President Bush's decision to support the use of existing embryonic stem cell lines surprised many and angered some. It also triggered a hunt to find them

Bush Squeezes Between the Lines on Stem Cells

Ending months of speculation, President George W. Bush told a national TV audience on 9 August that he would allow the federal government to fund work on embryonic stem (ES) cells. But rather than settling the debate, Bush's compromise has sparked a new round of scientific questions, including exactly how much research the new policy will permit. Although the president's decision may temporarily halt a political push for more research opportunities, his assertion that some 60 ES cell lines would be available for research is more than twice the number most scientists would cite.

In his first televised speech since January, Bush announced that the National Institutes of Health (NIH) can fund work with human ES cells—but only those cell lines derived before his announcement. The spin has been generally favorable: Both supporters and opponents of the research, who had condemned such a compromise last month (*Science*, 13 July, p. 186), praised the decision. "The compromise he's tried to achieve is a laudable one," says cell biologist Douglas Melton of Harvard University, who works with both human and mouse ES cells. And although some pro-life groups, including the U.S. Conference of Catholic Bishops, condemned the decision, others said the president had kept his campaign pledge to oppose research that destroys embryos.

Talking points. HHS Secretary Tommy Thompson, flanked by NIH's Ruth Kirschstein and Lana Skirboll, explains the president's decision.

Embryonic stem cells can in theory develop into any cell type in the body, and many scientists think they could eventually be used to treat chronic diseases such as diabetes or Parkinson's. Any clinical applications, however, are many years away. But because the cells are derived from week-old human embryos, which are destroyed in the process, their use has been controversial. Last summer, NIH issued guidelines to govern work on the cells, but the new Administration halted their implementation this spring while it reviewed the issue.

When the White House floated this compromise several weeks ago, scientists in favor of ES cell work said that too few cell lines would be available to fully determine the potential of this new field. They were also concerned that many of the existing cell lines have commercial strings attached that could limit research.

In response, Secretary of Health and Human Services Tommy Thompson asked Lana Skirboll, head of science policy at NIH, to tally the number of cell lines worldwide. To her surprise, Skirboll said at a 10 August press conference, her staff tracked down at least 60 from five countries: the United States, Australia, Sweden, Israel, and India. All 60 lines are propagating, she said, have cell surface markers characteristic of ES cells, and should be available to researchers within months. The unexpectedly high number of cell lines arose, Skirboll said, because many researchers have been keeping quiet and agreed to talk to NIH only under conditions of confidentiality.

"If there are 60 cell lines, that's news to me—and good news," Melton says. He cautions, however, that the properties of the purported cell lines are unclear, as are intellectual property rights. Cell surface markers, for example, are a "necessary but not sufficient" indication of an ES cell line's characteristics, he says.

An informal search by *Science* turned up 34 distinct cell lines in four countries. At least seven cell lines have been described in peer-reviewed publications: five by James Thomson of the University of Wisconsin (UW), Madison, and two by Martin Pera of Monash University in Melbourne, Australia, and his colleagues. (Scientists from the Jones Institute in Virginia published a description of two ES cell lines, but they do not qualify for NIH funding because they were derived from embryos specifically created for research.)

The remaining new lines have been described at scientific meetings or in conversations with *Science*. Pera's team has derived four more lines, he says. Joseph Itskovitz-Eldor of Technion University in Haifa, Israel, who collaborated with Thomson to derive the first ES cell lines, told *Science* he has derived three more of his own. Bresagen, a company based in Atlanta, announced having derived four. Peter Eriksson told *Science* that he and

STEM CELL POLICIES AROUND THE WORLD

No human embryo research permitted
Germany,* France,† Switzerland,* Norway, Ireland, Austria, Poland, Brazil

Use of already-derived stem cells permitted, but not the derivation of stem cells
United States (federal funding)

Both the derivation and use of stem cells from spare embryos permitted
Japan, Canada, Spain, Italy, Finland, Sweden, Israel, Singapore, and Australia

Derivation and use of stem cells from embryos created for research permitted
United Kingdom, privately funded researchers in the United States, de facto policy in China

* German and Swiss national ethics committees are considering allowing use of already-derived stem cells.

