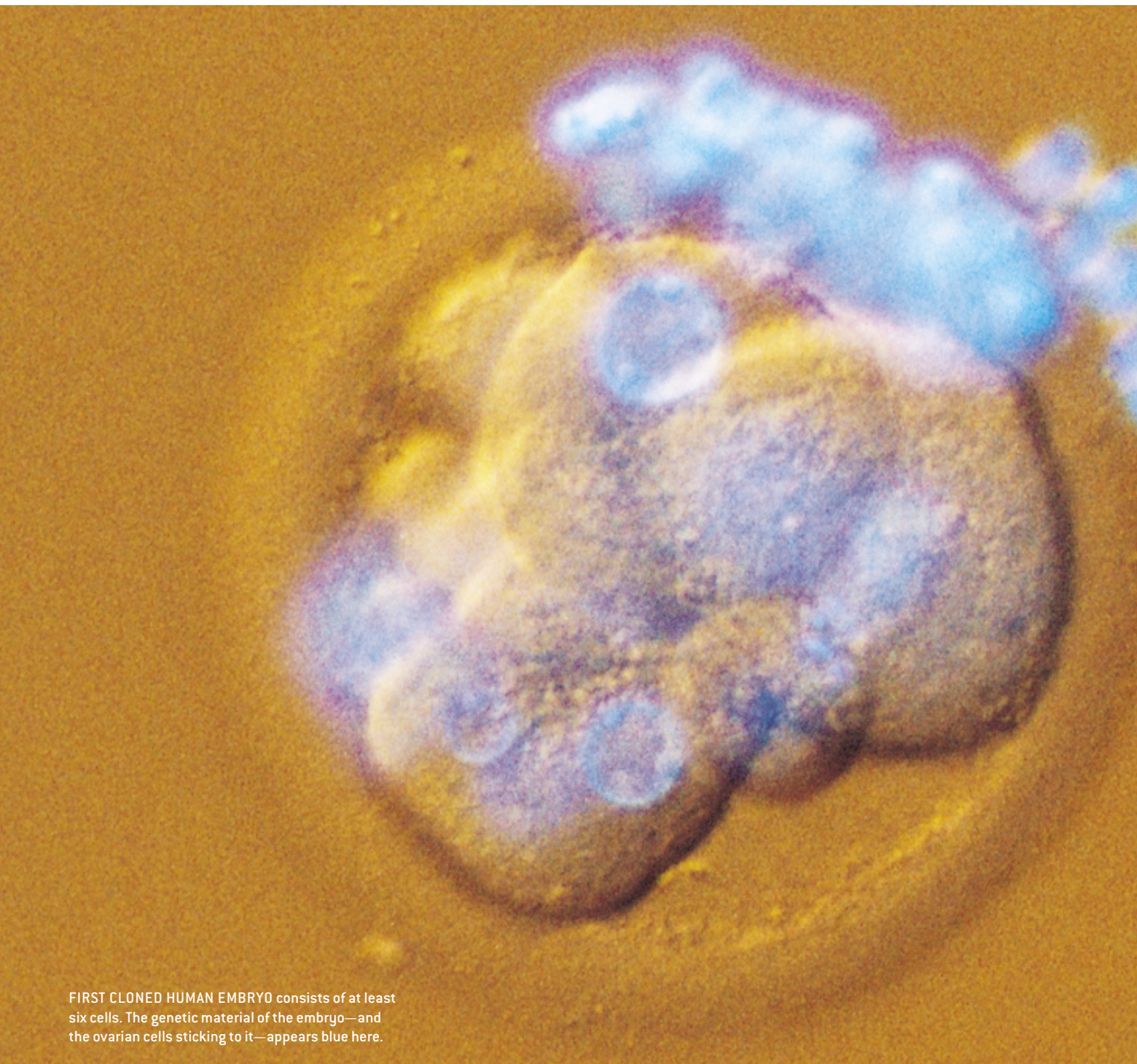
EXCLUSIVE

The First Human Cloned

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



FIRST CLONED HUMAN EMBRYO consists of at least six cells. The genetic material of the embryo—and the ovarian cells sticking to it—appears blue here.

