The New Atlantis

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Editor's Note: Since its founding, *The New Atlantis* has paid close attention to the ethical and political controversies arising from biotechnology—including especially the heated debates over stem cell research. We are pleased to devote the entirety of this issue to a major report on the stem cell debates, a comprehensive and up-to-date account of the scientific facts and the moral, political, and legal stakes. This is the inaugural report of an important new body, the Witherspoon Council on Ethics and the Integrity of Science.

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The New Atlantis *(1627) was the title Francis Bacon selected for his fable of a society living with the benefits and challenges of advanced science and technology. Bacon, a founder and champion of modern science, sought not only to highlight the potential of technology to improve human life, but also to foresee some of the social, moral, and political difficulties that confront a society shaped by the great scientific enterprise. His book offers no obvious answers; perhaps it seduces more than it warns. But the tale also hints at some of the dilemmas that arise with the ability to remake and reconfigure the natural world: governing science, so that it might flourish freely without destroying or dehumanizing us, and understanding the effect of technology on human life, human aspiration, and the human good. To a great extent, we live in the world Bacon imagined, and now we must find a way to live well with both its burdens and its blessings. This very challenge, which now confronts our own society most forcefully, is the focus of this journal.*

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Preface

A Letter from the Chairmen of the Witherspoon Council on Ethics and the Integrity of Science

We all owe an enormous debt of gratitude to modern science. The scientific enterprise is among the greatest collective intellectual achievements of mankind. The honest, dispassionate, and tenacious pursuit of truths about the natural world has elevated us and, in myriad ways, improved the conditions of our lives. From the very founding of the United States, the American character has been distinguished in part by its appreciation for science and its fruits.

Yet for all their blessings, modern science and technology pose immense and complicated legal, social, economic, and political problems. And underlying those practical problems are deeper moral and philosophical questions raised by our growing scientific knowledge and the power of our technologies—including questions about what it means to be human and about the meaning and protection of human dignity.

The Witherspoon Council on Ethics and the Integrity of Science, which we have the honor to chair, has been established to help the American public think through these practical problems and moral questions. Convened under the auspices of the Witherspoon Institute, a research and educational organization based in Princeton, New Jersey, this diverse body of academic experts studies the human and moral significance of modern science and technology, as well as the questions of policy, law, and politics raised by scientific and technological advancement. It focuses especially on the ethical and policy questions related to the human life sciences, including medicine, biotechnology, genetics, assisted reproductive technologies, embryo research, and neuroscience. Its members are drawn from a wide range of fields—science and medicine, political science and law, philosophy and theology.

In this inaugural report, the Witherspoon Council considers the proper relationship between science, ethics, and politics by examining the most prominent science-related controversy of the past decade: the stem cell debates. These debates touched on fundamental questions concerning the governance of science and the moral status of embryonic human life. More than just a scholarly assessment of those debates, this

report seeks to improve the public understanding of how science and democratic politics relate, including the responsibilities of scientists and policymakers. We consider the inevitable interplay between science and ethics and the conflicts of interest that arise when scientists are both advisors to policymakers and petitioners for their allocations. Among the report's most crucial lessons is that, in our system of participatory republican government, we are responsible for considering not only the potential benefits of scientific research but also the ethical implications of that research.

There is reason to hope that scientific advances may soon offer technologically superior alternatives to embryo-destroying research. But some of those technological solutions may raise novel ethical concerns of their own. And even if we do find a satisfactory technological resolution to the debate over embryonic stem cell research, we are left with the underlying moral questions raised by our growing power over the natural world, including over our own biology. It is to the work of understanding, clarifying, and answering those questions that this Council is dedicated.

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The Stem Cell Debates
Lessons for Science and Politics

In December 1994, a committee that advises the director of the National Institutes of Health met on the NIH campus in Bethesda, Maryland. The meeting focused on the recent recommendation of the NIH's Human Embryo Research Panel that the federal government should fund a range of research involving human embryos.[1]

The chairman of the panel told the committee about the "extremely high level of public ignorance" about human reproduction, which "invites exploitation by those who, for moral reasons, object to human embryo research."[2] That ignorance, he warned, could be "manipulated into public hostility" toward embryo research.[3] The conversation became frankly political, as several committee members voiced concern that the incoming Republican majority in the U.S. Congress would restrict funding for the research, including expected developments with human embryonic stem cells. The committee began to brainstorm ways to shape the policy and influence public reaction so that embryo research could receive government funding with minimum opposition. One committee member proposed a sophisticated strategy of political lobbying: "have us do our homework to determine which people in Congress…have family members with which particular illnesses and make individual visits to them to 'background' them and brief them and discuss their particular family history concerns."[4] Scientists would respond to ethical objections against the destruction of nascent human life by entering the political arena; to make their case, they would rely not only on scientific facts but on emotionally charged appeals.

Fast-forward a dozen years. Embryo research became a hot-button political issue, and strikingly, just as had been anticipated in 1994, public officials and candidates for office regularly spoke about the issue in terms of their family health problems. So it was that, in considering legislation to fund embryonic stem cell research in April 2007, a series of Senators, one after another, described illnesses suffered by relatives, constituents, and themselves—a parade of maladies, from cancer to Parkinson's to diabetes to asthma. One Senator, explaining his vote in favor of using taxpayer dollars to fund embryonic stem cell research, recounted his mother's physical and mental decline due to Alzheimer's disease: "When I look at her empty gaze and shriveled body, I cannot help but wonder, if we

had started embryonic stem cell research years ago, would she still be suffering today?"[5] While these Senators understandably focused on the face of the suffering that might be relieved if human embryos were destroyed for the sake of delivering a panoply of hoped-for cures, the imperative to relieve suffering was never in dispute, and they failed entirely to attend to the nature of the human embryo and its moral status—the ethical issue that was the very center of the debate.

