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Stem Cells: Saving Lives or Crossing Lines

Human Embryonic Stem Cell Research

Controversy has surrounded human embryonic stem cell (ESC) research since the creation of the first cell line in 1998. From the beginning, these small clusters of cells, obtained five to six days after fertilization, provoked as much excitement about their potential to unlock the mysteries of human development as shock about the use of fertilized human eggs for research. On one hand, ESCs have the potential to cure debilitating diseases such as Parkinson's and juvenile diabetes as well as treat injuries such as burns and spinal cord injuries. However, some say that using fertilized human eggs for research is immoral and can lead to an even more abhorrent act: the cloning of a human being. In the United States, this debate has resulted in a policy that allows partial federal funding of ESC research with limited governmental regulation over privately funded work.

In addition, during the past four years since this policy was implemented, research on human ESCs has stagnated in the United States due to significantly fewer cell lines being available than announced, contamination of cell lines with mouse cells, and a lack of genetic diversity within the lines. With the March 2004 publication in *Science* magazine of a procedure to generate human ESCs using somatic cell nuclear transfer (SCNT) by a South Korean research team, it is becoming evident that our country will no longer be leading the field of stem cell research. Without changes in the current policy, significant health benefits and intellectual capital, as well as investment capital, will be transferred from the United States to other nations, such as South Korea or the United Kingdom, that have more tolerant research policies. Some states, such as California and New Jersey, have begun to promote ESC research by funding areas the federal government has declined to fund. Other states, including Texas, have yet to determine where they stand on the issue and thereby run the risk of losing talented researchers and scientists to states and countries with more open policies.

To discuss these issues, as well as the role of the United States in stem cell research, the James A. Baker III Institute for Public Policy convened a two-day conference titled "Stem Cells: Saving Lives or Crossing Lines" November 20–21, 2004. Conference sponsors included the Baker Institute, the Richard Lounsbery Foundation, the University of Texas M.D. Anderson Cancer Center, the University of Texas Health Science Center at Houston, and Baylor College of Medicine.

The conference involved public presentations and discussions among more than 30 top leaders in science, public policy, ethics, advocacy, and business. Topics covered were the current state of stem cell research, ethical concerns and debates, media and public perceptions, international and U.S. policies, and the per-

spective of business leaders. The event itself brought in more than 200 policymakers, scientists, ethicists, opinion shapers, business leaders, and interested citizens. This conference report will address the current state of ESC research and the need for new public policy to address ethical concerns.

What Are Stem Cells?

To start the conference, Lawrence Goldstein, professor of cellular and molecular medicine at the University of California, San Diego School of Medicine, provided an overview of the basic definitions and uses of stem cells.

As reviewed by Goldstein, stem cells are cells that have the potential to replicate themselves for indefinite periods and the ability to divide into identical cells or into cells of a different type (a process known as differentiation). In humans, stem cells have been located in the early stages of development after fertilization (ESCs), the umbilical cord, the placenta, and several adult organs (adult stem cells). Regardless of their source, all stem cells have two general properties. First, stem cells are capable of dividing and renewing themselves for long periods. Unlike muscle cells, blood cells, or nerve cells, which do not replicate themselves, stem cells can divide continuously and keep their innate characteristics. The second property of stem cells is that they are undifferentiated, but remain totipotent, which means they all retain the potential to develop into multiple cell-types. Stem cells do not have any tissue-specific structures that allow them to perform specialized functions, but they can give rise to differentiated cells, including red blood cells and nerve cells that do perform specialized functions.

There are two main types of stem cells, embryonic and adult, that vary in their ability to differentiate. ESCs can give rise to any other cell-type of a given organism. Alternately, adult stem cells give rise only to cells of a given tissue type or to a few additional cell-types.

Many scientists are interested in this new area of research due to the potential of stem cells to offer a new look at old problems and diseases such as spinal cord injury and diabetes. Although the field is relatively new, the impact of new discoveries could profoundly change medical research and therapy. Advocates propose that stem cells could be used to produce tissues or organs to replace damaged ones, to understand and combat disease, and to test and develop new drugs.

Many of these new approaches involve the use of SCNT—also known as therapeutic cloning—to produce recipient-specific tissues by creating ESC lines. In SCNT, the genetic material (nucleus) of an unfertilized egg is removed and replaced with the genetic material (nucleus) of a normal or somatic cell from the body, i.e., a skin cell from a donor. The egg is then activated by chemical or electrical means and allowed to divide and proliferate, growing into a blastocyst five to six days later. The blastocyst is a minute hollow sphere containing a central mass of approximately 64 cells. Viable ESCs are obtained from the inner cell mass of the blastocyst, and these can then be used to develop new ESC lines or induced to become other differentiated cell-types. Much of the promise for ESCs lies in the potential of deriving or creating cell lines, which are specific to a human patient. Thus, SCNT can be used to create cell lines characteristic of individuals to study specific genetic diseases and potentially create tissues that are compatible with the original donor.

As pointed out by speaker James Battey, director of the National Institute on Deafness and Other Communication Disorders (NIDCD) at the National Institutes of Health (NIH), there are several matters that would have to be addressed for this new area of research to advance. Standard conditions need to be created that obviate the need for mouse or human feeder cells. New tools and technologies are necessary to further characterize stem cells as they become specialized. Molecular pathways should be defined

to allow differentiation into particular cell-types. Factors and conditions critical for long-term survival and function of transplanted cells need to be identified. Finally, researchers need to understand what controls cell division, because this process is essential to expanding cells before specialization and regulating them after transplantation.