† The French government has proposed allowing both derivation and use of ES cells.

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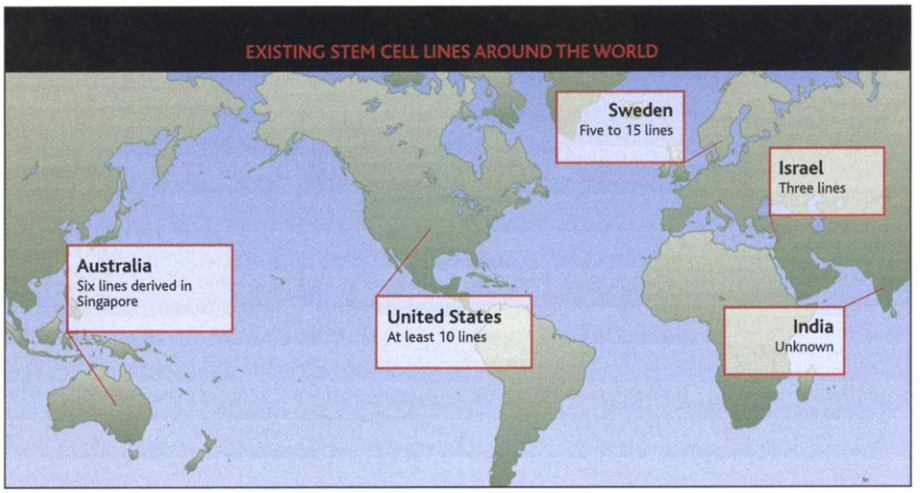
his colleagues at Göteborg University in Sweden have derived five lines and have so far characterized three. Michael Andäng of Huddinge University Hospital outside Stockholm told *Science* that he and his colleagues are characterizing "five to 10 human ES cell lines" they have derived. Roger Pedersen of the University of California, San Francisco (UCSF), has derived at least one.

Science could not confirm reports of work with human ES cells in India. Reliance Life Science of Bombay markets a product called ReliCord, derived from umbilical cord blood. The company was rumored to have ES cell lines, but Anand Rao, research director for cell biology, told *Science* it has none. Manju Sharma, India's biotechnology secretary, says she knows of no ES cell lines in the country.

Pera echoed the general surprise at NIH's total, suggesting that they may still be in early, uncertain stages of derivation. "It is no small chore to derive, cryopreserve, and properly characterize three or four lines," he says. "Someone must have a factory somewhere, or we are talking about *potential* cell lines." But at the briefing Skirboll stood by her number and predicted that even more cell lines would come to light.



Show me the cell lines. Scientists in four countries report developing a total of 34 cell lines, far short of the 60 mentioned by President Bush.

Relaxed requirements

Even as the president sought to limit criticism by opponents of ES cell research, the ethical requirements that he laid down last week are much simpler than those issued last summer by NIH. The new criteria require that cell lines have been derived from embryos that were created for fertility treatments but are no longer needed. In addition, the couples donating the embryos must have given their informed consent, without any financial inducements. By contrast, the NIH guidelines issued last summer stipulated that NIH-approved cell lines must have been derived from frozen embryos, and those doctors procuring the embryos could not also derive the cell lines. In addition, the consent form had to meet certain strict criteria, explicitly stating, for example, that the cell lines "may be kept for many years" (*Science*, 1 September 2000, p. 1442). The NIH guidelines, which were never implemented, would have forced researchers to derive new cell lines, while Skirboll says that all 60 lines meet Bush's looser ethical criteria.

The new policy may also ease some administrative burdens. Skirboll said that NIH was reviewing a prohibition against commingling any federal research funds—even support for building maintenance and upkeep—with private money used for embryo research that NIH is not allowed to fund. That policy has forced some researchers, including UW's Thomson and Pedersen at UCSF, to set up separate laboratory space for their human ES cell work.