Embryo

JOSE B. CIBELLI

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

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—

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.

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 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.

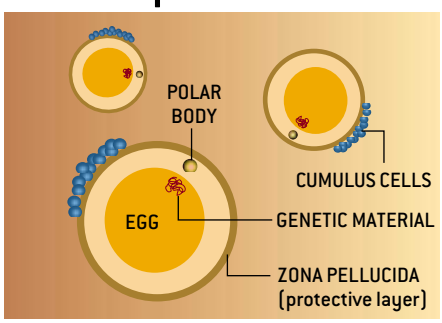
What We Did

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 box beginning on page 48*] before recommending that we go ahead.

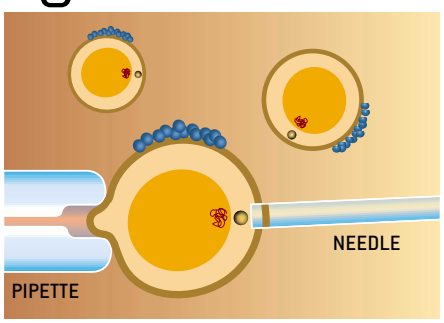
The next step was to recruit women willing to contribute eggs to be used in the cloning procedure and also collect cells from individuals to be cloned (the donors). The cloning process appears simple, but success depends on many small factors, some of which we do not yet understand. In the basic nuclear 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 illustration on these two pages*].

We found women willing to contribute eggs on an anonymous basis for use in our research by placing advertisements in

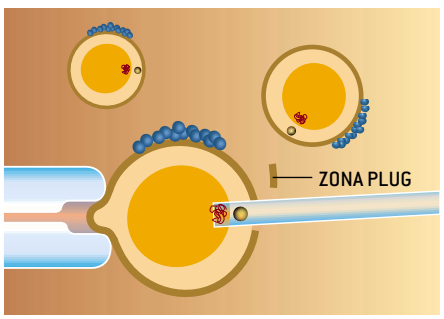
Therapeutic Cloning: How It's Done



1 Eggs are coaxed to mature in a culture dish. Each has a remnant egg cell called the polar body and cumulus cells from the ovary clinging to it.



2 While an egg is held still with a pipette, a needle is used to drill through the zona pellucida, removing a plug.



3 After ejecting the zona plug, the needle is inserted back in the egg through the hole to withdraw and discard the polar body and the egg's genetic material.

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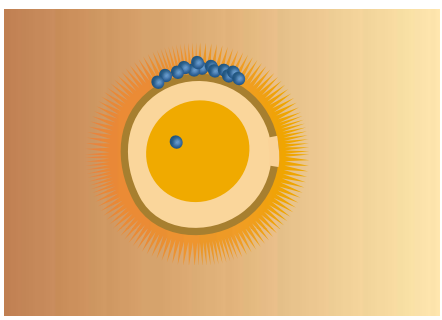
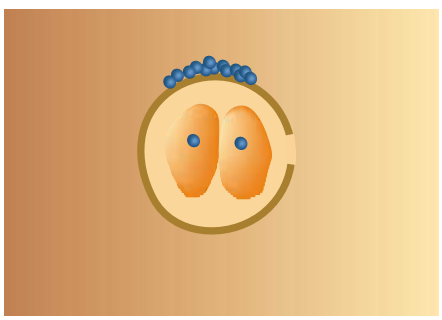
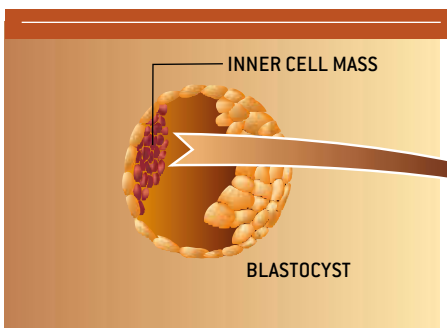


6 The injected egg is exposed to a mixture of chemicals and growth factors designed to activate it to divide.



7 After roughly 24 hours, the activated egg begins dividing. The cells contain genetic material only from the injected cumulus cell.