These two remarkable snapshots—a government scientific advisory board strategizing about political lobbying, and politicians making passionate personal pleas about science policy—give us a glimpse of the strangeness of the debates about embryonic stem cell research from the 1990s through today. The stem cell debates have shown American politics at its best and its worst, with examples both of principled democratic discourse and plainly dishonest demagoguery. And stem cell research itself has shown us science at its most noble and its most debased, with examples both of brilliant researchers pursuing cures for terrible afflictions, and others committing egregious scientific fraud in the hunt for glory. As a result, the stem cell debates have helped to reveal the knotty and complicated relationship between science and politics.

This report examines the stem cell debates in hopes of better understanding the relationship between science and politics. It lays out for the public record the most important facts and arguments, some of which have been long neglected or distorted, so that we might better understand the purpose and limits of science in a self-governing society, the proper role of scientists in American political life, and how citizens and policymakers should think about both. This report examines when, how, and why the stem cell debates sometimes lapsed into error and exaggeration. It also reflects on the value of public deliberations about the fundamental questions of bioethics.

A comprehensive history of every aspect of the stem cell debates is beyond our present purposes, although the five appendices following the body of this report, each of which can be read as a standalone chapter, offer up-to-date explanations of the science of stem cells, the medical promise of stem cells, the ethical questions raised by stem cell research, the relevant policy and legal history, and other nations' stem cell research policies.

From Discovery to Debates

Stem cells are cells that have the ability to differentiate into one or more of the types of cells of an organism's body, as well as the ability to self-renew, creating more stem cells like themselves. "Adult" stem cells—which

are found not only in adults but also in children, babies, and fetuses—are typically *multipotent*, meaning that they are capable of producing multiple (but not all) cell types.[6] Some adult stem cells have been used in medical therapies for decades. For example, bone marrow transplantation has been used to treat patients since the 1950s, years before scientists understood that it was specifically the presence of blood-forming adult stem cells in the marrow that made the treatment work.[7]

Unlike adult stem cells, embryonic stem (ES) cells are *pluripotent*, meaning that they are each theoretically capable of producing all of the cell types of the mature organism.[8] Human ES cells were first successfully derived in 1998 by cell biologist James A. Thomson of the University of Wisconsin.[9] Thomson used embryos that had been created through in vitro fertilization (IVF) but had not been used for the purpose for which they were created: being implanted in a womb so that a woman or couple undergoing fertility treatment could have a baby. There are hundreds of thousands of such unimplanted human embryos stored in freezers at IVF clinics across the United States and around the world.[10] (The science of stem cells is explained more fully in Appendix A.)

Thomson's derivation of human embryonic stem cells was a long-anticipated breakthrough. Based on studies with mice, biologists had years earlier recognized the potential value to science of human ES cells. Their potential to develop into any type of cell in the human body was expected to give researchers a powerful new tool for studying human development. But it was their hoped-for application in the new field of regenerative medicine—using ES cells to replace a patient's damaged or dying tissues—that captured the imagination of the public in the most dramatic way, as this ability could in theory allow doctors to reverse a myriad of degenerative conditions, from Parkinson's to diabetes to spinal cord injuries. Stem cells, and especially embryonic stem cells, it was believed, would help usher in a new era in medicine. (The medical promise of stem cell research is discussed in Appendix B.)

However, ES cell research has stirred persistent ethical concerns, as obtaining human ES cells typically requires destroying human embryos. Thus, ES cell research demands that we consider the moral status of the human embryo. Many proponents of ES cell research consider the human embryo to be merely a "clump of cells," morally no different from any other bit of tissue. By contrast, many critics of ES cell research argue that the human embryo is a human being at a very early stage of development, and therefore possesses at least the right not to be killed for research or to be exploited as a medical resource. Moreover, soon after human ES cells

were first derived, scientists proposed employing the same technique that had been recently used to clone Dolly the sheep to create cloned human embryos for producing patient-specific stem cells for treatments, raising public concern over the ethics of human cloning. These and other ethical dilemmas divided the public over the hope of regenerative medicine and concerns for nascent human life. (The ethical questions raised by stem cell research are explored more thoroughly in Appendix C.)

Following Thomson's discovery, stem cell research quickly became a contentious issue in American politics. The chief policy question was not whether such research should be made illegal, but whether human embryonic stem cell research should receive government funding—especially from the federal government, which is the largest source of funding for scientific and medical research in the country. On August 9, 2001, President George W. Bush announced a policy that would allow federal funding of the controversial research to proceed, but only for ES cell lines that had already been created, "where the life or death decision [had] already been made."[11] This policy would allow the government (and by extension, the American people) to support this promising area of medical research without encouraging future destruction of human embryos. The Bush funding policy became the subject of intense political conflict over the course of his presidency. It was eventually overturned by the Obama administration, which in 2009 put in place a new policy that encourages the destruction of some embryos—those produced for but not used in IVF procedures—in order to create new ES cell lines. The Obama funding policy has been challenged in a lawsuit that is currently wending its way through the federal courts. (The policy and legal history of ES cell research is laid out in Appendix D.)

Scientists, policymakers, political candidates, patient-advocacy groups, religious organizations, and other members of the public became embroiled in the debates over stem cell research. American scientists politically mobilized—as they rarely had before—in opposition to President Bush's funding policy. Stem cell research became a prominent issue in the 2004 presidential race. There were various congressional attempts to overturn President Bush's policy, and numerous initiatives at the state level, including a high-profile California referendum on funding for ES cell research. These heated debates raised important questions about the relationship between science and democracy and about how democratic politics should regulate ethically controversial research. By revisiting these debates, we address not only the particular questions regarding the ethics of embryonic stem cell research, but also questions of the place of science in the American polity.

Science, Policy, and Politics

Before focusing on the interplay of science and politics in the stem cell debates, it is useful to step back and consider how they relate in general. Broadly speaking, we can distinguish between two ways science and politics relate to one another in the United States. First, government funds, regulates, organizes, directs, endorses, and prohibits different aspects of the scientific enterprise. Second, science provides policymakers with information and advice regarding natural phenomena, technology, and other matters relevant to public policy. These different relationships between science and policy correspond to two distinct senses in which we use the term "science." When we speak of science policy as the way government supports or limits science, we are speaking of science *as a project or practice*, carried out by members of our society and subject to democratic political authority like any other activity. When we speak of the way government seeks science or scientific advice, we speak of science *as a kind of knowledge* concerning the natural world, knowledge that is subject to critical analysis and debate but not to political authority or regulation.

