Stem Cells: A Status Report

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ESSAYS

EDITOR'S NOTE

As stem cells move from basic science to clinical trials and eventually, perhaps, toward doctors' offices, questions about the moral status of the embryo give way to questions about the conduct of the research and the development of therapies. This special set of essays assesses the state of play in the science and in the new debates attending it.

Stem Cells:
A Status Report

BY STEPHEN S. HALL

Last October, during one of those periodic flurries of news that push the Stem Cell Wars back onto the front pages for a day or two, the telephone in the Harvard Medical School office of Dr. George Q. Daley kept ringing off the hook.

On one occasion, it was a reporter seeking Daley's assessment of a new technique for creating embryonic stem cells that had just been reported in the online edition of the journal *Nature*. Researchers in the laboratory of Rudolf Jaenisch at the Whitehead Institute in Cambridge, Massachusetts, had managed to clone a deliberately crippled mouse embryo, with the idea that if a genetically manipulated embryo lacked the ability to form a placenta and attach to the uterus, it would therefore lack the biological potential to become a mature creature. If the same trick worked with human embryos, Daley was asked, would this solve the ethical dilemma? He wasn't so sure. "The embryo that is established in the first few days," he pointed out, "is substantially normal."

Another reporter wanted to know what Daley thought about a second technique, also published in *Nature*, that sought to answer the ethical objections of stem cell critics. A team of researchers at Advanced Cell Technology in Worcester, Massachusetts, led by Robert Lanza, had found that at a very early stage of embryonic development, a single cell could be plucked away from an eight-cell embryo and used to derive mouse embryonic stem cells. Did this represent another alternative to the more "traditional" approaches to stem cell harvest, which require the destruction of human embryos and have thus aroused so much political and moral debate? Daley had his doubts about this one, too. The experiments, he said, "raise more questions than they answer."

And later that same week, researchers at Seoul National University in South Korea, led by Woo Suk Hwang, announced a plan to set up satellite labs in California and England to create, on order, cloned human embryos for the purpose of deriving customized stem cell lines. The Koreans, who had stunned the world in June 2005 with the report in *Science* that they had established eleven new human embryonic stem cell lines from cloned human embryos, now offered to franchise their expertise through a "World Stem Cell Hub." What did Daley think? "The details have yet to be divulged," he told the *Wall Street Journal*, "and the devil's in the details." (The details later became very devilish: soon thereafter Hwang withdrew from the initiative following reports of ethical improprieties in the group's egg harvesting program, and subsequently withdrew the *Science* paper amid allegations that some of the results were fraudulent.)

Having just set up a new stem cell laboratory at Children's Hospital in Boston, nothing would please Daley more than to devote all his time, energy, and expertise to

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the biology of blood-forming stem cells. But the continuing ethical controversy, superimposed on the considerable scientific challenges of making advances in the basic research, has left Daley, like many stem cell researchers in the United States, caught in a pattern of occluded political weather that impedes their work. More than four years after President George W. Bush announced a policy that restricted federal funding for embryonic stem cell research, scientists like Daley have been forced to create new laboratories from scratch to pursue research with "nonpresidential" stem cell lines, tap private sources of financial support, provide a Greek chorus of commentary to journalists on every tangential new development, and routinely travel to Washington to testify before lawmakers who have annually threatened but to date failed to legislate any changes in national policy. It has all added up to distraction and, most important, delay.

In 2002, Daley and Jaenisch published a significant advance in which they used mouse embryonic stem cells, obtained by cloning—technically, "somatic cell nuclear transfer"—to partially restore immune function in immune-deficient mice. "It's now three years later," Daley lamented, "and I am still struggling to gain regulatory approval through our institution to be able to do those experiments with human material. And the increased sensitivity around doing these experiments has led to *countless* hours and months of work on the part of many, many people, countless committee meetings talking about whether we have the right mechanisms in place to insure no federal money is spent on any 'nonpresidential' research, time spent picking through the finer points of how protocols are written so that you don't run afoul of these highly sensitized issues around egg donation, embryo donation—I mean, I could go on for *hours* about how cumbersome and arduous this process has been. And we *still* haven't been able to do the research."