8 By the fourth or fifth day, a hollow ball of roughly 100 cells has formed. It holds a clump of cells called the inner cell mass that contains stem cells.

9

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.)

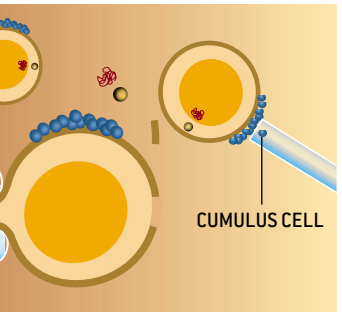
We asked potential egg contributors to submit to psychological and physical tests, including screening for infectious diseases, to ensure that the women were healthy and that contributing eggs would not adversely affect them. We ended up with 12 women who were good candidates to contribute eggs. In the 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.

On the Web/*Human Cloning*

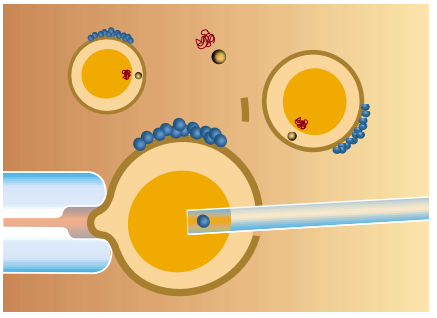
- For updates on this breaking story, visit a special report on human cloning and stem cells at our Web site, **www.sciam.com/explorations/2001/112401ezzell/**
- The site includes previous *Scientific American* articles on the subject as well as reports on adult stem cells and the current status of reproductive cloning projects.

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.

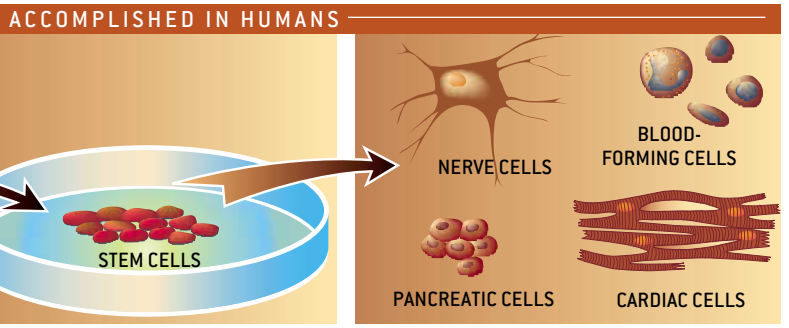
We had a glimmer of success in the third cycle of attempts when the nucleus of an injected fibroblast appeared to divide, but it never cleaved to form two distinct cells. So in the next cycle we decided to take the tack used by Teruhiko Wakayama and his colleagues, the scientists who created the first 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.



A cumulus cell from another egg is taken up into the needle. Cells called fibroblasts (or their nuclei) can also be used in this step.



5 The cumulus cell is injected deep into the egg that has been stripped of its genetic material.



The blastocyst is broken open, and the inner cell mass is grown in a culture dish to yield stem cells.

10 The stem cells, in turn, can be coaxed to grow into a variety of cells that might one day be injected into patients.

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.

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

JANA BRENNING

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.

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 ex-

The Ethical Considerations

Advanced Cell Technology assembled a board of outside ethicists to weigh the moral implications of therapeutic cloning research, which aims to generate replacement tissues to treat a range of diseases. Here are the five major questions the board considered before the company went forward with cloning the first human embryo.

By Ronald M. Green

What is the moral status of the organisms created by cloning?
If a cloned organism were implanted into a womb, as was done in the case of Dolly the sheep, it could possibly go on to full development and birth. Because of this potential, some would argue that the organism produced in human therapeutic cloning experiments is the equivalent of any ordinary human embryo and merits the same degree of respect and protection.