This new area of research has great potential, but it is not without its controversies. Many ethical dilemmas arise concerning the creation and use of human blastocysts for research purposes as well as the potential that an attempt might be made to clone an entire human being (commonly referred to as reproductive cloning). In order to determine whether adult or embryonic stem cells hold the key to new disease discoveries and therapies, more experiments need to be performed. In Goldstein's opinion, "the way we resolve these things [questions] in the scientific community is by doing more experiments and getting more data, not by deciding to do one thing or another or prohibiting one line of experimentation or another." But no matter where society designates the boundary to be for this research, or whether stem cells can live up to their high expectations, a great deal can be learned through careful and thoughtful studies.

Embryonic Stem Cell Policy in the United States

Neal Lane, Rice's Malcolm Gillis University Professor, professor of physics and astronomy, and Senior Fellow in Science and Technology at the Baker Institute, presented an overview of the U.S. policy on embryonic research.

Embryonic research regulation began in the 1970s when the code of federal regulations was amended to include a section allowing for research to be performed on human embryos for in vitro fertilization (IVF). This law authorized an ethics advisory board, which only met once before being dissolved in 1980 without ever federally funding any embryonic research. In 1993, the rule was rescinded.

Later, regulation of embryonic research was replaced by the Dickey Amendment, which first appeared in 1996 as a Department of Health and Human Services (DHHS) appropriation rider. Each year, this amendment has been attached to the appropriation bill for DHHS (which oversees NIH), thereby prohibiting federal funding for embryo research or embryonic stem cell research. However, private funding of research on embryos has been allowed and is completely unregulated.

In February 1997, a group of researchers at the Roslin Institute in the United Kingdom, led by Ian Wilmut, announced the creation of the first cloned mammal, a ewe named Dolly, using SCNT. This landmark event and the media attention it received created an immediate reaction from the public and politicians in Washington, D.C., who became concerned about the potential cloning of humans using this technique. After Dolly, President Clinton charged the National Bioethics Advisory Commission (NBAC) to study the issue of human cloning. In June of that year, NBAC released a report addressing reproductive cloning, stating that it was "morally unacceptable for anyone in the public or private sector, whether in a research or clinical setting, to attempt to create a child using somatic cell nuclear transfer." Taking the NBAC suggestion, President Clinton offered a legislative proposal to bar anyone, either federally or privately funded, from attempting to clone a human through SCNT. In addition, Clinton intended that the law should be written so it would not interfere with biomedical research.

In November 1998, the researchers at the University of Wisconsin–Madison, led by James Thomson, announced the derivation of the first human ESC line. With this new breakthrough, the issue of human cloning became considerably more complex since SCNT could now be linked to potential disease-curing research. After the announcement by Thomson's group, Washington politicians started to readdress the issue of human cloning and embryonic research.

NIH and the legal council for DHHS determined that federal law (the Dickey Amendment) prohibited the use of federal funds to create human ESC lines, but that it was legal to fund research on already existing lines created with nonfederal money. Clinton agreed with that position. Since no barriers existed on privately-funded research, private sources could be used to derive the ESC lines. Public funding could then support further research on those lines. NIH released guidelines for the federal funding; however, before NIH was able to grant money, the Bush administration was elected to office, and the previous rulings by DHHS and NIH were set aside.

One of President George W. Bush's first actions in office was to stop, temporarily, all federal funding of human ESC research while his administration considered its position on the matter. On August 9, 2001, Bush announced that he would allow the federal funding of the research of human ESCs, but only for lines that had been derived before the date of the announcement. Thus, no new human ESCs could be created with federal funds, nor could federal funds be used to do research on new lines created after August 9, 2001. NIH estimated at the time that there were as many as 60 cell lines available for research; however, since that time, NIH has revised its numbers downward. The current total now is only 22. As before, no restrictions were placed on privately-funded research.

Current Advances in Stem Cell Research

Even before the derivation of human ESCs in 1998, work performed in the field using mouse cells was paving the way for current research on human cells. Previous work demonstrated the ability of scientists to direct ESCs toward the production of neurons, cardiomyocytes (heart muscle cells), hematopoetic (blood) cells, hepatocytes (liver cells), bone cells, cartilage, and beta (insulin-producing) cells of the pancreas. In his keynote address, Jose Cibelli, professor of animal biotechnology at Michigan State University, gave a review of how the field is proceeding in the differentiation of mouse and human ESCs to different cell-types. Other scientists who spoke about research being done in their labs were Julia Polak, professor of endocrine pathology at Imperial College London; Steven Goldman, professor and chief of cell and gene therapy at the University of Rochester Medical Center; James Willerson, president of the University of Texas Health Science Center at Houston; Stephen Minger, director of the Stem Cell Biology Laboratory in King's College in London; and Thomas Okarma, president and chief executive officer of Geron Corporation.

Neural Tissue

In the past decade, research has shown that ESCs have great potential to differentiate into neuronal stem cells. Cibelli described previous research, which found neural markers on differentiated human ESCs. Other scientists used mice ESCs to study neuronal differentiation and Parkinson's disease. In addition, Minger discussed the successful transplantation of a stem cell graft in a patient with Parkinson's. Although the recipient had improved health, it took 12 to 15 fetuses to treat one patient, making a similar ESC treatment more appealing since a vast number of cells can be produced from a single blastocyst. In Goldman's opinion, the limitations of human ESC therapy on the brain and spinal cord include insufficient understanding of how to direct production of specific cell-types, the lack of purity of desired cell-type, the persistence of undifferentiated ESCs, and the inability to establish appropriate connections with original tissue after implantation. Despite these limitations, Okarma's company, Geron, has injected glial progenitor cells (a type of brain cell derived from ESCs) into mice with spinal cord injuries and shown an improvement in the functioning of the injured mice. Although this technique can be used only in a 7-to-10-day window after the injury, it

nonetheless demonstrates the reengineering of the damaged tissue, specifically the spinal cord. Okarma suggested that "these high-value therapeutics, we hope, will fundamentally change the course of the disease by reversing or correcting the fundamental damage at the tissue."