Delay, some scientists are now arguing, is an ethical issue in and of itself. Stanford University professor Irving Weissman, a longtime proponent of stem cell research (as well as strict ethical oversight of it), finds it troubling to ask biomedical scientists to put basic research on hold and concoct alternative, politically palatable solutions to appease critics of the technology. "You are taking somebody else's life in your hands—those people who could have been helped in that narrow window of opportunity that they have. That," he added, "is the part that's morally unacceptable."

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A Long-Running Controversy

The continuing stalemate in embryonic stem cell research in the United States is tethered to two signal events. In November 1998, James A. Thomson and coworkers at the University of Wisconsin reported in the journal *Science* that they had isolated human embryonic stem (ES) cells from leftover embryos and created self-perpetuating colonies in culture. The news stirred enormous public excitement, given the cells' ability to "differentiate" into any of some two hundred distinct human tissues, from brains and brawn to skin and bones; that power, if harnessed, had the potential to revolutionize medicine and the understanding of disease.

The Thomson experiments simultaneously announced a scientific triumph and a bioethical dilemma, however, because human embryos (obtained, in this case, with the consent of donors from several in vitro fertilization clinics) had to be destroyed in order to start the ES cell cultures. To some people, the destruction of human embryos for research purposes was tantamount to murder; it also appeared to trespass upon legislation, inserted with minimal debate in a budget bill by Congressional Republicans in 1995, that banned federal funds for research in which a human embryo was damaged or destroyed. So the Thomson article in *Science* lit the fuse on an extraordinarily polarizing, three-year political debate in which social conservatives spoke of "embryo farms" for spare human body parts, while scientists and other proponents touted, perhaps too optimistically, the therapeutic promise of stem cells to treat dozens of diseases. That debate culminated in President George W. Bush's decision, announced on August 9, 2001, that the National Institutes of Health could issue federal research grants only for ES cell lines that had been created by that date.

According to many scientists, embryonic stem cell research has been held hostage—scientifically, bioethically, and financially—by the Bush policy. Although the president asserted that "more than sixty" ES cell lines existed, in truth less than a dozen were available to scientists for the first two years of the policy (the NIH Stem Cell Registry currently lists twenty-two lines). And with each passing year, the quality of many cell lines has deteriorated. Jaenisch echoed widespread scientific sentiment when he said, "They're *really* abnormal. Many people believe they have a lot of chromosomal rearrangements already, so it's sort of ludicrous to be con-

stricted to their use." Moreover, scientists used mouse cells to nourish the initial growth of the NIH-approved cell lines, which probably renders their clinical use in humans problematic due to potential contamination.

But the impact of the Bush policy does not stop at the laboratory bench. Shortly after August 2001, a number of academic institutions, medical research organizations, and foundations took steps to create privately funded stem cell institutes. Stanford University and the University of California, San Francisco set up separate, multimillion dollar biomedical institutes devoted to ES cell research. In 2004, Harvard University launched the Harvard Stem Cell Institute with plans to raise $100 million to support its research. At the same time, organizations like the Juvenile Diabetes Research Foundation and the Howard Hughes Medical Institute began to issue multimillion dollar grants to support research that went beyond the restrictions of the Bush policy. By contrast, in 2004, five years after *Science* magazine heralded embryonic stem cell research as the "breakthrough of the year," annual NIH funding for ES work amounted to $24.3 million out of an overall budget of close to $28 billion.

Recent polling data suggests that the current federal stem cell policy does not reflect public opinion. About 67 percent of Americans support embryonic stem cell research even though it requires the destruction of embryos, according to a survey reported last September by the Genetics and Public Policy Center at Johns Hopkins University. A breakdown of the survey results hint at the surprising breadth of that support. A majority of Republicans (55 percent) supported the research; 69 percent of Roman Catholics and 74 percent of Protestants did so as well. Even 50 percent of people who identified themselves as Fundamentalist or Evangelical approved of stem cell research. As authors Kathy L. Hudson, Joan Scott, and Ruth Faden noted, the survey "reveals a public opinion landscape that bears little resemblance to the polarized, deep moral divide expressed on the floor of the Congress and in the op-ed pages of American newspapers."