Most members of our advisory board did not agree. We pointed out that, unlike an embryo, a cloned organism is not the result of fertilization of an egg by a sperm. It is a new type of biological entity never before seen in nature. Although it possesses some potential for developing into a full human being, this capacity is very limited. At the blastocyst stage, when the organism is typically disaggregated to create an embryonic stem cell line, it is a ball of cells no bigger than the period at the end of this sentence. (Embryos normally do not attach to the wall of the uterus and begin development until after the blastocyst stage.) It has no organs, it cannot possibly think or feel, and it has none of the attributes thought of as human. Although board members understood that some people would liken this organism to an embryo, we preferred the term "activated egg," and

A cloned organism is a NEW

we concluded that its characteristics did not preclude its use in work that might save the lives of children and adults.

Is it permissible to create such a developing human entity only to destroy it?
Those who believe that human life begins at conception—and who also regard activated eggs as morally equivalent to human embryos—cannot ethically approve therapeutic cloning research. For them, such research is equivalent to killing a living child in order to harvest its organs for the benefit of others. Some of those who think this way, however, might nonetheless find acceptable research on human stem cells derived from embryos left over from in vitro fertilization (IVF) procedures. They reason, rightly or wrongly, that these embryos are certain to be destroyed and that at least some good might result from using the cells. But therapeutic cloning remains totally unacceptable to such people because it involves the deliberate creation of what they deem to be a human being in order to destroy it.

Many who do not accord moral status to the entities produced by therapeutic cloning disagree with that view. Like our board members, they argue that the benefits of this research and the

MELISSA SZALKOWSKI

sensitive ethical issues in therapeutic cloning research. In each of her monthly cycles, a woman usually produces only one or two mature eggs. To increase that to a number that can be used in research, she must be given stimulatory medications such as those used in reproductive IVF procedures. In rare cases, these drugs can provoke a so-called hyperstimulation syndrome that can lead to liver damage, kidney failure or stroke. According to some studies, ovulation-stimulating drugs have also been associated with a heightened risk for ovarian cancer. The surgery to retrieve the eggs also carries risks, such as the dangers of general anesthesia and bleeding. Is it ethical to subject a woman to these risks for research purposes? If women are offered payment to undergo these risks, might that cause human reproductive material to become viewed as a commodity that can be commercialized? We do not permit the sale of human organs or babies. Are eggs any different?

In responding to these concerns, members of the board took note of two facts. First, a substantial market in human eggs for reproductive purposes already exists. Young women are being paid substantial sums to provide eggs that can help single women or couples have children. If women can undergo risks for this purpose, we asked, why should they not be allowed to undertake the same risks to further medical research that could save human lives? And if they can be paid for the time and discomfort that egg donation for reproductive purposes involves, why can't they receive reasonable payment for ovulation induction for research purposes?

Second, we noted that research volunteers often accept significant risks to advance medical knowledge. If a person can agree to undergo a dangerous malaria vaccine study to help cure disease, why should they be prevented from donating eggs for similar lifesaving research?

In the end, we concluded that it would be unduly paternalistic to prohibit women from donating eggs for this research. At the same time, we established a rigorous informed-consent procedure so that egg donors would be made fully aware of the possible dangers. We insisted that ovulation-stimulating medications be administered at safe dosages. And we set payment for participation at a modest level: $4,000 (about $40 an hour), which is roughly the average paid in New England for egg donation for reproductive purposes. We wanted to prevent payment from becoming an undue influence that could blind women to the risks.

What are the ethical issues relating to the person whose cells are being cloned?

It may seem that individuals who provide the cells (usually skin fibroblasts) that are fused with enucleated eggs in therapeutic cloning research face no risk apart from the remote possibility of an infection at the site of the skin biopsy. But cloning is a controversial issue that exposes all research participants to novel risks. Cell

TYPE OF BIOLOGICAL ENTITY never before seen in nature.

possible therapies it could produce far outweigh the claims of the activated eggs. Remarkably, some who share this moral view nonetheless oppose the research on symbolic grounds. They maintain that it is unseemly to create human life in any form only to destroy it. They worry that it might start society down a slippery slope that could lead to the scavenging of organs from adults without their consent.