Cardiomyocytes

Human ESCs also have been differentiated into cells with cardiac-specific genes and transcription factors that can produce spontaneous contractions similar to cardiomyocytes. This is of particular interest in the biomedical community because as Willerson, of the University of Texas Health Science Center, stated, "heart disease and vascular disease are major killers of our time."

At Geron, cardiomyocytes, which have been derived from ESCs and elicit expected responses to certain drugs, have been added to mice with injured hearts due to heart failure. Heart function improved after two weeks. Researchers also have observed long-term survival in the damaged tissue area, because of embryonic traits of the "healing" cells. However, tenfold more cells are needed for this therapy than for the spinal cord repair.

Willerson presented the recent work he and others have done using adult stem cells to repair chronic heart failure. They treated heart disease by injecting patients' bone marrow-derived stem cells directly into their hearts. German and American scientists have shown that patients who have suffered heart attacks have improved blood flow and heart function after the adult stem cells are injected. Although Willerson had some success with adult stem cells, he agreed with other speakers that adult stem cells are "clearly good enough for certain purposes and yet limited in some ways." Willerson contends that "embryonic stem cells . . . will be necessary to do everything we want in tissue repair, even replacement of an organ."

ß-cells

Diabetes is a serious disease with side effects including heart disease, stroke, blindness, kidney disease, and amputations when left untreated. One of the uses of stem cells is the creation of new ß-cells—insulin-producing cells—to replace destroyed or damaged cells in the pancreas. As with many fields in science, most work progresses after a set of standards is established. In 2003, Douglas Melton, of the Howard Hughes Medical Institute at Harvard University, created certain criteria for cells to be labeled ß-cells. Cibelli, of Michigan State University, said that the most promising results thus far in ß-cell differentiation have been seen in Spain, where a group led by Franz Martin differentiated mouse ESCs into insulin-producing cells. These cells, when grafted into mice, normalized their hyperglycemia.

Other work is progressing in the field. Okarma talked about research at Geron where human ESCs were differentiated to produce cells that exhibit pancreatic islet-specific hormones and respond to glucose levels by producing insulin. These cells still need to be fully purified and fully characterized.

Other Tissues

While much new research has been conducted on differentiating ESCs to neural, heart, and ß-cells, there are other tissues and cell-types ESCs can be used to create. Several research groups have produced hematopoetic (blood) cells and determined genes involved in their differentiation. This technique for derivation has been efficient and potentially can be used as a source of cells for transfusions or transplantation therapies in the future. In mice, ESCs were differentiated into hepatocytes (liver cells) in vivo and in vitro, while human cells have been generated that look like mature hepatocytes. In addition, mouse ESCs were differentiated into cartilage cells, which expressed the appropriate set of genes and proteins.

Future Embryonic Stem Cell Research

ESCs have great potential for uses in regenerative medicine. Regenerative medicine is the concept that new tissues can be implanted in patients with damaged or diseased organs. In the case of stem cell research, ESCs could be differentiated into a specific cell-type, such as a neuron, and be used to repair a site of injury. It was the hope of Battey, from NIDCD, that "someday regenerative medicine will be a mainstay technology and that it will be, in fact, the tool that will allow us to do something about these awful diseases." However, Polak, of Imperial College London, pointed out that there are many challenges in regenerative medicine: specifying and then purifying cell types; creating genetic stability; understanding timing, dosage, and delivery; understanding issues associated with immunology and immune rejection; finding methods for visualization; finding procedures for engraftment; choosing animals for experimentation; and maintaining clinical safety. Like Battey, she also is optimistic and noted that many fields are starting to converge. She sees "people working on bone marrow, working on embryonic stem cells, working on adult stem cells, fat cells, cord blood, and the people working on producing decent materials, converging to create what will be the future of medicine—regenerative medicine."

A new area of ESC research is using SCNT to produce cells that are identical to the donor source. Scientists at Seoul National University in South Korea, led by Woo Suk Hwang, pioneered this work in humans in 2004. Their research generated cloned human blastocysts, which shows evidence that a human ESC line could be a perfect match to the woman whose DNA is used. In the experiment, SCNT was conducted on the eggs from 16 women, producing only one human ESC line. It was noted that the cell silenced somatic cell genes and activated embryonic ones. According to Minger, of King's College in London, researchers in China and South Korea have been working toward human ESC treatment by practicing techniques in sophisticated facilities. From his observations, there were 35 human ESC lines in Seoul, Korea alone. Since the conference, the South Korean researchers reported, in May 2005, improved SCNT rates of 35.4 percent, which was more than 10 times higher than the 3.3 percent from their 2004 study.

In the United Kingdom, Minger and his team are leading the field. They received a license from the Human Fertilisation and Embryology Authority (HFEA) to use IVF embryos, half of which are normal and the other of which have some genetic disorder. Those with genetic disorders are used for study in the development of such cells. According to Minger, their goal "is to generate somatic stem cells from human embryonic stem cells that we could expand in culture, to get away from some of the problems—that Steven [Goldman] talked about, and others—in terms of teratomas. . . . We want to generate these very large populations for cell therapy." He also warned that Americans "stand to lose a lot because [the Koreans and Chinese] are moving very fast."

Before these ESC-derived tissues can be used in human patients, there are scientific challenges and certain standards that these cells must meet. Cells have to proliferate extensively and generate sufficient quantities of tissue, differentiate into the desired cell type, survive in the recipient after transplant and integrate into the surrounding tissue, function appropriately for the duration of the recipient's life, and not harm the recipient in any way. In the opinion of Goldman, of the University of Rochester Medical Center, "It's important to realize that just generating the proper cell type in vitro, even when it's generated to purity, is not going to be good enough to take care of any of the clinical disorders."