Although the policy questions in the stem cell debates chiefly concerned the first sort of relationship between science and politics, namely how the government ought to support or regulate this medically promising but ethically controversial field, the second sort of relationship has also been integral to the stem cell debates: scientific knowledge concerning the nature of the human embryo has been essential in informing policymakers and the public in their moral reasoning on the topic.

Historically, the federal government has provided considerable support for the scientific project. The classic articulation of postwar science policy in the United States is found in Vannevar Bush's 1945 report to President Franklin Roosevelt, *Science, The Endless Frontier*.[12] In this influential report, Bush (no relation to President Bush) argued that government funding for science, particularly for what he dubbed "basic research," was essential to ensuring that America continue to enjoy the technological progress necessary for the nation's strength and prosperity. Vannevar Bush's model of scientific progress held that basic research leads to applied research which leads to the development of useful technologies and products.[13] Following this model, the U.S. government has since the end of the Second World War provided considerable funding for scientific and medical research, with consistent public approval.

During the latter half of the twentieth century, the U.S. government also came to recognize the importance of regulating scientific research,

particularly biomedical and behavioral research conducted on human subjects. The horrific scientific experiments performed by Nazi doctors during the Second World War, along with other cruel and unethical experiments performed in the United States and around the world, clearly demonstrated the need for ethical oversight of scientific research. Governments around the world instituted policies on research ethics and the protection of human subjects, based on the principles articulated in such documents as the Nuremberg Code and the Belmont Report.[14]

Meanwhile, science, understood as our most reliable source of knowledge about the natural world, rightly enjoys a great measure of authority. In our political life, we rely on science to settle questions regarding purely physical phenomena: the toxicity of different chemicals, the efficacy of medical treatments, the sturdiness of bridges, the effects of pollution, and so on. In crafting policy, we weigh these scientific facts against other facts, interests, and values. Scientific knowledge can also inform our moral reasoning. A scientifically accurate description of biological death, for instance, is critical for determining the ethics of organ donation, and for developing sound policies to regulate organ donation.

The Bush Funding Policy: How Science Informed Ethics and Politics

Crafting morally sound policies for stem cell research requires at least three kinds of scientific knowledge: first, an account of the medical treatments that stem cell research might make possible—along with an account of the likely challenges facing this research—so that we might judge whether funding such research is in the public interest; second, an understanding of biology and specifically embryology, so that we can reason about the moral status of the human embryo; and third, an assessment of the methodology and viability of alternative sources of stem cells for research and therapy so we can consider alternative policies.

In developing his administration's stem cell funding policy, President Bush sought out scientific advice on precisely these questions.[15] These scientific matters were also central to the deliberations on stem cell research conducted by the President's Council on Bioethics that he established.[16] President Bush was aware of the potential benefits of stem cell research; he and his staff consulted a wide range of scientific and medical experts in formulating his 2001 policy, and in his speech unveiling the policy, he spoke of the "great promise" of the research to "help improve the lives of those who suffer from many terrible diseases—from juvenile

diabetes to Alzheimer's, from Parkinson's to spinal cord injuries."[17] He also alluded to scientific facts about the developing embryo: "Like a snowflake," Mr. Bush said, "each of these embryos is unique, with the unique genetic potential of an individual human being."[18]

As the science evolved in the wake of President Bush's 2001 decision, it seemed increasingly likely that new alternative techniques would make possible the creation of pluripotent stem cells without the destruction of human embryos. President Bush adjusted his administration's policy accordingly, directing the NIH in 2007 to vigorously pursue these alternatives.

Once again, scientific knowledge was crucial not only to evaluating the technical feasibility of these alternative sources for pluripotent stem cells, but also in informing the ethical judgments about the proposed alternatives. Most of the alternative sources of stem cells involve complex technical procedures, and deciding whether a particular alternative is ethically acceptable can hinge on complicated scientific questions. Recent advances in the fields of embryology, developmental biology, and epigenetics have helped scientists to better understand early human embryonic life, making it possible to distinguish between living embryos and the component parts of embryos that it would be less ethically objectionable to use for research. (The most prominent alternative stem cell techniques are discussed in detail in Appendices A and C.)

Ten Common Misrepresentations

The debates over stem cell research have dealt with a wide range of topics and issues, from cutting-edge science to deeply held moral values to arcane aspects of policy and law. In part due to the complexity of the subject, and in part due to the passionate intensity inspired by the concerns and interests on both sides, many misrepresentations, misunderstandings, and sometimes even willful deceptions became part of the debate. Public officials who may not have understood the relevant facts sometimes made misinformed and misleading claims regarding the science, while scientists sometimes misrepresented the intentions and effects of public policy. The ethical stakes in the debate were hotly contested and were subject to both accidental and knowing misinterpretation. Even academic bioethicists, who would seem to bear a professional responsibility to understand and clearly communicate the complexities of these issues to policymakers, scientists, and the general public, often twisted the facts.

We present here ten of the misrepresentations most frequently heard during the stem cell debates. In doing so, we aim to clarify the public

record and to correct some common, but important, errors that have made an already vexed controversy even more difficult. Furthermore, by better understanding the origins of these misrepresentations—when and why policymakers, scientists, bioethicists, and the public went wrong—we can better understand the relationship between science and politics.