These symbolic and "slippery slope" arguments often have powerful emotional force, but they are hard to assess. Is it really true that using activated eggs for lifesaving therapies will lead to these imagined abuses? On the contrary, if medical science can increase people's chances of healthy survival, might not this research even enhance respect for human life? Members of the board took note of the fact that the U.K., until very recently, has legally permitted the deliberate creation and destruction of human embryos in research since the early 1990s [*see box on page 51*]. There has been no apparent ill effect of this permission on British society. In the end, the symbolic and slippery slope arguments did not persuade board members that therapeutic cloning research should not go forward.

Is it right to seek human eggs for scientific research?

The need to obtain a supply of human eggs leads to one of the most

Cell donors might find themselves at the CENTER OF A MEDIA STORM if they are identified as having allowed themselves to be cloned.

donors, for example, might find themselves at the center of a media storm if they are identified as having allowed themselves to be cloned. To prevent this, the ethics advisory board insisted on procedures ensuring strict confidentiality for both egg and cell donors (unless they choose to come forward).

One question that occupied much of our time was whether children could donate cells for this research. We concluded that in general this is not advisable, because on reaching maturity the child may feel morally compromised by having been made to contribute to a cloning procedure. We made an exception, however, in the case of an infant with a fatal genetic disease. We knew that a stem cell line based on the child's DNA might be a powerful tool in research aimed at curing the disease. Although the child would probably not survive long enough to benefit from this research, we concluded that the parents had a right to make this decision on the child's behalf. This child's cells have not yet been used in a cloning procedure.

Will therapeutic cloning facilitate reproductive cloning, the birth of a cloned baby?

A final major question raised by this research is whether it will hasten the day when people undertake human reproductive cloning. This concern presumes that reproductive cloning is and always will be ethically wrong. Many who hold this view cite the incidence of deaths and birth defects in cloned animals. Others worry about more remote dangers. They point to possible psychological risks to children produced in families in which a parent may also be a child's genetic twin. They fear that cloned children may face unrealistic expectations to live up to the achievements of their genetic predecessor. And they worry about possible social risks of cloning if societies decide to replicate a limited number of desired genomes on a large scale for military or other purposes. In opposition to this, some people hail the prospect of cloning. They see it as a new way to provide biologically related offspring for some infertile couples or as a means of reducing the risks of some inherited genetic diseases.

Whatever one thinks about the ethics of reproductive cloning, placing a ban on therapeutic cloning will not make reproductive cloning less likely. Although therapeutic cloning could help scientists perfect techniques for reproductive cloning, it could also make much clearer the dangers of trying to produce a human being in this way. There is already evidence that some cloned animals can experience improper gene expression and disruptions in imprinting, the normal pattern of silencing genes not needed in particular tissues. Such problems could discourage prospective parents from using this technology to have a baby. Thus, therapeutic cloning research could actually reduce the likelihood that cloning would be seen as a viable reproductive option.

A ban on therapeutic cloning also would not prevent unsupervised researchers from going ahead with reproductive cloning efforts on their own. Groups such as the Raëlians, a religous cult, or renegade scientists such as Richard G. Seed, a physicist based in Riverside, Ill., who has also been involved in embryology, have announced their intent to clone a human being and presumably will try to do so regardless of whether therapeutic cloning research is banned. A ban on therapeutic cloning will block useful research while allowing less responsible people to try reproductive cloning wherever they can find a permissive legal environment. By shutting down responsible research on the cell biology of human cloning, such a ban would also guarantee that the first efforts at cloning a human being would be based on scanty scientific information.

Our ethics board has had to wrestle with new and challenging questions, but we believe we have managed to give Advanced Cell Technology a firm ethical base for its therapeutic cloning research program. After researchers derive stem cells from cloned human activated eggs, ethicists will need to determine at what point it will be safe to try to transplant such cells back into volunteer donors. The tasks ahead for ethics boards like ours are demanding. The reward is assisting at the cutting edge of medical knowledge.