Cibelli concluded by pointing out that, in the end, "after you see the work that we need to do . . . [you see that] we don't have the funds and [that] it's a legal minefield." He questioned: "Why in the world do you really want to get into this research?" His personal

reason for continuing is a friend named Irv who suffered a severe spinal cord injury. This, Cibelli said, is the only "reason why we should be doing this."

The Ethics of Human Embryonic Stem Cell Research

The field of ESC research has created excitement in the hearts of many individuals struck down by debilitating illnesses and injuries. But there are those who consider the use of fertilized human eggs for research an abomination that should not be performed regardless of the cures that might be obtained. Such dramatically differing opinions have opened a debate across the country about the role the federal government should play in these controversial research subjects. Three speakers at the conference gave differing ethical and moral views on the subject: John Robertson, Eric Cohen, and Rebecca Dresser. Robertson, the Vinson and Elkins Chair at the University of Texas School of Law, argued that the current policy was arbitrary and should be reversed, allowing ESC research to proceed with federal funding. On the contrary, Cohen, the director of the Biotechnology and American Democracy Program at the Ethics and Public Policy Center, a conservative think tank in Washington, D.C., said that he believes that Bush made a compassionate decision to allow some federal funding. Cohen stated that the August 9, 2001, date should stand, and no more ESC research should be funded. The final speaker, Dresser, the Daniel Noyes Kirby Professor of Law and professor of ethics in medicine at Washington University as well as a member of the President's Council of Bioethics, promoted the need for open and respectful dialogue, with the best outcome involving all sides finding common ground to improve the state of biomedical research.

The Right to Research

Robertson said that he believes there were two views on embryonic research: Blastocysts are moral subjects, or they are "too rudimentary in development to yet have rights or interests." It was Robertson's opinion that "the preimplantation embryo, which consists of undifferentiated cells . . . is not clearly an individual." He also went on to assert that the arguments were not "compelling or persuasive that the early embryo is either a person or, because of its potential, has a claim on us that we owe duties to."

The August 2001 decision by Bush stated that if the embryo or blastocyst already was destroyed and ESCs already were derived, it was acceptable to use them. Robertson's analysis was that Bush was approving the use of cell lines resulting from someone else performing the moral wrong, and therefore it was acceptable to use the resulting cell line. Because of this reasoning and what Robertson said that he felt was an arbitrary date restricting ESC lines, he argued that the government should allow federal funding for all ESC lines created, even after August 9, 2001. Robertson added that, although the government should take into account minority views, they should not push those views on the majority.

Robertson also considered the bans on SCNT and reproductive cloning premature. Furthermore, he maintained that "if reproductive cloning was shown to be safe and effective . . . there are some serious questions about whether it should be banned." It could have valid uses in helping people with fertility issues. He also proposed that any federal ban of ESC and cloning research was unconstitutional due to the Commerce Clause, the Fifth and Fourteenth Amendments to the U.S. Constitution for the "right to life," and the First Amendment for the "right to research."

One of Us

Cohen started by speaking about the role of politics in science. Although he abhorred the distortion of science, he advocated the discussion of scientific projects, risks, and ethics while staying true to the scientific facts. The debate from the 2004 elections raised

essential questions, he said, and forced Americans to discuss the meaning of our ideals as well as discuss life, human development, and genetic manipulation. Cohen disagreed with the majority in the scientific community regarding ESC research. He argued that scientists should not "sacrifice human equality in the name of medical progress."

In his comments on the embryonic research debate, Cohen said that he perceived four groups. He described the "let's roll" scientists as eager to make advances and as viewing the embryo as a clump of cells. His second group, the "enlightened" liberals, believes scientists should be allowed to do their research with only minor regulations. The third group, the "mysterious" moderates, consider the embryo a mystery and somewhere between a human and a mere clump of cells. They think that we should keep some restraints and regulations on scientists. He defined the final group as the "one of us" conservatives who regard the embryo as a vulnerable person. Members of this group are grounded in faith and biology that shows the continuity of life from conception to birth and beyond. Cohen questioned whether we will "become a better society or a lesser society if we engage in a systematic program of embryonic destruction."

Cohen expressed the hope that there might be a way to work around the ethical issues. There were some proposals to create embryo-like entities for ESC research or use embryos that have arrested and no longer can survive in vivo. Although it is unknown how practical these ideas are, further discussion should be considered. That aside, he supported the current policy, a policy of silence, which keeps the government out of most ESC research. He said that he believes that, as a society, we can determine the role of the federal government, and that, in his opinion, should be to avoid research on the human embryo.

Research with Consequences

The last ethicist to speak was Dresser. She discussed the moral status of the embryo and how to address its intermediate status between a simple cell or tissue and a full human. One proposal was to allow extra embryos from IVF clinics to be used for research purposes, but to forbid the creation of new embryos. This would only be permitted if the scientist justified the purpose and essentialness of using the embryo. But Dresser expressed concern that this could lead to the objectification of women—women being used as a means for producing embryos. The procedure for obtaining eggs for IVF is extremely difficult and can lead to serious harm or death in women. NBC chief science and health correspondent, Robert Bazell, who spoke on a later panel, confirmed that the American Association for Reproductive Medicine set a $10,000 ceiling for reproductive eggs from a woman, because offers to pay women were steadily increasing. He also noted that ads for eggs from women with high SAT scores already can be found on college campuses.

Dresser also advocated the truth-telling duties of scientists and science advocates as well as the need to respect public deliberation. ESC research is in its early stages, and cautious language should be used about therapies since none are proven yet. Exaggerating the speed and likelihood of curing a particular disease at this point is unwise and disrespectful of patients. Overall, unrealistic optimism is bad for science. Saying cures will be quick when they may take years or decades could hurt science funding in the future.