Misrepresentation 1: The Bush administration banned stem cell research. The chief policy question concerning human ES cell research in the United States has *not* been its legality. Although there have been proposals to outlaw human cloning that would have impacted the ability of researchers to produce embryos for research purposes,[19] these measures were not passed, and there have been no serious federal proposals for a general prohibition on research destroying human embryos. Instead, the central policy question at the national level has been whether and how such research will receive taxpayer funding. The Bush policy on embryonic stem cell research—like the Dickey-Wicker Amendment, a law passed by Congress every year since 1995 to regulate embryo research (described in Appendix D)—only concerns the ability of the federal government to allocate research funding. Neither the Bush policy nor the Dickey-Wicker Amendment outlaws any kind of scientific research, nor do they pertain to the allocation of state or private funding. Indeed, in terms of the kinds of stem cell research that are legally permissible, the United States has always ranked among the most liberal countries in the world, even under the Bush policy. (Laws of other countries pertaining to human embryonic stem cell research are discussed in Appendix E.)

Nonetheless, over the past decade, the Bush policy on federal funding for embryonic stem cell research—which explicitly permits funding on cell lines derived before August 9, 2001—was frequently characterized by the media and by opponents of the policy as a "ban on stem cell research."[20] During the 2004 presidential campaign, Senator John Kerry (D.-Mass.), then running for president against Mr. Bush, said the following in a prepared radio address: "Three years ago, the President enacted a far-reaching ban on stem cell research, shutting down some of the most promising work to prevent, treat and cure Alzheimer's, Parkinson's, diabetes, AIDS and so many other life-threatening diseases."[21] Senator Kerry used the word "ban" three more times during the course of the short speech—clearly a considered and deliberate word choice intended to muddy the public understanding of the Bush funding policy, and to play into a growing political narrative that President Bush and his party were "anti-science."

To be sure, some critics of the Bush policy may have called it a "ban on stem cell research" as shorthand, as a simpler way of saying a "ban on federal funding of research on embryonic stem cell lines derived after August 9, 2001." University of Pennsylvania bioethics professor Arthur L. Caplan argued in an editorial published during the 2004 campaign season that the two ways of speaking about the Bush policy were equivalent: "prohibiting the expenditure of federal funds on embryonic stem cell research after August 2001 is a ban."[22] He has continued to repeat this claim up to the present, writing in April 2011 that the policy was "nothing more than a ban dressed up as a compromise."[23]

But describing the Bush policy as a "ban" on stem cell research obscures the important fact that stem cell research, including embryonic stem cell research, actually received federal funding under the Bush policy.[24] In fact, under the Bush policy the NIH provided $294 million for embryonic stem cell research. In fiscal year 2008 alone, the NIH distributed over $88 million in grants for more than 250 projects involving human embryonic stem cells.[25]

Moreover, describing the Bush policy's restriction on federal *funding* as a ban on *research* implies that the freedom to carry out research in the United States is tantamount to a right to receive federal funding for that research. Yet the U.S. government has always permitted many more activities than it funds, and it is not immediately clear why scientific research has more right to receive federal funding than any other socially valued activity in America. Research that involves practices that raise ethical concerns—such as the destruction of human embryos—may not enjoy a level of approbation among Americans that would justify support from the federal government.[26]

Misrepresentation 2: Embryonic stem cells are superior to adult stem cells, or adult stem cells are superior to embryonic stem cells. One of the most common misrepresentations of stem cell science and therapy has been the idea that one kind of stem cell is definitively better than other kinds. Advocates of embryonic stem cell research have often emphasized and exaggerated the potential of ES cells without acknowledging the extent to which adult stem cells may be useful to research and therapy. Meanwhile, some opponents of embryonic stem cell research have claimed that adult stem cells are definitively better than embryonic stem cells for providing therapies.

The pluripotency of ES cells makes them potentially a much more powerful medical resource than adult stem cells, which have more a limited

developmental capacity. It may be possible to use pluripotent stem cells to create nearly any kind of cells for researchers to work with in modeling diseases and testing treatments at a cellular level. And since they can make nearly any kind of cell in the body, they have long been anticipated as uniquely valuable for regenerative medicine (although the threat of transplant rejection and the risk of tumorigenicity pose significant hurdles to the successful translation of stem cell research to clinically useful medicine). Work with adult stem cells, meanwhile, faces a number of difficulties, including the problem of isolating, purifying, and cultivating them *in vitro*; and their limited potency, along with the difficulty of finding adult stem cells for every tissue type, make it particularly difficult for researchers to use adult stem cells to create tissue types for a wide variety of conditions. Researchers therefore have good reason to suppose that ES cells could be a more effective tool than adult stem cells for understanding and treating many diseases. While there are as yet no treatments in regular use that rely on human ES cells, a handful of clinical trials are now underway.

Adult stem cells, as mentioned above, have been used for years in treating patients. Some such treatments, such as the use of bone-marrow transplantation for blood diseases like leukemia, antedated the knowledge that it was specifically stem cells that made the treatment work. Even now, many of the most exciting medical advances using stem cells rely on adult stem cells, including the recent creation of an artificial trachea and the successful treatment of HIV using bone marrow transplantation.[27] Experimental studies have found evidence for the effectiveness of adult stem cells in treating a number of diseases, but it is important to remember that most stem cell-based therapies are still in the early stages of development, and it is too soon to say whether or not adult stem cells will prove effective in treating complex degenerative conditions like Parkinson's disease or spinal cord injuries. Likewise, it is too soon to say definitively whether embryonic stem cells will prove more effective than adult stem cells for treating these diseases. (For a more detailed analysis of the potential applications of adult and embryonic stem cells, see Appendices A and B.)

Critics of ES cell research generally object to it on ethical grounds, and so have an incentive to exaggerate the promise of adult stem cells, which do not raise the same ethical concerns. These critics have also unfairly downplayed the promise of ES cell research, belittling it as "wishful thinking and hype."[28]

Meanwhile, supporters of ES cell research have their own incentives to spin the science, including the desire to ensure that the research receives

government funding. As a result, they have exaggerated the promise of ES cell research. Although there has been a perception among some opponents of ES cell research that advocates deliberately denigrated the value of adult stem cells, it would be more accurate to say that advocates simply focused most of their attention on the line of research they believed to be the greater prize and did not meet less morally problematic alternatives with the same level of interest, generally because they did not see embryonic stem cell research as morally problematic in the first place.