New Chair of Bioethics Panel Wants National Debate on Issues

President George W. Bush's decision on embryonic stem cells may have dimmed the hopes of some federal researchers, but it has given ethicists a new lease on life. The president intends to create a new White House Council on Bioethics, to be chaired by University of Chicago moral philosopher Leon Kass. The new panel will succeed one created by President Bill Clinton—the National Bioethics Advisory Commission (NBAC)—that will disappear on 3 October.

The White House has provided little information on the new council. In a telephone interview, Kass said that he was invited to become its chair only 2 weeks ago. According to the White House, the panel will monitor studies of embryonic stem cells, recommend regulations, and "consider all of the medical and ethical ramifications of biomedical innovation." Kass hopes that its members—numbering "in the teens"—will be named soon.

The panel will include people with a wide spectrum of views and have a "broad mandate," says Kass, adding that it will do what "the president himself did in reaching his decision: namely, consult widely and make sure that all responsible points of view are heard." Regulatory issues will be handled by the National Institutes of Health (NIH), according to a government spokesperson.

With an M.D. from the University of Chicago and a Ph.D. in biochemistry from Harvard University, Kass worked at NIH in the late 1960s and later contributed to the founding of a bioethics research group, the Hastings Center in Garrison, New York. The center's founder, Daniel Callahan, thinks that Kass "will be very careful to get a fair range of people on the council." NBAC's chair, former Princeton University president Harold Shapiro, says that "while I disagree with a lot of things Leon Kass says, I have a lot of respect for him." Shapiro adds that he's glad the president "feels the need for continuing advice" on biomedical ethics.

Moral instructor. Ethicist Leon Kass sees a "pedagogical" mission for the new White House group.

Kass worries that his opposition to human cloning and advocacy of restraints on medical technology will cause some researchers to regard him as "a Luddite." But he expects to prove them wrong by making the council a forum for debate. "People who are nervous about me should wait and see. ... My vision is for this council to become a kind of teacher to anybody who is interested" in bioethics. **—ELIOT MARSHALL**

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"I Have Given This Issue a Great Deal of Thought ... and I Have Found Widespread Disagreement"

The White House released this transcript of President Bush's nationally televised 9 August speech on stem cell research.

Good evening. I appreciate you giving me a few minutes of your time tonight so I can discuss with you a complex and difficult issue, an issue that is one of the most profound of our time.

The issue of research involving stem cells derived from human embryos is increasingly the subject of a national debate and dinner table discussions. The issue is confronted every day in laboratories as scientists ponder the ethical ramifications of their work. It is agonized over by parents and many couples as they try to have children, or to save children already born.

The issue is debated within the church, with people of different faiths, even many of the same faith coming to different conclusions. Many people are finding that the more they know about stem cell research, the less certain they are about the right ethical and moral conclusions.

My administration must decide whether to allow federal funds, your tax dollars, to be used for scientific research on stem cells derived from human embryos. A large number of these embryos already exist. They are the product of a process called in vitro fertilization, which helps so many couples conceive children. When doctors match sperm and egg to create life outside the womb, they usually produce more embryos than are planted in the mother. Once a couple successfully has children, or if they are unsuccessful, the additional embryos remain frozen in laboratories.

Some will not survive during long storage; others are destroyed. A number have been donated to science and used to create privately funded stem cell lines. And a few have been implanted in an adoptive mother and born, and are today healthy children.

Based on preliminary work that has been privately funded, scientists believe further research using stem cells offers great promise that could help improve the lives of those who suffer from many terrible diseases—from juvenile diabetes to Alzheimer's, from Parkinson's to spinal cord injuries. And while scientists admit they are not yet certain, they believe stem cells derived from embryos have unique potential.

You should also know that stem cells can be derived from sources other than embryos—from adult cells, from umbilical cords that are discarded after babies are born, from human placenta. And many scientists feel research on these type of stem cells is also promising. Many patients suffering from a range of diseases are already being helped with treatments developed from adult stem cells.

However, most scientists, at least today, believe that research on embryonic stem cells offer the most promise because these cells have the potential to develop in all of the tissues in the body.