A recent survey hints at a surprising breadth of support for stem cell research: a majority of Republicans, Roman Catholics, Protestants, and even half of those identifying themselves as Fundamentalist or Evangelical support it.

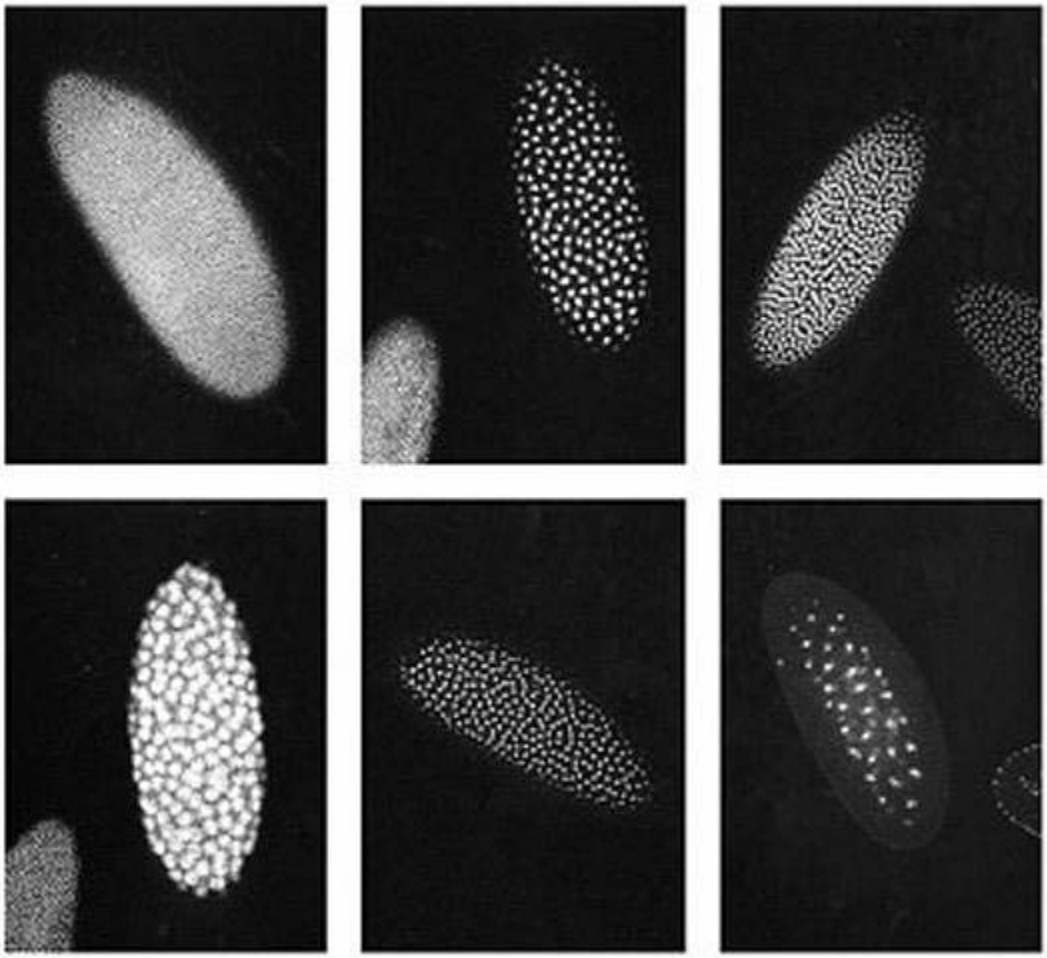
Indeed, the past calendar year passed without any substantive changes on the congressional front. Although the House of Representatives passed legislation (H.R. 841) in May 2005 allowing federal funds for research on new cell lines created from leftover IVF embryos, the Senate became bogged down in hurricane relief and other business and never voted on its version of the measure. Senate majority leader Bill Frist has reportedly promised to allow a vote by next Easter. Even if the Senate bill passes, however, its future is uncertain; President Bush has already vowed to veto it.