An illustration of the distortions and exaggerations on both sides can be found in an exchange of four letters published in *Science* in 2006 and 2007. First, in July 2006, three scientists who publicly supported human ES cell research—Shane Smith, William Neaves, and Steven Teitelbaum—wrote a letter to the journal condemning the work of David A. Prentice, a biologist affiliated with a conservative think tank, who opposes human ES cell research. Smith and his colleagues argued that Prentice had exaggerated the therapeutic applications of adult stem cells in a widely publicized list of 65 diseases (and counting) that Prentice claimed were treatable by adult stem cell therapies. Most of the treatments Prentice cited, Smith and his coauthors noted, "remain unproven and await clinical validation," while others, such as those for Parkinson's and spinal cord injury, were "simply untenable." They called Prentice to task for the quality of his references, which included "various case reports, a meeting abstract, a newspaper article, and anecdotal testimony before a congressional committee," along with publications that had "nothing to do with stem cell therapy."[29]

In January 2007, *Science* published a reply from Prentice (co-written with Gene Tarne, another critic of human ES cell research) in which he defended his work on the grounds that he had not claimed adult stem cell treatments were "generally available," that they were "cures," or that they were fully approved by the FDA, merely that adult stem cell treatments have provided "observable and measurable benefit to patients." He complained that his critics had failed to acknowledge several of his more legitimate sources, and also argued that there were at the time over 1,200 clinical trials related to adult stem cells underway. However, Prentice also took the opportunity to go on the offensive, pointing out that backers of human ES cell research—including two of the authors who had criticized him in *Science*—supported groups that irresponsibly exaggerated the potential of ES cells by claiming that they could someday be used to treat or cure over 70 conditions, even though the evidence for that claim was shaky.[30]

In June 2007, the journal published another letter from Smith and his colleagues critiquing Prentice's work. This time they argued that the "enrollment of an experimental therapy in a clinical trial does not mean that it is an effective therapy." They again criticized Prentice's methods, noting that some of the 1,200-plus clinical trials he had found had nothing to do with adult stem cells. They further noted that, based on Prentice's published claims, a major conservative organization was reporting on its website that patients "have access to adult stem cell therapy which currently provides safe and successful treatments for more than 70 diseases and injuries.... These are tangible therapies that are available today."[31]

Their letter was immediately followed in the same issue of *Science* by another reply from Prentice and Tarne. They argued that their central claim that adult stem cells have provided medical benefits for patients was unaffected by the points raised by their critics regarding the amount of evidence, and reemphasized their criticism of Neaves and Teitelbaum's political involvement and the exaggerations of the value of embryonic stem cells. Each of the four letters ended with a stern rejoinder against "cruelly deceiv[ing] patients."[32]

Exaggerations and misrepresentations about the supposed superiority of embryonic or adult stem cells have waned in the last few years, partly because of the Obama administration's decision to undo the Bush policy, and partly because of the arrival on the scene of promising new sources of pluripotent stem cells that do not require the destruction of human embryos. But the exaggerations and misrepresentations have not entirely abated. While everyone hopes that stem cell therapies—whether using adult, embryonic, or some alternative source of stem cells—will deliver on their promise to provide treatments for a long list of afflictions, it is important to temper that hope with critical analysis of the scientific evidence. Experts who mischaracterize the facts risk distorting the public debate and inappropriately raising—or dashing—the hopes of patients.

Misrepresentation 3: Somatic cell nuclear transfer is not cloning and does not produce embryos. As mentioned above, the technique used to create Dolly the cloned sheep has been advocated by some scientists as a way to procure embryonic stem cells with a known genome, either to study genetic diseases or to treat particular patients. The idea of cloning human embryos in order to destroy them for the sake of creating stem cells is disturbing to many Americans in its own right, but it also raises the specter, long envisioned in works of science fiction like the 1932 novel *Brave New World*, of using the same technique to produce cloned children.

The terms "reproductive cloning" and "therapeutic cloning" came into common parlance in the 1990s to distinguish between cloning intended to create a genetically identical organism and cloning intended to produce stem cells.[33] The two terms denote the different ends to which cloning techniques might be applied, while making clear that the means in each case is cloning.

Some proponents of ES cell research responded to public concerns about cloning by engaging in terminological chicanery. They suggested that the technique used to create Dolly, somatic cell nuclear transfer (SCNT), should not be considered a kind of cloning unless it results in a viable pregnancy in the womb. This claim was most notably spelled out in a 2002 report from a National Research Council panel. The panel, chaired by Stanford University stem cell scientist Irving L. Weissman, argued that SCNT intended for reproduction and SCNT intended to create stem cell lines are "very different procedures" and that it is wrong to think of them both as kinds of cloning.[34] The product of SCNT when intended for reproduction is a cloned embryo that will be implanted in a woman's uterus, resulting in a newborn child. But, the panel argued, if SCNT is used to produce ES cells, the end product is the ES cells. Since the final step is "entirely different," the panel argued, the two procedures should be considered distinct, and should be regulated differently.[35] Weissman later explained that his panel was trying "to use neutral language…devoid of emotion-bearing terms,"[36] and so it opted to use the terms "reproductive cloning" and "nuclear transplantation to produce stem cells."[37] Many scientists, policymakers, and commentators have similarly insisted that SCNT is not cloning but is rather a technique that can be used for cloning.[38]

Relatedly, some have argued that it is inappropriate to call the artifact created by SCNT an "embryo," since that term connotes the earliest stage of a developing life, while the artifact might be destined for destruction so that its stem cells can be harvested. For example, Dr. Paul R. McHugh, a member of the President's Council on Bioethics, proposed that instead of calling the product of SCNT an embryo, we should call it a "clonote" (parallel to the word "zygote," which McHugh would restrict to the product of fertilization).[39] Other commentators have suggested still other terms for this artifact.[40]