Scientists further believe that rapid progress in this research will come only with federal funds. Federal dollars help attract the best and brightest scientists. They ensure new discoveries are widely shared at the largest number of research facilities and that the research is directed toward the greatest public good.

The United States has a long and proud record of leading the world toward advances in science and medicine that improve human life. And the United States has a long and proud record of upholding the highest standards of ethics as we expand the limits of science and knowledge. Research on embryonic stem cells raises profound ethical questions, because extracting the stem cell destroys the embryo, and thus destroys its potential for life. Like a snowflake, each of these embryos is unique, with the unique genetic potential of an individual human being.

As I thought through this issue, I kept returning to two fundamental questions: First, are these frozen embryos human life, and therefore, something precious to be protected? And second, if they're going to be destroyed anyway, shouldn't they be used for a greater good, for research that has the potential to save and improve other lives?

I've asked those questions and others of scientists, scholars, bioethicists, religious leaders, doctors, researchers, members of Congress, my Cabinet, and my friends. I have read heartfelt letters from many Americans. I have given this issue a great deal of thought, prayer and considerable reflection. And I have found widespread disagreement.

Promising start. President Bush says that "leading scientists" have told him about the potential for "breakthrough therapies and cures" from embryonic stem cells.

On the first issue, are these embryos human life—well, one researcher told me he believes this five-day-old cluster of cells is not an embryo, not yet an individual, but a pre-embryo. He argued that it has the potential for life, but it is not a life because it cannot develop on its own.

An ethicist dismissed that as a callous attempt at rationalization. Make no mistake, he told me, that cluster of cells is the same way you and I, and all the rest of us, started our lives. One goes

Bush's announcement does not affect research in the private sector. Companies or university researchers with non-NIH funding can derive new cell lines, but the NIH will not fund work with such lines. NIH is also scrapping its Human Pluripotent Stem Cell Review Group (HPSCRG), which was to have met in April to determine whether several newly derived cell lines would qualify. "There will be no new derivations for the NIH to approve," says Skirboll, "so there is no need for the HPSCRG."

NIH has already begun setting up a registry of qualifying cell lines, said Skirboll, with cell lines that pass muster going into a database. Scientists will have to specify which cell line or lines they plan to use and make the necessary material transfer agreements (MTAs) with companies that own the cells.

At the 10 August press conference, Thompson said that a scientist has been chosen to lead the database compilation but declined to disclose the name. He also said NIH could begin funding new grants to work with ES cells by early next year, and scientists could apply for supplemental grants even sooner—perhaps within weeks.

Which cell lines come with strings attached—and how tight those strings are—remains unclear, as much of the derivation research to date has been funded by companies. "There are strong property and patent issues to work through," Thompson acknowledged at

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with a heavy heart if we use these, he said, because we are dealing with the seeds of the next generation.

And to the other crucial question, if these are going to be destroyed anyway, why not use them for good purpose—I also found different answers. Many argue these embryos are byproducts of a process that helps create life, and we should allow couples to donate them to science so they can be used for good purpose instead of wasting their potential. Others will argue there's no such thing as excess life, and the fact that a living being is going to die does not justify experimenting on it or exploiting it as a natural resource.

At its core, this issue forces us to confront fundamental questions about the beginnings of life and the ends of science. It lies at a difficult moral intersection, juxtaposing the need to protect life in all its phases with the prospect of saving and improving life in all its stages.

As the discoveries of modern science create tremendous hope, they also lay vast ethical mine fields. As the genius of science extends the horizons of what we can do, we increasingly confront complex questions about what we should do. We have arrived at that brave new world that seemed so distant in 1932, when Aldous Huxley wrote about human beings created in test tubes in what he called a "hatchery."

In recent weeks, we learned that scientists have created human embryos in test tubes solely to experiment on them. This is deeply troubling, and a warning sign that should prompt all of us to think through these issues very carefully.

Embryonic stem cell research is at the leading edge of a series of moral hazards. The initial stem cell researcher was at first reluctant to begin his research, fearing it might be used for human cloning. Scientists have already cloned a sheep. Researchers are telling us the next step could be to clone human beings to create individual designer stem cells, essentially to grow another you, to be available in case you need another heart or lung or liver.