The climate of continuing controversy and uncertainty has chased money away from the field, leading to what Peter Lomedico, head of strategic alliances and industry partnerships at the Juvenile Diabetes Research Foundation, calls a "funding gap" in the stem cell field—one that affects not just embryonic, but also adult stem cell research. "There's a *lot* happening on the academic side, and some of it is pretty exciting," he said. "But what's very clear is that there's precious little money for companies to exploit this work, and so in the field there's a crisis, and we're right in the middle of it. We want to see things move into the clinic and into the market. With the combination of Big Pharma not spending any money and venture capitalists not funding it, the [biotech] companies are struggling and the transfer of technology is grinding to a halt."

Stem Cells as a States Rights Issue

With only a trickle of federal money to support work on cells of limited quality, stem cell research has inspired an unusual version of states rights. Several states have passed legislation earmarking funds to support the kind of research proscribed by the Bush policy, including the creation of new embryonic stem cell lines from leftover embryos destined to be destroyed by IVF clinics and the use of somatic cell nuclear transfer techniques, popularly known as therapeutic or research cloning, to create new stem cell lines. In January of 2005, the state of New Jersey announced plans to fund a $150 million stem cell research institute, with future plans to raise an additional $230 million. In May of 2005, Connecticut pledged $100 million over ten years to support stem cell research in that state. Illinois, too, has committed $10 million to support local stem cell research.

By far the most visible local uprising against federal policy occurred in California, however, where voters approved Proposition 71, a ballot initiative that created the California Institute for Regenerative Medicine and empowered the state to issue bonds equal to $3 billion to fund stem cell research over the next decade. The initiative passed by a margin of 59-



Cell Wall,
by Catherine Wagner,
1999-2000. 6 Iris prints,
46 x 34 inches each.
Courtesy of the artist.

to-41. So far, though, it too has become a monument to obstruction and delay.

More than a year after the passage of Proposition 71, the CIRM had yet to dispense a dollar in grant money. It has been hobbled on the one hand by lawsuits challenging the constitutionality of the ballot initiative, and bogged down on the other hand by a massive effort to reinvent the NIH's peer-review process, grant-making apparatus, and administrative structure at the local level.

The three lawsuits—filed by organizations that have ties to antiabortion or conservative tax groups—have had the practical effect of preventing the state of California from selling the bonds that would have funded the first year's round of grants. Robert Klein, leader of the Proposition 71 initiative and chairman of CIRM's governing Independent Citizens' Oversight Committee, has been forced to raise money through a separate strategy, the "Bond Anticipation Note." Klein hopes to raise $50 million by early 2006; CIRM anticipates that legal appeals in the court case may affect the state's ability to issue bonds perhaps until early 2007, according to an organization spokesperson, and the Anticipation Notes would fund grants until then. A superior court trial on the initial legal challenge is scheduled to begin February 27, 2006.

From afar, the California initiative seems dogged by controversy and delay; one out-of-state observer privately described its status as "on life-support," and even Klein recently charged that Proposition 71 was "held hostage by a small group that is politically opposed to stem cell research." But Nobel laureate Paul Berg, professor emeritus of biochemistry at Stanford, expressed optimism that the California initiative may be in better shape than it appears to outsiders. "Bear in mind," he said, "nothing existed [before Proposition 71]. Suddenly, on November 3, 2004, everybody woke up and said, 'Wow, how do we do all this?' The NIH has been doing this for fifty years. So this really took a lot of brainstorming and organizing." CIRM has now established three review committees—on science proposals and training grants, building and infrastructure, and ethical standards—and has approved about $12 million in training grants for postdoctoral fellows, graduate students, and trainees.

On November 29, 2005, a judge denied virtually all of the constitutional objections to Proposition 71, but the court case remained unresolved. If any legal challenges were to succeed, some observers fear that the language of the initiative might have to be reworded, which in turn might require voters to return to the polls to vote on the initiative all over again.

Politically Palatable Alternatives

In an attempt to break the fundamental bioethical logjam involving ES cell science, some recent research has attempted to devise technical solutions to the "embryo problem." But these efforts, to borrow a relevant term, may have arrived stillborn.