In 2004, the leadership of the International Society for Stem Cell Research (ISSCR), an influential global organization of scientists formed in 2002, encouraged researchers to replace the term "cloning" with "nuclear transfer."[41] The ISSCR formed a "nomenclature task force" to

deal with the public-perception problems posed by the term "therapeutic cloning," and in September 2004 the organization released a position statement calling on researchers to abandon the term.[42] The following year, biotech entrepreneur Paul Abrams lectured the ISSCR annual meeting about the need to junk the term "embryonic," too: "If we adopt the view that an embryo means a cell is going to implant to make a baby, and none of what we're doing is [making] cells to implant to make a baby, and we come up with different terminology, I think we will have more long-term political success."[43]

The problem with these forays into terminological revisionism is that *the result of a successful SCNT attempt is always a cloned embryo*, a living organism at its earliest stage, genetically identical (or nearly identical) to the organism whose somatic cells were used in the procedure. While human SCNT has not yet been successfully performed to create human embryos beyond a few cell divisions, evidence from animal studies indicates that the product of SCNT would have the developmental potential of a human embryo. The entity produced by a successful SCNT procedure, if taken out of the petri dish and placed in the womb, has the potential to grow to maturity. The claim that the intention to implant or destroy this entity determines whether or not it is an embryo is confusing at best and mendacious at worst. In either case, it is certainly not based on scientific facts.

This terminological dispute arrived in a California courtroom in 2004, in a legal episode flowing from Proposition 71—a proposal that would commit the state to funding ES cell research at a large scale. Three leaders of the campaign for Proposition 71 sued to demand revisions to the state's official voter pamphlet explaining the proposed law. The pamphlet included "pro and con" statements written by advocates for and against the proposition, with the "con" statement referring to "human cloning" and noting that "the perfection of embryo cloning technology…will increase the likelihood human clones will be produced."[44] The lawsuit called those statements "false and misleading" since Proposition 71 and existing state law banned human cloning to produce children.[45] The court had to decide whether or not it was false and misleading to describe SCNT as cloning.

To support their contention that SCNT is not cloning, the plaintiffs called as expert witnesses Weissman and another stem cell scientist, Evan Y. Snyder of the Burnham Institute for Medical Research. They argued that the SCNT procedure was not the same as cloning, because researchers would never intend to implant the "product" into a woman's uterus, and therefore the process would never result in the creation of a human

child. Weissman claimed that SCNT does not produce a "human embryo clone," because the researchers destroy the blastocysts to extract ES cells, so the process "results in an embryonic stem cell line" rather than a cloned human embryo.[46]

Among the expert witnesses for the respondents was cell biologist Stuart A. Newman of New York Medical College. Newman argued that a scientist's intention to implant a cluster of liver cells in a uterus would not make them an embryo, and neither does an intention not to implant a blastocyst make it anything other than an embryo. Newman rebuked the supporters of Proposition 71 for claiming that "the material nature of a biological entity changes depending on the intention of the investigator," calling it "an example of magical thinking, which is antithetical to modern science."[47] The judge agreed, siding with the respondents and allowing the voter pamphlet to continue to mention "human embryo cloning."[48]

It is interesting to note, as Newman pointed out in his testimony, that despite the effort to police the language used to describe human cloning, "cloning" remains a widely used term of art in the field of stem cell science. In fact, one of the scientific journals dedicated to SCNT-related studies—edited by no less a luminary than Ian Wilmut, the scientist best known for creating Dolly—was called *Cloning and Stem Cells* until as recently as 2010 (when it was renamed *Cellular Reprogramming*).[49] The first apparently reliable report of human embryos created through SCNT, which was published in 2008, referred to "cloned human blastocysts" and "cloned human embryos."[50] So it is disingenuous to claim that the term cloning is simply inaccurate.

To be sure, the terms "reproductive cloning" and "therapeutic cloning" are imperfect in various ways, and several more precise terms have been proposed. For example, the President's Council on Bioethics, in its first report, *Human Cloning and Human Dignity* (2002), used the terms "cloning-to-produce-children," "cloning-for-biomedical-research," and "cloned human embryo," offering a thoughtful explanation for its choices.[51] These terms convey not just the difference of the ends of SCNT but also the similarity of the means, and they indicate that the inherent nature and status of the entity created by SCNT is the same regardless of what researchers or doctors intend to use that entity for. Any terms intended to obscure these key facts—that SCNT is a cloning technique, and that SCNT produces an embryo that must be destroyed if researchers wish to obtain ES cells from it—distort the science and mislead the policy debate. Newman's chastisement of his fellow scientists for indulging in "magical thinking" shows how advocates of ES cell research obfuscated

ethically relevant scientific facts to protect the political interests of their research project.

Misrepresentation 4: As a result of the Bush funding policy, the United States fell behind other countries in stem cell research. Commentators, advocates, and policymakers opposed to President Bush's funding policy frequently claimed over the last decade that the policy was causing the United States to fall behind other countries in stem cell research. In 2004, a group of over two hundred members of the House of Representatives signed a letter addressed to President Bush claiming that "leadership in this area of research has shifted to the United Kingdom."[52] In 2005 congressional debates, many Representatives offered variants of this claim, saying that the United States is "already falling behind the rest of the world," "falling far behind other countries, like South Korea and Singapore," "being left behind," and so on.[53] Senator Dianne Feinstein (D.-Cal.) said on the Senate floor in 2006 that Bush administration policies "have left our researchers far behind the rest of the world.... Evidence that the United States is no longer the world leader in embryonic stem cell research is mounting.... The United States... remains at the starting line."[54] Senator Barack Obama, during his 2008 presidential campaign, claimed that the Bush policy had "handcuffed our scientists and hindered our ability to compete with other nations."[55]

Were these rhetorical contentions about the effects of the Bush funding policy supported by the facts? A paper by Jason Owen-Smith and Jennifer McCormick published in *Nature Biotechnology* in 2006 purported to show that the Bush policy had resulted in a "productivity gap" between American and foreign stem cell research that posed a "danger for U.S. biomedicine."[56] This analysis was widely publicized, with major news outlets repeating the authors' judgment that U.S. stem cell researchers were "falling behind" their international counterparts.[57]