I strongly oppose human cloning, as do most Americans. We recoil at the idea of growing human beings for spare body parts, or creating life for our convenience. And while we must devote enormous energy to conquering disease, it is equally important that we pay attention to the moral concerns raised by the new frontier of human embryo stem cell research. Even the most noble ends do not justify any means.

My position on these issues is shaped by deeply held beliefs. I'm a strong supporter of science and technology, and believe they have the potential for incredible good—to improve lives, to save life, to conquer disease. Research offers hope that millions of our loved ones may be cured of a disease and rid of their suffering. I have friends whose children suffer from juvenile diabetes. Nancy Reagan has written me about President Reagan's struggle with Alzheimer's. My own family has confronted the tragedy of childhood leukemia. And, like all Americans, I have great hope for cures.

I also believe human life is a sacred gift from our Creator. I worry about a culture that devalues life, and believe as your President I have an important obligation to foster and encourage respect for life in America and throughout the world. And while we're all hopeful about the potential of this research, no one can be certain that the science will live up to the hope it has generated.

Eight years ago, scientists believed fetal tissue research offered great hope for cures and treatments—yet, the progress to date has not lived up to its initial expectations. Embryonic stem cell research offers both great promise and great peril. So I have decided we must proceed with great care.

"While we're all hopeful ... no one can be certain that the science will live up to the hope it has generated."

As a result of private research, more than 60 genetically diverse stem cell lines already exist. They were created from embryos that have already been destroyed, and they have the ability to regenerate themselves indefinitely, creating ongoing opportunities for research. I have concluded that we should allow federal funds to be used for research on these existing stem cell lines, where the life and death decision has already been made.

Leading scientists tell me research on these 60 lines has great promise that could lead to breakthrough therapies and cures. This allows us to explore the promise and potential of stem cell research without crossing a fundamental moral line, by providing taxpayer funding that would sanction or encourage further destruction of human embryos that have at least the potential for life.

I also believe that great scientific progress can be made through aggressive federal funding of research on umbilical cord, placenta, adult and animal stem cells which do not involve the same moral dilemma. This year, your government will spend $250 million on this important research.

I will also name a President's council to monitor stem cell research, to recommend appropriate guidelines and regulations, and to consider all of the medical and ethical ramifications of biomedical innovation. This council will consist of leading scientists, doctors, ethicists, lawyers, theologians and others, and will be chaired by Dr. Leon Kass, a leading biomedical ethicist from the University of Chicago.

This council will keep us apprised of new developments and give our nation a forum to continue to discuss and evaluate these important issues. As we go forward, I hope we will always be guided by both intellect and heart, by both our capabilities and our conscience.

I have made this decision with great care, and I pray it is the right one.

Thank you for listening. Good night, and God bless America.

the press conference. Several scientists, for instance, chafed at the requirements of an earlier MTA from WiCell, the not-for-profit company UW set up to distribute the human and rhesus monkey ES cells derived by UW researchers. Skirboll said that the owners of several cell lines have promised to work with scientists.

The compromise seems to have slowed momentum in Congress for passage of a bill, sponsored by Senators Arlen Specter (R–PA) and Tom Harkin (D–IA), that would allow NIH also to fund work on the derivation of new cell lines. Robert Rich, president of the Federation of American Societies for Experimental Biology, which had lobbied hard for the Specter-Harkin bill, predicted that advocacy groups would ease up on their efforts, at least in the short term. Says Rich: "Most of us will take a deep breath for now and will wait for the 60-plus stem cell lines that the president says are available for research to appear."

Even if the research community gains access to all 60 cell lines, Philip Noguchi of the Food and Drug Administration says that it is very unlikely that any of the existing cell lines would be approved for clinical trials. That drives home one point in President Bush's speech: Despite the promise of ES cells, real treatments are still many years away. **–GRETCHEN VOGEL**

With reporting by Constance Holden, and Pallava Bagla in New Delhi.