Dresser also warned that, with all the difficult issues the country has to address, such as the large population of uninsured individuals, spending more money on ESCs may not be our highest priority as a society. Our limited resources may need to be divided in order to serve the best purpose. She questioned whether this money should be spent on global health issues such as AIDS, tuberculosis, and malaria. In the end, these ESC therapies and treatments may be too

expensive for the majority of the world population to have access to them.

It is Dresser's hope that the prolonged debate on ESCs will foster more respect and accommodation in public deliberations. She said that she believes that we must "accept that arguments over U.S. federal research policy will be resolved through the democratic process." In her opinion, the best outcome that she could imagine would be "for different factions in this debate to try to find some common ground, affecting research and healthcare strategies to help people coping with disease."

Media and Public Perceptions

The public perceptions of stem cell research and the ethical dilemmas that shape the current public debate are predominately formed by the media. With such a complicated subject in the early stages of research and not yet defined entirely in the minds of scientists, it is easy to confuse even the most eager citizens yearning to learn about the subject. A group of distinguished journalists, advocates, and media experts at the conference discussed their insights on how the media and public perceived this complex issue.

In general, when ESC research was broached to a naïve and uninformed audience, the reaction of using fertilized human eggs for research was not positive, explained Matthew Nisbet, assistant professor in the School of Communication at Ohio State University. Previously, Leon Kass, chair of the President's Council on Bioethics, described this reaction as the "Yuck Factor." Kass defined it as a "visceral repugnance" and "emotional opposition" felt by many members of the public when they first hear about biomedical research involving human embryos. Kass went even further, saying that the repugnance is an "emotional feeling of deep wisdom" that leads an individual to "intuit and feel, immediately without argument, the violation of things that we rightfully hold dear."

Although there may be this instinctive reaction to say "no" to embryonic stem cell research, Nisbet believes that with more information the public can be swayed. Mary Woolley, president of Research!America, agreed with Nisbet. She believes that "people want more information about research, and they want it from reliable sources." The only setback, Nisbet believes, is the fact that individuals are "cognitive misers" and they "select and sample from the media coverage" ideas that match with their predispositions, specifically their religious beliefs and ideology, during the ESC debate. This idea was validated by the campaign for Proposition 71 in California in November 2004. As advocates for stem cell research—such as the Juvenile Diabetes Research Foundation (JDRF), headed by speaker Peter Van Etten—spent money advertising their side of the issue, support for the proposition in the general public increased. By the election, 82 percent of the voters were aware of the issue and the proposition passed with 59 percent of the vote. Although Woolley agreed with Nisbet, she feels that "the important thing here . . . is getting more information to the public and engaging in a dialogue with them."

Unfortunately, the issue was complicated by the fact that it turned from a scientific discussion to a broader ethical and morality-based discussion. This caused the issue to be politicized and, as perceived by Rome Hartman, producer for *60 Minutes* on CBS, "the bulk of reporting on embryonic stem cell research . . . has not been done by the medical or science correspondent," but by the White House or political correspondent. Policy is discussed only during crises, Hartman commented. We talk about vaccines when there is a shortage of flu vaccines. We talk about the drug approval process when a drug is taken off the market. This leads to short-term discussions about complex issues, which, in turn, leads to the topic being reported by correspondents with limited knowledge about the science they are covering. The issue also was celebrity-driven, with actors

such as Michael J. Fox, Christopher Reeve, and Brad Pitt lending their voices in support of a particular side. Because nonscience journalists reported the issue, in Hartman's opinion, they often became lazy and did not research the topic enough. Hartman argued that, because journalists "have to find a way to make things understandable in a short period of time, it demands that we do even more research and more homework and have a better and more comprehensive understanding of the issue ourselves, so that when we do boil it down to its essence, we really capture the essence rather than . . . a caricature."

Further complicating the challenge of bringing complex information to the public is the over- and under-promising by both sides of the discussion. Bazell, chief science and health correspondent for NBC News, was "astounded by the ignorance of scientists." He found that there was confusion about what you can do with adult and embryonic stem cells, the need for therapeutic cloning, and its role in curing diseases. In addition, Bazell urged scientists to avoid overselling. Hype is not new, nor will it go away. Bazell gave the example that, "in 1892, a young surgeon named Roswell Park went before the New York state legislature . . . and said, 'If you give me $10,000, the cure for cancer is just around the corner.'" Bazell also pointed to Nixon's "War on Cancer" in the 1970s. Although hype is not new, it is never good for science in the long run. Van Etten, president and chief executive officer of JDRF International, agreed. He stated, "We need to be very careful not to raise expectations unrealistically while, at the same time, trying to gain public support for technology which we think could be of enormous value to us."

Embryonic Stem Cell Policy and Regulations in the United States and United Kingdom

President Bush's August 9, 2001, executive order regarding ESC policy has led us into in disjointed regulation. NIH is permitted to fund a limited set of experiments, regulated and approved by the federal government, while the remaining vast majority of ESC research in the United States is relatively unregulated and being carried out by private industry, states, and other organizations. At the conference, two speakers—James Battey, director of NIDCD and chair of the Stem Cell Task Force at NIH, and Gregory Glover, partner at Ropes & Gray LLC—discussed current federal and state ESC policies. To provide an outside perspective on ESC research regulation, Suzi Leather, chair of HFEA, and Lord Naren Patel, chair of the U.K. Stem Cell Bank and chair of the House of Lords' Steering Committee on Stem Cells, spoke about their experiences with regulation in the United Kingdom.