In claiming to see a "productivity gap," Owen-Smith and McCormick echoed Cold War-era talk of a "bomber gap" and "missile gap" between the United States and the Soviet Union—and just as those earlier "gaps" proved to be illusory, so too was the supposed gap in stem cell research. Notwithstanding the authors' conclusions, the data they presented told a less drastic story, showing that the United States was in fact leading the field of human embryonic stem cell research: American scientists had published nearly half of the 132 articles reviewed by the study, with the remainder of the articles divided among authors from 17 other countries. Moreover, the number of stem cell papers authored by American

scientists rose each year after the Bush policy was put in place. And 85 percent of all of the world's published ES cell research during the years the authors studied used stem cell lines approved for funding under the Bush policy.[58] The authors emphasized their finding that the proportion of studies authored by Americans declined, but that finding likely just indicated the growth of international science, in which the United States continued to provide the lead.

Two other analyses also released in 2006 confirmed that American scientists were out-publishing those from other nations. One, which counted the publications about human ES cells listed in the PubMed database between 1998 and 2005, found that 40 percent came from the United States, with the rest divided among 20 other countries. The nation with the next highest proportion was Israel, with just 13 percent.[59] The other analysis surveyed the scientific literature regarding all kinds of stem cell research (not just human ES cell research), and found that the 13,663 articles about stem cells published by American researchers between 2000 and 2004 constituted 42 percent of the world's total. German researchers were second, with just 10 percent of the total.[60] (It is worth noting that Germany's policy, which we describe in Appendix E, is more restrictive than the Bush policy.)

More recent analyses show that stem cell research flourished in the United States during the years that the Bush policy was in place, due to a combination of federal funding using the approved stem cell lines, state-funded initiatives, and private funding. In a survey of the human ES cell research literature over the past decade, *New Scientist* found that the United States has consistently dominated the field, with at least 40 percent of the world's publications in every year since 2000.[61] In the first half of 2011, 45 percent of the world's scientific publications about human ES cells had at least one American author.[62] It might be "tempting" to blame the Bush policy for making the United States fall behind in stem cell research, the magazine editorializes, but such blame would be "misplaced," both because the country *hasn't* fallen behind and because, to the extent that American researchers have proceeded slowly in bringing stem cell therapies to clinical trial, they have done so out of caution. "Again," *New Scientist* editorializes, "don't blame Bush."[63] (Of note, in the wake of President Obama's lifting of the funding restrictions, some scientists are reportedly finding that intellectual property law in the United States poses a greater obstacle to their research than did the Bush policy.[64])

The argument that the Bush policy caused the United States to fall behind other countries in embryonic stem cell research also perpetuates

a related misunderstanding, namely that the Bush policy was more onerous and restrictive than other nations' policies. In reality, many European countries have policies that are equally or more restrictive than the Bush policy. Some have banned certain forms of stem cell research and related techniques, including SCNT, while the only federal policies in the United States that explicitly touch on stem cell research have related to the qualifications for receiving government funding. Many of the nations with restrictive policies on ES cell research have produced innovative and impressive work using adult and non-embryonic pluripotent stem cells; for instance, the recent creation of an artificial trachea using adult stem cells was a collaborative effort involving researchers from several European countries, including Italy and Germany, which have some of the world's most restrictive stem cell policies.[65] (Appendix E discusses the legal and regulatory status of stem cell and embryo research in several countries and international entities.)

Meanwhile, if the Bush policy made the United States fall behind the rest of the world, then it is hard to understand why the world's first three clinical trials seeking to translate ES cell research into potential therapies have been taking place in the United States; why one of those clinical trials used ES cell lines approved for funding under the Bush policy; and why the first European clinical trial of a potential ES cell therapy, which was given the green light in 2011, is really only an extension of one of the three U.S. clinical trials, and is conducted by the same American company.[66]

Finally, it is worthwhile to state openly and to scrutinize an unspoken premise of the claim that the United States is falling behind other countries in stem cell research. To speak of "falling behind" is to suggest that the United States is in a race with other countries.[67] This suggestion is true in at least two senses: if American researchers make important discoveries in basic science, American scientific institutions will enjoy greater prestige and will attract better minds and more funding; similarly, if American researchers are the first to make marketable discoveries in applied science, American businesses will presumably profit before foreign businesses. In light of both of these hopes, the United States indeed has an interest in remaining competitive in international science. But it is surely not the *only* national interest, and to claim that the nation is falling behind in a given scientific field is not a decisive argument for rushing ahead in that field. The nation has moral responsibilities that must not be sacrificed on the altar of international competitiveness. The Bush policy sought to take those moral responsibilities seriously while allowing the science to

progress—and, as we have seen, stem cell science has indeed continued to flourish in our country.

Misrepresentation 5: More than 100 million Americans with serious illnesses could be helped with treatments derived from stem cells. A claim often repeated over the last decade by proponents of stem cell research, especially human ES cell research, is that over 100 million Americans might potentially benefit from stem-cell derived treatments. The statistic was bandied about to indicate the miraculous potential of ES cells. It appears on hundreds of thousands of websites. It was featured in the 2004 Democratic Party's national platform: "Stem cell therapy offers hope to more than 100 million Americans who have serious illnesses—from Alzheimer's to heart disease to juvenile diabetes to Parkinson's."[68] President Barack Obama cited the statistic during his 2008 campaign.[69] The 100 million figure is ubiquitous, its source is almost never mentioned, and it is rarely challenged.

Of course, we have no way of knowing how many people might be helped with stem cell-derived treatments—the science is still far too young and uncertain for any informed estimates. What, then, is the source of this statistic? How could it be that 100 million Americans—one out of every three—is ailing and in need of stem cell therapy?