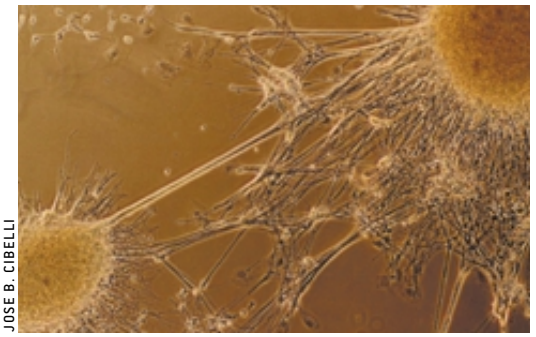
RONALD M. GREEN is director of the Ethics Institute at Dartmouth College and chair of the ethics advisory board of Advanced Cell Technology in Worcester, Mass.

Other current board members are Judith Bernstein of Boston University ; Susan Crockin, a health care lawyer in private practice in Newton, Mass.; Kenneth Goodman, director of the Forum for Bioethics at the University of Miami; Robert Kaufmann of the Southeastern Fertility Center in Mount Pleasant, S.C.; Susan R. Levin, a counselor in private practice in West Roxbury, Mass.; Susan L. Moss of San Diego State University; and Carol Tauer of the Minnesota Center for Health Care Ethics. Michael D. West, president and CEO of Advanced Cell Technology, is an ex officio member of the ethics advisory board.

Cloning and the Law

Will therapeutic cloning end up being against the law?

Legislative activities threaten to stand in the way of the medical benefits that therapeutic cloning could provide. On July 31, 2001, the House of Representatives voted for a broad ban on human cloning that would not only prohibit the use of cloning for reproduction but would also prohibit cloning for research purposes, such as to derive stem cells that could be used in therapies. The legislation, which was sponsored by Representatives David Weldon (R-Fla.) and Bart Stupak (D-Mich.), would carry penalties of up to 10 years in prison and fines of $1 million for anyone who generates cloned human embryos. An amendment introduced by Representative Jim Greenwood (R-Pa.) that would have allowed therapeutic cloning failed. (Greenwood has his own pending bill on the subject that would outlaw only reproductive cloning.) Such laws would affect all scientists in the U.S., not only those working with government funding.



JOSE B. CIBELLI

PRIMATE NERVE CELLS derived from stem cells growing in culture look like normal nerve cells.

The Weldon/Stupak bill has now been referred to the Senate, which is expected to take up the issue in early 2002. Senator Sam Brownback (R-Kan.), who has also introduced a bill, opposes human cloning for any purpose. He tried to add amendments banning human cloning to the fiscal 2002 spending bill for the Department of Health and Human Services last November. Such measures face an uphill battle, however, in the Democrat-controlled Senate. The Bush administration supports a total cloning ban and has endorsed the Weldon/Stupak bill.

The matter of human cloning is also being taken up once again by the U.K. Parliament. In 2000 the U.K. altered its Human Fertilization and Embryology Act of 1990 to specifically allow human therapeutic cloning. But last November antiabortion activists succeeded in having the provision struck down on the grounds that cloning does not involve an embryo created by the union of an egg and a sperm and therefore cannot be included under the act.

In a related issue, last August President George Bush barred the use of federal funds for research involving stem cells derived from embryos, including those generated using cloning. The bar permits federally funded scientists to experiment only with stem cell cultures, or lines, created before the August announcement. But many scientists have criticized the quality and availability of these stem cell lines. Others claim that without cloning, stem cells have no promise, because they would probably be rejected as foreign by a patient's immune system.

Legislative attempts by Senator Arlen Specter (R-Pa.) in November that would have allowed scientists to use government money to make new stem cell lines were squelched when Brownback threatened to counter with a total ban on human stem cell research.

—Carol Ezzell

ams, 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. SA

MORE TO EXPLORE

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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.

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