In 1998, Paul Berg and fellow biologist Maxine Singer, then president of the Carnegie Institute of Washington, had one of their informal annual meetings with clergy from the United States Conference of Catholic Bishops to discuss new developments in biology. This particular meeting came on the heels of the cloning of Dolly the sheep; nuclear transfer was a hot topic because cloned human embryos seemed possible. Way back then, Berg and Singer floated the theoretical possibility of genetically tinkering with a human embryo so that it would lack the biological ability to mature, thus allowing embryo research on an entity lacking any potential to become a human being. "In the end, the consensus was, you've just invented another way to murder," Berg recalled recently. "We had talked about that and we got shot down. They said that was not acceptable."

Nonetheless, the notion came back to life about a year ago, when University of Toronto researcher Janet Rossant identified an early developmental gene in mice, *Cdx2*, that controls the creation of the tissue known as the trophectoderm; without this gene, an embryo can't make a placenta and can't implant in the uterus. This gave new life to the idea, known as altered nuclear transfer (or ANT), that scientists could create a crippled embryo that would produce harvestable embryonic stem cells, but would be unable to continue its development. When Irv Weissman first heard about the research, he suggested Rossant get in touch with William Hurlbut, a member of the President's Council on Bioethics, who had been searching for a scientific technique that might break the ethical impasse. Even as Hurlbut pushed the idea last year at meetings of the Bush bioethics council, however, critics from both the scientific and social sides expressed serious misgivings. George Daley and several colleagues wrote a commentary for the *New England Journal of Medicine* in December 2004 that questioned the value of these alternative approaches. From a different perspective, members of the Bush bioethics council raised serious ethical questions about the techniques. Even a stem cell proponent like Michael Sandel of Harvard called ANT "morally creepy."

Despite signs of widespread opposition, several scientific groups pursued ANT strategies. Alexander Meissner, a member of Jaenisch's group at the Whitehead, began experiments to accomplish this around the beginning of 2005. The technique involves a variation on somatic cell nuclear transfer. Researchers take an adult mouse cell and temporarily suppress the *Cdx2* gene, robbing it of the ability to form the trophectoderm. Then these cells are inserted into mouse egg cells from which the DNA has been removed. The resulting embryo-like entities can't implant, but they *can* produce embryonic stem cells. Jaenisch calls these cloned embryos "knockdowns" because the *Cdx2* gene, although initially turned off, can be turned back on, and indeed it needs to be on for normal ES cell development.

The second alternative approach, reported by Lanza and his colleagues, begins with a technique that is already in place at many fertility clinics: preimplantation genetic diagnosis, or PGD. Starting with an eight-cell preimplantation embryo, researchers delicately pry a single cell, or blastomere, away from the rest of the embryonic mass; in IVF clinics, this single cell can be analyzed for potential inherited diseases while the remaining seven-cell embryo can be implanted to produce a pregnancy. In a research setting, Lanza showed that the single blastomere, when fused with existing embryonic stem cells, can essentially "reformat" itself and go on to produce ES cells.

Each of these techniques, hailed as potential breakthroughs when initially reported in the press last fall, poses considerable technical and bioethical hurdles. Time—and therefore delay—is certainly one of them. How long before either of these approaches might be reduced to practice with human material? "Both of them are years away," Weissman predicted. Another problem, especially with the Jaenisch technique, is what Weissman calls the "egg problem." Because the technique would ultimately require the use of human oocytes, it immediately reignites well-known ethical concerns about women who donate their eggs for such experiments, including their recruitment, informed consent, the medical risks of egg harvesting, and possible remuneration.

But perhaps the most significant shortcoming of the new derivation techniques is that, despite all the time it may take to perfect them, they likely will not make a difference in the bioethical debate. While praising the elegance and ingenuity of the recent ANT experiments, Dr. Markus Grompe, a Roman Catholic who directs the Oregon Stem Cell Center at Oregon Health & Science University, said, "I don't think either method, as described, is a completely, across-the-board acceptable way of doing this." In terms of specific objections, he said a problem with the blastomere approach is that even at the eight-cell stage, removing a single cell might be creating two embryos (one of which would be destroyed), since eight-cell embryos can naturally divide to produce twins. Grompe believes the *Cdx2* approach has more potential, but noted that some people would still consider the entity created by the technique an embryo. "I would say it's chipped away at the ethical problems in that it's provided a solution for some," he said, "but not for everyone." Indeed, Richard M. Doerflinger of the United States Conference of Catholic Bishops said in an e-mail that neither of the techniques is acceptable, adding, "It's not clear that either of these approaches fills the bill."

