenetically into blastocysts. We believe that together these achievements, the details of which we reported November 25 in the online journal *e-biomed: The Journal of Regenerative Medicine*, represent the dawn of a new age in medicine by demonstrating that the goal of therapeutic cloning is within reach.

Therapeutic cloning, which seeks, for example, to use the genetic material from patients, own cells to generate pancreatic islets to treat diabetes or nerve cells to repair damaged spinal cords, is distinct from reproductive cloning, which aims to implant a cloned embryo into a woman's uterus leading to the birth of a cloned baby. We believe that reproductive cloning has potential risks to both mother and fetus that make it unwarranted at this time, and we support a restriction on cloning for reproductive purposes until the safety and ethical issues surrounding it are resolved.

Disturbingly, the proponents of reproductive cloning [see [Reproductive Cloning: They Want to Make a Baby](#)] are trying to co-opt the term "therapeutic cloning" by claiming that employing cloning techniques to create a child for a couple who cannot conceive through any other means treats the disorder of infertility. We object to this usage and feel that calling such a procedure "therapeutic" yields only confusion.

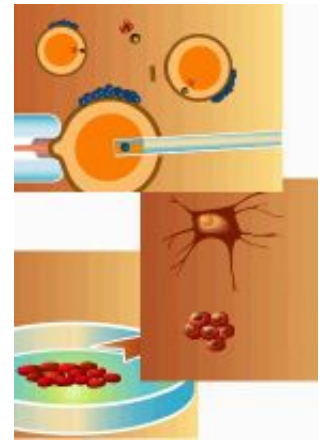
What We Did

WE LAUNCHED OUR ATTEMPT to create a cloned human embryo in early 2001. We began by consulting our ethics advisory board, a panel of independent ethicists, lawyers, fertility specialists and counselors that we had assembled in 1999 to guide the company's research efforts on an ongoing basis. Under the chairmanship of Ronald M. Green,

director of the Ethics Institute at Dartmouth College, the board considered five key issues [see [The Ethical Considerations](#)] before recommending that we go ahead.

The next step was to recruit women willing to contribute eggs to be used in the cloning procedure and also collect cells from individuals to be cloned (the donors). The cloning process appears simple, but success depends on many small factors, some of which we do not yet understand. In the basic nuclear transfer technique, scientists use an extremely fine needle to suck the genetic material from a mature egg. They then inject the nucleus of the donor cell (or sometimes a whole cell) into the enucleated egg and incubate it under special conditions that prompt it to divide and grow [see [Therapeutic Cloning: How It's Done](#)].

We found women willing to contribute eggs on an anonymous basis for use in our research by placing advertisements in publications in the Boston area. We accepted women only between the ages of 24 and 32 who had at least one child. Interestingly, our proposal appealed to a different subset of women than those who might otherwise contribute eggs to infertile couples for use in in vitro fertilization. The women who responded to our ads were motivated to give their eggs for research, but many would not have been interested in having their eggs used to generate a child they would never see. (The donors were recruited and the eggs were collected by a team led by Ann A. Kiessling-Cooper of Duncan Holly Biomedical in Somerville, Mass. Kiessling was also part of the deliberations concerning ethical issues related to the egg contributors.)



[THERAPEUTIC CLONING: HOW IT'S DONE](#)

We asked potential egg contributors to submit to psychological and physical tests, including screening for infectious diseases, to ensure that the women were healthy and that contributing eggs would not adversely affect them. We ended up with 12 women who were good candidates to contribute eggs. In the meantime, we took skin biopsies from several other anonymous individuals to isolate cells called fibroblasts for use in the cloning procedure. Our group of fibroblast donors includes people of varying ages who are generally healthy or who have a disorder such as diabetes or spinal cord injury; the kinds of people likely to benefit from therapeutic cloning.

Our first cloning attempt occurred last July. The timing of each attempt depended on the menstrual cycles of the women who contributed eggs; the donors had to take hormone injections for several days so that they would ovulate 10 or so eggs at once instead of the normal one or two.

We had a glimmer of success in the third cycle of attempts when the nucleus of an injected fibroblast appeared to divide, but it never cleaved to form two distinct cells. So in the next cycle we decided to take the tack used by Teruhiko Wakayama and his colleagues, the scientists who created the first cloned mice in 1998. (Wakayama was then at the University of Hawaii and is now at Advanced Cell Technology.) Although we injected some of the eggs with nuclei from skin fibroblasts as usual, we injected others with ovarian cells called cumulus cells that usually nurture developing eggs in the ovary and that can be found still clinging to eggs after ovulation. Cumulus cells are so small they can be injected whole. In the end, it took a total of 71 eggs from seven volunteers before we could generate our first cloned early embryo. Of the eight eggs we injected with cumulus cells, two divided to form early embryos of four cells; and one progressed to at least six cells; before growth stopped.