U.S. Federal Funding of Embryonic Stem Cell Research

Battey reviewed the current policy and granting opportunities at NIH. As of fall 2004, 78 ESC derivations are eligible for federal funding, of which 22 are officially derived and accessible to NIH researchers. In 2003, NIH awarded eight infrastructure awards to generate 20 ESC lines (these companies had already derived inner cell masses before August 9, 2001), 26 investigator-initiated awards, 67 administrative supplements, three pilot and feasibility projects, two postdoctoral fellowships, six training grants (five were short-term cell culture training courses), and three Exploratory Center research grants. In addition, the Centers of Excellence for Translation Stem Cell Research were working to create multidisciplinary teams of stem cell experts, clinical researchers, and transplant surgeons to work together in the near future when stem cell technologies are available. Furthermore, NIH supports research on many types of adult stem cells where other breakthroughs may be made. Overall, NIH awarded $109.7 million to nonembryonic stem cell research and $24.8 million to embryonic stem cell research in FY 2003. Of course, this was from a working budget of approximately $25

billion. In comparison, Cibelli, from Michigan State University, pointed out that California proposed to spend $300 million in 2005.

In addition, NIH has plans to establish the National Embryonic Stem Cell Bank. This cell bank would be a ready source of human ESCs that could be compared, expanded, and made available to NIH-supported scientists. It also would be able to ensure consistent quality and reduced costs for those on the NIH registry and be used to deliberate on matters of intellectual property rights.

Regulation of Embryonic Research

Glover reviewed the current state of embryonic research regulation on the state and federal levels. He described several means to regulate embryonic research in the United States. Research can be regulated by the allocation of federal or state research funds and federal and state laws encouraging or discouraging it. Current regulation in the United States has focused on IVF embryos, embryos created by SCNT, and aborted fetuses and embryos.

Besides the presidential executive order in 2001, the Dickey Amendment on the DHHS Appropriations Bill restricted all federal funding of stem cell research. It defined a human embryo as "any organism, not protected as a human subject . . . that is derived by fertilization, parthenogenesis, cloning, or any other means from one or more human gametes or human diploid cells." In addition, the Federal Drug Administration (FDA) regulates adult and embryonic stem cells that will be used in human testing.

On the state level, there are three different approaches to regulating ESC research. One set of laws encourages ESC research. Examples of this are found in California (Proposition 71 will raise $3 billion in bonds over the next 10 years), New Jersey (the second state to formally legalize embryonic stem cell research), and Rhode Island. The second set of laws virtually bans all embryonic research, including cloning. In South Dakota, there is an outright ban on the sale or transfer of *any* embryos. A human embryo is defined in that state as "a living organism of the species Homo sapiens at the earliest states of development that is not located in a woman's body." Nontherapeutic research is defined as anything "not intended to help preserve the life and health of the particular embryo subjected to risk."

Finally, other states have adopted laws that only partially ban some sources of embryos potentially used for ESC research. Arizona explicitly bans research on aborted fetuses and embryos. The law states, "A person shall not knowingly use any human fetus or embryo, living or dead . . . resulting from an induced abortion . . . for scientific or medical investigation purposes." Louisiana explicitly bans research on IVF fetuses and embryos. Louisiana law states, "No in vitro fertilized human ovum will be farmed or cultured solely for research purposes or any other purposes."

In some states with only partial bans, the language used does not distinguish between therapeutic and reproductive cloning, while other states explicitly or implicitly allow therapeutic cloning. Terminology and definitions play key roles in understanding boundaries. Glover argued that the most important concern for legislators at the state and federal levels is determining definitions. Legislators should consult scientists when writing laws and definitions, otherwise "they can back into prohibitions" and unintentionally hurt research. In the Arkansas Total Cloning Ban, there was a lack of distinction between "therapeutic" and "reproductive" cloning because the word cloning was not defined. This resulted in the misinterpretation and, perhaps, even unintentional passing of the bill. Glover observed, "I have sat on panels with legislators from states that I would put in Category 2 who did not think their legislation was in Category 2 because of a substantial confusion as to what these terms really mean." In Missouri, for example, legislators correctly made the differentiation after the language was questioned at the last minute.

In addition, Glover perceived that U.S. research institutions "need to know what [they] can do with the kinds of funding [they] have." Glover also pointed out that "if you are a research institute anywhere else in the world you need to know what you can do with the cells that you actually make." Moreover, he suggested that if an organization chooses to fund research, "you need to know what you can fund."

While considering the laws and regulations, one also must address constitutional considerations. Glover asked, "Does the Commerce Clause give Congress the power to actually go in and play around with this in any way other than by restricting funding? That is, historically, the government's ability to fund or not fund has not gotten the same degree of scrutiny as it would if Congress actually passed a law saying, 'We're going to regulate something that is otherwise deemed to be in control of the state.'" Again, Glover pointed out, definitions are important. For example, what exactly might "commercial activity" entail? Furthermore, he said that there are other legal questions to ponder: Do federal and state bans on cloning infringe on a person's right to privacy in terms of reproductive rights? Is there a "right to clone" possessed by the individual? Is it a personal decision? How do ESC and cloning statues affect *Roe v. Wade* and other abortion cases? At what point can the aborted fetus still be used, and how are the trimester rules affected since that ruling was based on 1970s medical abilities? Where do embryo rights come into play? Can leftover IVF eggs have adoption and protection rights?

Regulation in the United Kingdom

Unlike the United States, the United Kingdom had a history of regulation of embryonic research before the issue of ESC and SCNT was addressed. Leather, of HFEA, believes that there was public confidence in the U.K. regulatory system because it began 13 years ago with the Warnock Committee. She argued, "There is a strand in U.K. thinking which sees regulation as a way of controlling a process rather than quality-assuring or perhaps ethically-auditing an outcome or product." Initially, IVF was not accepted because of religious and family concerns. To address these issues, the Warnock report of 1984 was commissioned. It considered the benefits of IVF and embryonic research beyond these concerns and expressed approval.