Many scientists view the ANT work as a fruitless digression. As Davor Solter noted in the *New England Journal of Medicine* in December 2005, "Playing politics for the sake of science is probably necessary and sometimes noble; manipu-

lating science for the sake of politics is usually a waste of time."

Into the Clinic

If the impasse over stem cell research remains essentially political, since conservative objections are backed by a threatened presidential veto of any alteration of current policy, then many believe the strongest agency for change will be a dramatic clinical advance. "An advance could change the way the issue is seen," conceded Larry Soler, vice-president for government relations at the Juvenile Diabetes Research Foundation. "But then the question is: How much are the limitations currently in place keeping that from happening sooner? It's kind of a chicken-and-egg thing."

Public opinion polls suggest that successful ES cell treatment of a serious disease like diabetes would significantly shift public opinion in favor of more relaxed federal policies. But how close are stem cell researchers to delivering on the promise that has been dangled so attractively before the public?

To hear most scientific observers, not very close at all. But that doesn't mean they won't try soon, and a battle is already shaping up—pitting stem cell companies and patient advocates on the one side against some doctors and bioethicists on the other—over what promises to be a particularly thorny issue in the next few years: what kind of safety precautions need to be in place before the Food and Drug Administration, and local medical institutions, allow a human trial of ES-derived cells to proceed? And what sorts of patients should be eligible for these experimental, and potentially dangerous, treatments?

Many experts believe that a clinical success for *embryonic* stem cell therapies is still a long shot. "With embryonic stem cells, it looks like we're a ways off from being ready for prime time in man," said the Juvenile Diabetes Research Foundation's Lomedico. Added Grompe, "Long-term, I think there will be some therapeutic benefit, but I mean *really* long-term. I think Proposition 71 is going to be old news by the time we have a success. I'm thinking ten years before we have an actual cure or benefit that's really tangible, and I'm being optimistic."

Nonetheless, several therapeutic situations appear likely to test the promise of stem cell therapies sooner rather than later. George Daley's group at Children's Hospital in Boston has been working on the idea of using ES cells derived from cloned embryos to create an entire new blood system from scratch, which could be used to treat classic childhood hematopoietic disorders, including immune deficiencies, Fanconi's anemia, sickle cell anemia, and thalessemia. This therapeutic reconstitution of the blood and immune system would essentially mirror the same effect achieved by the adult stem cells currently used in bone marrow transplants, but with a significant potential advantage—deriving ES cells from a cloned embryo, as Daley hopes to do, could provide immunologically compatible blood cells. Moreover, this approach has the added benefit of an enormous medical, scientific, and regulatory infrastructure that already exists around this form of therapy, since bone marrow transplants have been routine hospital procedures for decades—an advantage, Daley conceded, "that we are not unaware of."

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Another promising area for ES cells is the treatment of spinal cord injury. Hans R. Keirstead, a researcher at the University of California, Irvine, has been testing the ability of ES cells to repair spinal cord injuries in rats. In 2005, his group, working in conjunction with the biotechnology company Geron, reported that neural progenitor cells derived from human ES cells allowed paralyzed rats to partially regain the ability to walk after their spinal cords had been damaged. Keirstead said "everything is on track" in terms of preclinical safety studies, and Geron has announced its intention to begin clinical trials in 2006.

But this promising clinical intervention has also served as an advertisement for the bioethical rows to come. Last November, Geron confirmed plans to seek FDA approval to test neural derivatives of its embryonic stem cells in humans with spinal cord injuries. News accounts reporting this development quoted patient advocates who, not surprisingly, applauded this impending step toward clinical testing. But some doctors and bioethicists have expressed reservations about going directly from rodents to humans without testing the cells in nonhuman primates first—an expensive, time-consuming bit of preclinical research that could easily take two or more years. Arnold Kriegstein, director of the University of California, San Francisco's Institute for Stem Cell and Tissue Biology, told reporters, "There is a great potential for harm."

A somewhat different but related bioethical quandary seems to confront a proposed clinical test of fetal stem cells.