Parthenogenesis

WE ALSO SOUGHT TO DETERMINE whether we could induce human eggs to divide into early embryos without being fertilized by a sperm or being enucleated and injected with a donor cell. Although mature eggs and sperm normally have only half the genetic material of a typical body cell, to prevent an embryo from having a double set of genes following conception, eggs halve their genetic complement relatively late in their maturation cycle. If activated before that stage, they still retain a full set of genes.

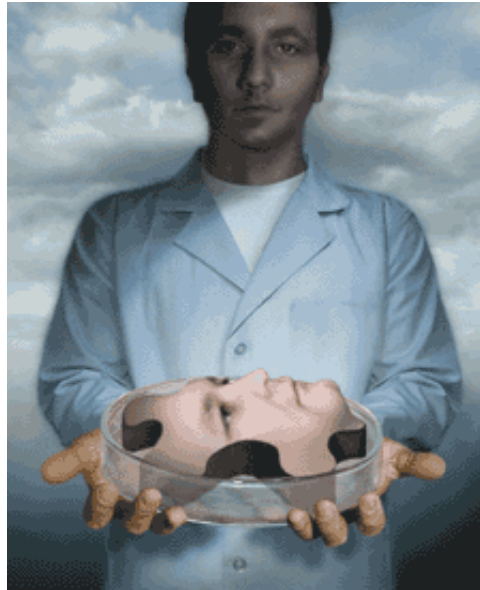


Image: MELISSA SZALKOWSKI
[THE ETHICAL CONSIDERATIONS](#)

Stem cells derived from such parthenogenetically activated cells would be unlikely to be rejected after transplantation because they would be very similar to a patient's own cells and would not produce many molecules that would be unfamiliar to the person's immune system. (They would not be identical to the individual's cells because of the gene shuffling that always occurs during the formation of eggs and sperm.) Such cells might also raise fewer moral dilemmas for some people than would stem cells derived from cloned early embryos.

Under one scenario, a woman with heart disease might have her own eggs collected and activated in the laboratory to yield blastocysts. Scientists could then use combinations of growth factors to coax stem cells isolated from the blastocysts to become cardiac muscle cells growing in laboratory dishes that could be implanted back into the woman to patch a diseased area of the heart. Using a similar technique, called androgenesis, to create stem cells to treat a man would be trickier. But it might involve transferring two nuclei from the man's sperm into a contributed egg that had been stripped of its nucleus.

Researchers have previously reported prompting eggs from mice and rabbits to divide into embryos by exposing them to different chemicals or physical stimuli such as an electrical shock. As early as 1983, Elizabeth J. Robertson, who is now at Harvard University, demonstrated that stem cells isolated from parthenogenetic mouse embryos could form a variety of tissues, including nerve and muscle.

In our parthenogenesis experiments, we exposed 22 eggs to chemicals that changed the concentration of charged atoms called ions inside the cells. After five days of growing in culture dishes, six eggs had developed into what appeared to be blastocysts, but none clearly contained the so-called inner cell mass that yields stem cells.

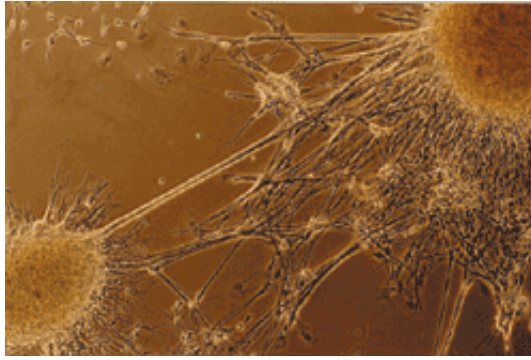
Why We Did It

WE ARE EAGER FOR THE DAY when we will be able to offer therapeutic cloning or cell therapy arising from parthenogenesis to sick patients. Currently our efforts are focused on diseases of the nervous and cardiovascular systems and on diabetes, autoimmune disorders, and diseases involving the blood and bone marrow.

Once we are able to derive nerve cells from cloned embryos, we hope not only to heal damaged spinal cords but to treat brain disorders such as Parkinson's disease, in which the death of brain cells that make a substance called dopamine leads to uncontrollable tremors and paralysis. Alzheimer's disease, stroke and epilepsy might also yield to such an approach.

Besides insulin-producing pancreatic islet cells for treating diabetes, stem cells from cloned embryos could also be nudged to become heart muscle cells as therapies for congestive heart failure, arrhythmias and cardiac tissue scarred by

heart attacks.