In 1990, the Human Fertilisation and Embryology Act was initiated by an act of Parliament "to regulate, through a system of licensing and inspection, the creation—outside the body—of human embryos, and their use both in treatment and research." The Act created HFEA, which regulated IVF, donor inception, storage of gametes and embryos, and all embryonic research. HFEA made sure Parliament's rules were followed by licensing and monitoring clinics, regulating storage of gametes and embryos, maintaining a register of information, and delineating a Code of Practice.

The United Kingdom regulated embryonic research by allowing it to be conducted only under licenses, approving research on a case-by-case basis with no distinction between private and publicly funded research, and by strictly reviewing research goals for necessity and intended purpose. Embryonic research is only approved after scientists show that it will further knowledge about embryonic development and serious diseases, or can be applied to the development of treatments for serious diseases. The United Kingdom prohibits the introduction of animal eggs, sperm, or embryos into a woman's body; the introduction of a human embryo into an animal; the use or storage of a human embryo after primitive streak formation (14 days after fertilization); and the alteration of the genetic structure of an embryo. There should be no creation of an embryo unless there is a demonstrated need, and SCNT is performed only when necessary.

In 2003, a pro-life group, ProLife Alliance, challenged HFEA's authority and rules concerning embry-

onic research by asking for a judicial review to clarify and ban cloning and experimentation. In response, a parliamentary committee was formed in March 2001 to consider and report on issues of human cloning and stem cell research. The committee determined that the U.K. government should consider establishing an oversight body for clinical studies. They also called for the establishment of a stem cell bank where all lines would require donor consent forms.

The U.K. Stem Cell Bank is not a statutory authority like HFEA, but it holds research and clinical grade stem cell facilities and, Patel believes, is an ethically sound and quality-controlled center for storage of human adult, fetal, and embryonic stem cell lines. The stem cell bank is governed by an independent steering committee. It has codes of practice for its use and reviews applications of deposition and access. The facilities where stem cell lines are derived are required to satisfy the Stem Cell Steering Committee's inspections. Furthermore, clinical trials and therapy development undergo regulation and inspection by the Medicines and Healthcare Regulatory Authority and EU Stem Cell Regulation.

Although this model has been highly successful in the United Kingdom, Leather pointed out, "It would be wrong to assume that the institutional structure designed to facilitate public control over an ethically problematic area of science in one country can simply be exported or copied elsewhere." But she went on to argue, "Whatever the origins of the acceptance of regulation in the United Kingdom, we have certainly benefited very much from the regulatory approach. Our regulation has given us public confidence, and with this confidence, we have been able to consider squarely the potential offered by stem cells and embryonic stem cells for the treatment of many disorders." In addition, Patel affirmed, "An important principle here was that it is important that the legislators recognize that, whenever they regulate, particularly the scientific areas, they mustn't stop scientific developments and they must allow scientific progress but, at the same time, set up regulation that will allow the public to have confidence."

Current Policy Affecting Business

The final session in the conference focused on the future of ESC research, addressing the effect current policy has on business and biotechnology innovations. Three speakers—Debora Spar, Spangler Family Professor of Business Administration at Harvard School of Business; C. Thomas Caskey, managing director of Cogene Ventures, Ltd.; and Thomas Okarma, president and CEO of Geron Corporation—gave their perspectives on ESC research and its potential in the biotechnology industry.

Spar said that she believes that, in order to talk about the business side, one has to address the business and potential market of stem cells on the conceptual level. She affirmed, "At the moment, this topic is completely immature. There is not yet an awful lot of business in stem cells." The current stem cell industry consists of 10 private firms spending $70 million a year, which is not a significant financial impact. In her opinion, the interesting point about the stem cell industry is that there *will* be business in stem cells and it will be a very *big* business. She remarked that rules and guidelines have a profound effect on how science develops, but, she argued, "The market will shape politics." She foresees that there will be business in stem cells because of a widespread and deep-seated demand for products that stem cells might provide. The government could try to restrain or prohibit such actions, but it would not work well or last very long.

Spar said that she believes that stem cells could be a big business because there is an annual $106 billion U.S. pharmaceutical market, an annual $400 billion world pharmaceutical market, and an annual $207 billion market capitalization of U.S. publicly traded biotech firms. Currently, $7.3 billion is spent for insulin and oral drugs for diabetes each year in the United States alone, while an additional $132 billion

is consumed for medical cost expenditures on the disease. Spar remarked, "If stem cells can address even a tiny sliver of any of these markets, it's huge. You don't need for stem cells to cure everything to get a massive business interest. You need . . . one cure, one treatment . . . and at that point, the venture capitalists and the private equity people who are now kind of waiting on the sidelines . . . are going to be all over this."

Historically, with a strong demand and an attractive product, a market can be created even if some do not agree with it. Government preventions will not keep markets from developing in the long run, but they can shape how and where markets develop. Sustainable development of commercial markets in breakthrough technology requires vision and money. In a field with such societal impact, people will be passionate for and against the development, and businesses will have to understand this. Spar maintained that in order to resolve the current conflicts over ESC research, we need "the emergence of a market, a large mainstream market over time, which supplies what a good portion of society [is] demanding, and it's the birth of that market and the growth of that market that ultimately removes the spotlight, if you will, [from] the political debate."

Caskey compared ESC research to gene therapy in the 1990s. Although initial ideas of using gene therapies with viral vectors were unsuccessful, they were later used successfully in pharmaceuticals. The initial idea may have been wrong, but it paved the way for a new and more innovative use. Caskey stated, "So here is a technology [gene therapy], highly touted, everybody thought you knew what it was going to be doing, and in fact, we were all wrong. In fact, you see that out of this breakthrough technology comes totally different applications of the technology than were originally proposed." Caskey maintained that, in science, it is important to see if new technologies are successful or unsuccessful. Scientists learn from their mistakes and should not shy away from acknowledging them to the public. To move forward, Caskey argued, we need scientific leadership as well as an educated public.