In October 2005, StemCells, Inc., of Palo Alto, California, announced that the FDA would allow the company to proceed on a phase I clinical trial to test the safety of its neural stem cells in children with Batten disease, an enzyme deficiency in neural cells that is invariably fatal. As of this writing, the protocol for the trial had not yet been approved by the institutional review board at Stanford University, one of the potential sites, and university officials were unusually tight-lipped about the pending trial.

The Batten disease trial raises a particularly sensitive ethical issue: testing the safety of a highly experimental stem cell treatment in children. While he said he was "not at liberty to discuss" particulars of the Batten disease protocol, University of Stanford bioethicist David Magnus argued that in general, if the research poses more than incremental risk to a patient, there had to be a legitimate prospect of therapeutic benefit before children could be treated. "My view is, for almost all these techniques, that they would not meet that standard for a prospect of benefit. . . . When you have front-line, cutting-edge research, I'm very concerned that we are seeing a repeat of gene therapy—very thin, 'just-so' stories told about clinical benefit, but with very little chance of things happening to benefit patients."

The short-term prospects for success may be better with adult stem cells, although success there could have ethical and political implications for ES cell research. Dr. Joshua M. Hare, a cardiologist at Johns Hopkins Medical School, is heading a six-center, placebo-controlled clinical trial, in conjunction with the Maryland biotech company Osiris Therapeutics, Inc., testing the safety of stem cell therapy for heart attack victims. In the study, begun last March, adult mesenchymal stem cells isolated from human bone marrow donors are given intravenously. Experiments in pigs have demonstrated that these cells home in on damaged tissue and affect "profound reduction" of scar formation and "near-normalization" of cardiac function following a heart attack. In a surprising scientific twist that has implications for the debate over therapeutic cloning, animal experiments have suggested that the infused adult stem cells do not provoke an immunological response, even though they come from an unmatched donor. Although the human trial is still in progress, Osiris recently reported that safety monitors reviewing the first group of cardiac patients approved the use of a higher dosage of cells, suggesting that immunological reactions have not to date produced serious side effects.

Anthony Atala, Mark Furth, and their colleagues at the Wake Forest Institute for Regenerative Medicine in Winston-Salem, North Carolina, are testing the potential of nonembryonic but developmentally early stem cells to differentiate into functional cells. Although the work is still confined to animals at this point, they are exploring the ability of fetal stem cells isolated from the amniotic fluid and placenta to mature into cells that might serve as replacement tissues in the treatment of disease.

Successful adult stem cell therapies will no doubt bolster the argument of those who maintain that there's no need to destroy embryos for ES cells because adult stem cells are sufficient (Hare, like many researchers, insists both approaches must be pursued). Further, some of these early clinical trials are proceeding at great speed and have the potential to create high-profile mistakes that may cast a cloud over the entire stem cell field. Hare noted, for example, that American patients and doctors are currently traveling outside the U.S. to test experimental stem cell treatments. "In Ecuador," he said, "fetal stem cells, obtained in the Ukraine, are being used to treat patients from the U.S. There are cowboys who want to do this, and are going to do it."

"There's a bit of a Wild West mentality out there," agreed Lomedico. "A lot of clinicians, and mostly surgeons, are driving the work into man, and it's just wild."

Five Years and Counting

When *Nature* published the two new stem cell derivation techniques last October, William Hurlbut told the *Washington Post*, "This is just the beginning of the conversation. It's time for everyone to humbly enter a constructive dialogue and listen deeply here."

In truth, doctors, scientists, patients, and indeed many bioethicists are growing weary of all the talk. There is evidence that neither the public nor the scientific community has an infinite appetite for delay. One of the surprising findings in the Hopkins opinion poll is that the clock on public patience is ticking on how long people are willing to delay progress in medical research to find sources for stem cells that circumvent the destruction of embryos: nearly half (48 percent) wanted no delay, while 9 percent were willing to wait one year, and 12 percent were willing to wait five years. But to hear some tell it, the research has already been held up that long.

It was five years ago that George Daley and Rudy Jaenisch completed the experiments demonstrating the proof of principle of therapeutic cloning in mice. "To think that five years later we're not yet able to even get started in the human," Daley said, "is pretty much a testimony to the effectiveness of the Bush policy in delaying what clearly the international research community considers vital research."