CLONING AND THE LAW

A potentially even more interesting application could involve prompting cloned stem cells to differentiate into cells of the blood and bone marrow. Autoimmune disorders such as multiple sclerosis and rheumatoid arthritis arise when white blood cells of the immune system, which arise from the bone marrow, attack the body's own tissues. Preliminary studies have shown that cancer patients who also had autoimmune diseases gained relief from autoimmune symptoms after they received bone marrow transplants to replace their own marrow that had been killed by high-dose chemotherapy to treat the cancer. Infusions of blood-forming, or hematopoietic, cloned stem cells might "reboot" the immune systems of people with autoimmune diseases.

But are cloned cells—or those generated through parthenogenesis—normal? Only clinical tests of the cells will show ultimately whether such cells are safe enough for routine use in patients, but our studies of cloned animals have shown that clones are healthy. In the November 30, 2001, issue of *Science*, we reported on our success to date with cloning cattle. Of 30 cloned cattle, six died shortly after birth, but the rest have had normal results on physical exams, and tests of their immune systems show they do not differ from regular cattle. Two of the cows have even given birth to healthy calves.

The cloning process also appears to reset the "aging clock" in cloned cells, so that the cells appear younger in some ways than the cells from which they were cloned. In 2000 we reported that telomeres—the caps at the ends of chromosomes—from cloned calves are just as long as those from control calves. Telomeres normally shorten or are damaged as an organism ages. Therapeutic cloning may provide "young" cells for an aging population.

A report last July by Rudolf Jaenisch of the Whitehead Institute for Biomedical Research in Cambridge, Mass., and his colleagues gained much attention because it found so-called imprinting defects in cloned mice. Imprinting is a type of stamp placed on many genes in mammals that changes how the genes are turned on or off depending on whether the genes are inherited from the mother or the father. The imprinting program is generally "reset" during embryonic development.

Although imprinting appears to play an important role in mice, no one yet knows how significant the phenomenon is for humans. In addition, Jaenisch and his co-workers did not study mice cloned from cells taken from the bodies of adults, such as fibroblasts or cumulus cells. Instead they examined mice cloned from embryonic cells, which might be expected to be more variable. Studies showing that imprinting is normal in mice cloned from adult cells are currently in press and should be published in the scientific literature within several months.

Meanwhile we are continuing our therapeutic cloning experiments to generate cloned or parthenogenetically produced human embryos that will yield stem cells. Scientists have only begun to tap this important resource.

THE AUTHORS:

JOSE B. CIBELLI, ROBERT P. LANZA and MICHAEL D. WEST are vice president of research, vice president of medical and scientific development, and president and CEO, respectively, of Advanced Cell Technology, a privately held biotechnology company in Worcester, Mass. Cibelli received his D.V.M. from the University of La Plata in Argentina and his Ph.D. from the University of Massachusetts at Amherst. His research led to the creation of the first cloned genetically

modified calves in 1998. Lanza has an M.D. from the University of Pennsylvania. He is a former Fulbright scholar and is the author or editor of numerous popular and scientific books, including the text *Principles of Tissue Engineering*. West holds a Ph.D. from Baylor College of Medicine and is particularly interested in aging and stem cells. From 1990 until 1998 he was founder, director and vice president of Geron Corporation in Menlo Park, Calif., where he initiated and managed research programs in the biology of telomeres (the ends of chromosomes, which shrink during aging) and the effort to derive human embryonic stem cells. Carol Ezzell is a staff writer and editor.

MORE TO EXPLORE:

Human Therapeutic Cloning. Robert P. Lanza, Jose B. Cibelli and Michael D. West in *Nature Medicine*, Vol. 5, No. 9, pages 975-977; September 1999.

Prospects for the Use of Nuclear Transfer in Human Transplantation. Robert P. Lanza, Jose B. Cibelli and Michael D. West in *Nature Biotechnology*, Vol. 17, No. 12, pages 1171-1174; December 1999.

The Ethical Validity of Using Nuclear Transfer in Human Transplantation. Robert P. Lanza et al. in *Journal of the American Medical Association*, Vol. 284, No. 24; December 27, 2000.

The Human Embryo Research Debates: Bioethics in the Vortex of Controversy. Ronald M. Green. Oxford University Press, 2001.

The full text of our article in *e-biomed: The Journal of Regenerative Medicine* can be viewed at www.liebertpub.com/ebi

Further Reading

[Test-Tube Babies May Face Greater Health Risks Than Naturally Conceived Children](#)

[Bacteria Transformed into Biofuel Refineries](#)

[Worlds Away: Astronomers Begin to Uncover Nearby "Super-Earths"](#)

[Nerd a Vacation?: Travel with *The Geek Atlas*](#)

[Privacy and the Quantum Internet](#)

[Reality Check: The Inevitable Disappointments from Stem Cells](#)

[Treating Wrinkles with Cutting-Edge Technology--Without Going Under the Knife](#)

[Bush bioethics advisors take potshot at Obama stem cell platform](#)