Representing a company actively involved in the business of stem cells, Okarma described Geron's model for finding therapies and bringing them affordably to the general public. In 1995, Geron entered the field of stem cell research because of its background in telomerase research. Telomerase was the "enemy" in cancer, which basically kept cells from losing their ability to replicate and thereby allowed them to live forever. What led Geron into ESC research were the large amounts of telomerase produced by these cells, which allowed them to divide continually. Geron currently has federally fundable ESC lines that have not been cultured or stored on mouse feeder cells in the past three years. Four of these lines have undergone heavy examination and tested negative for mouse, cow, and even human diseases and contaminations.

Okarma said that he believes that one of the major concerns surrounding stem cell research is affordability. Other business ventures related to medical products or therapies have failed because of standardization and "cost of goods" problems. In the case of stem cell therapies or resulting practices, there must be some uniform and reliable product that can have scalability so that the procedure is regulated and costs are decreased. Scalability of production is an important factor in testing and, one day, in distributing therapies. As of now, Geron is able to produce 1.3 million glial progenitor cell doses from 200 vials of human ESCs. Geron also has a master bank facility that is Good Manufacturing Practice certified, so the generated cells and tissues can be used in human trials. In his opinion, "the actual therapy 10, 15, 20 years from now may not be cellular at all, but through the lessons learned from embryonic and adult stem cell research and, hopefully, through nuclear transfer . . . we may learn how to in vivo reprogram and enable the body to make more of itself endogenously.

And that obviously is the object of the exercise."

Conclusion

Currently, the United States is at a pivotal but uncertain threshold for human ESC research. Many are not convinced that the existing policy is sufficient or agreeable, and the discussion continues for and against the research. William Brinkley, senior vice president for graduate studies at Baylor College of Medicine, commented in the closing remarks of the conference that the stem cell debate during the 2004 presidential election "provided yet another opportunity to briefly reflect on both the retrospective and prospective evolution of American science policy." Unfortunately, the questions addressed in this debate have never been fully resolved in the general public. As Van Etten of JDRF observed, "We continue to debate the issue as if there had not been this decision [by President Bush]." In reality, Bush did make a decision, but many in the public are having a hard time accepting it.

In order to move forward, the United States needs to reconsider the issues of ESC research, SCNT, reproductive cloning, and the regulation of privately-funded research. Lane, of Rice University, observed, "We, so far, don't have any law on cloning of any kind. . . . That's an unacceptable policy situation for the United States, however you feel about how it ought to come out in the end." The fate of SCNT and reproductive cloning must be decided, and private funding should have some form of federal regulation or oversight. Brinkley concurred, "Regulations, as we've heard, have not developed, and yet there is one element of our population in America [that] can go freely and work on these things without government control."

Since the conference, an April 2005 report by the National Academies, "Guideline for Human Embryonic Stem Cell Research," reviewed these issues and concluded that an oversight committee should be established at each research institution performing embryonic stem cell research. This committee would be charged with documenting all ESC lines, researchers, and research proposals at their institutions. The committee also would be required to monitor proposals for appropriateness and validate all international collaborations under similar guidelines. In addition, the National Academies report recommended the establishment of a national body to assess the adequacy of guidelines and provide a forum for continued discussions.

While discussion is continuing in Washington and at state capitals, research is progressing in selected states and overseas. California is moving ahead with the establishment of the California Institute for Regenerative Medicine, filling in the void of ESC research funding left by the federal government. As Lane pointed out, "states are moving ahead . . . countries are moving ahead. . . . I think, as next steps, we're going to have to reconsider the issue of federal funding of embryonic stem cell research." Brinkley also concluded that "the limited approval that we are now given, by executive order of the president, to use existing cell lines is insufficient." Federal funding is necessary for researchers to maintain or increase peoples' enthusiasm and excitement in the field as well as to bring in new scientists. Brinkley commented that the "true American science gold standard [consists of] the individual investigators out in academia and universities that have the funding and the privilege and the opportunity to work on whatever they find to be exciting and challenging. . . . Without funding we're eliminating this entire population of brilliant students." He believes it is necessary that the right scientists do research, that leaders make new policies, and that reproductive cloning is not used.

It also was pointed out by Hartman, of CBS News, that "the eggs that exist in the IVF clinics don't offer the kind of diversity on the genetic level that researchers are going to need." The IVF eggs used to create the cell lines are predominately from the white middle or upper class and do not offer the

racial multiplicity necessary to truly understand and appreciate early development and genetics. To do good and balanced research, scientists need to have the appropriate tools. Those tools are lacking in the limited ESC lines offered for federal funding.

In order to progress from our current debates, Brinkley and many other speakers advocated the role of scientists in communicating with the public. Brinkley commented, "We [scientists] need to get involved in the community more. We need to become more effective in describing the science, understanding the science, perhaps ourselves in some cases, and in involving all elements." He also thought that researchers should look for help and support in "dedicated disease advocates, bioethicists, physicians, parents, patients, and policymakers." As a means for public acceptance, Nisbet, of Ohio State University, recommended that public opinion polls be used to gauge what the public thinks about how and from whom the president receives advice on this issue. With a balanced and publicly accepted forum for counsel, the decisions made could be more readily received. Furthermore, this debate could disappear once a child or adult is successfully treated. Elizabeth Cohen, of CNN, remarked, "Once you have one child, just one child, whose juvenile diabetes goes away because of embryonic stem cell research, no one will really care where that cure came from."

Whether or not a cure arrives in the near or far future, there remains the issue of policy and regulation concerning the area of embryonic stem cell research in the United States. The delicacy of the subject is apparent, but the implications of such research and related research should be weighted appropriately and accurately by scientists, ethicists, the media, the public, businesses, and policymakers in order to make any progress in the debate.

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