The figure apparently originates in a one-page opinion piece published in *Science* in February 2000. The author, the leader of a patient advocacy group, claimed that 128 million Americans would benefit from therapies derived from pluripotent stem cells (which at the time meant only embryonic stem cells).[70] He reached this figure simply by adding up the number of Americans "affected by" cardiovascular diseases (58 million), autoimmune diseases (30 million), diabetes (16 million), osteoporosis (10 million), cancer (8.2 million), Alzheimer's disease (4 million), Parkinson's disease (1.5 million), severe burns (0.3 million), spinal cord injuries (0.25 million), and birth defects (150,000 per year).

The most charitable interpretation of the statistic is that one in three Americans might *eventually* suffer from a disease for which embryonic stem cells might *possibly* someday provide a treatment. But the statistic is usually cited in the present tense; note, for example, how the 2004 Democratic platform refers to Americans who *have* "serious illnesses." The idea that one in three Americans *currently* suffers from conditions requiring cell therapy or regenerative medicine is comically alarmist. The Centers for Disease Control and Prevention reported that in 2009, 9.4 percent of Americans described themselves as having "fair or poor

health."[71] Even if *all* of these unhealthy Americans wished to be treated with stem cell therapies, that would still only be one in ten Americans, or 30 million people. And even that scenario would depend on there being a stem cell-derived treatment for every condition affecting the health of Americans.

The methodology used to construct this figure is flawed, to put it mildly. It assumes that *all* of the patients with these ailments could be helped by stem cell-derived therapies. The notion that embryonic stem cells will provide "cures" for such broad categories of conditions as cardiovascular disease, cancer, and birth defects has only the most tenuous connection to actual stem cell science.

Misrepresentation 6: Therapies relying on stem cells are imminent. In addition to exaggerating the scope of therapeutic benefits from ES cell research, supporters of the research have exaggerated how soon such therapies would become available. There are specific examples of exaggerations from scientists, corporate spokesmen, and advocates.[72] Some of these exaggerations may have been intended to attract funding; others may have been spoken out of ignorance about the science or about the long road from basic research to clinically effective treatment. Also contributing to the overall public sense of imminent cures was the constant press coverage—headlines day after day reporting on even minor scientific papers as though they were major breakthroughs, creating the misimpression that many stem cell-based cures were only a few years away. (This kind of exaggeration has not been confined to the United States: Robert Winston, a prominent British fertility scientist, said in a 2005 speech in his capacity as president of the British Association for the Advancement of Science that "During the political campaign to encourage the U.K. Parliament to accept liberal legislation [governing ES cell research], some parliamentarians were clearly led to believe that a major clinical application was just around the corner."[73])

Policymakers also exaggerated the imminence of the research. For example, on October 11, 2004, Senator John Edwards (D.-N.C.), then a vice presidential candidate on the ticket with Senator Kerry, claimed, "If we can do the work that we can do in this country—the work we will do when John Kerry is president—people like Christopher Reeve are going to walk. Get up out of that wheelchair and walk again."[74] Reeve, who had died the day before, had been a quadriplegic since a 1995 horse-riding accident. The clear implication of Edwards's comment is that a cure for paralysis was imminent, and that a particular political result was the

necessary prerequisite of that cure. Even some supporters of ES cell research have criticized Edwards's statement as a "canonical example" of "unjustified hype."[75]

Embryonic stem cell research faces considerable hurdles before we can expect to see successful therapies from it. As we describe in Appendices A and B, stem cell therapies of all kinds are extremely complex, difficult procedures that require detailed knowledge and expertise to perform successfully. Transplanting ES cells or their products raises the problem of immune rejection, and while many have argued that therapeutic cloning could provide patient-specific stem cells, scientists have had considerable difficulty creating human embryonic stem cells using this technique, not least because of the problems associated with procuring the vast number of human eggs necessary to perform the experiments. As of this writing, ES cell therapies have only reached the earliest stages of clinical trials, and many questions related to their safety and efficacy will need to be answered before they can ever become part of regular clinical practice.

Misrepresentation 7: A clear majority of Americans supports embryonic stem cell research. A number of polls over the past decade have indicated that a majority of Americans seems to support human ES cell research—and to the extent that congressional action is a proxy for public opinion, the repeated congressional attempts to repeal the Bush funding policy suggest that ES cell research has enjoyed relatively widespread political support.[76] Critics of the Bush policy have pointed to these claims as an argument against the decision to withhold federal funds for research that most Americans wish their government to support.[77]

However, polls that found high levels of support for embryonic stem cell research were often worded in ways that obscured the ethical issues concerning the research while highlighting the potential benefits. For example, a poll of registered U.S. voters by *The Economist* during the 2004 presidential election found that 65 percent of the respondents supported embryonic stem cell research. But the question was formulated so as to tell the respondents that the reason that some people oppose stem cell research is that "it uses cells from potentially viable human embryos," while the reason some people favor the research was said to be that "the embryos otherwise would be discarded and that this research could lead to breakthroughs for treating serious diseases."[78] The respondents were not informed of the substantive ethical concern raised by the research, which is that the embryos are not just "used" but destroyed. Without this information, it is difficult for a voter who is unfamiliar with the techniques

involved in embryonic stem cell research to see what is controversial about it.

Perhaps the most careful and probing attempt to understand public opinion about stem cells was a poll conducted in 2008 by the Ethics and Public Policy Center.[79] That poll's results revealed deep public ignorance about the facts of embryonic stem cell research and confusion about the moral questions the research raises. A third of the respondents believed, incorrectly, that ES cells had "actually resulted in a cure or treatment for any diseases."[80] The poll found that 69 percent of the respondents said they supported "stem cell research"; the number dropped to 52 percent when the question asked about embryonic stem cells specifically and explained that human embryos are destroyed.[81] But when asked whether it is ethical or unethical to destroy human embryos, a majority (51 percent) said that it is unethical.[82] And 62 percent of the respondents agreed with the following statement: "An embryo is a developing human life, therefore it should not be destroyed for scientific or research purposes."[83] The poll's plainly contradictory findings show that the American public has less than a full and coherent understanding of the facts and the ethical questions of stem cell research. They also suggest a clear desire to pursue medical cures alongside a broad willingness to take into account moral challenges.

Even setting aside the empirical question of whether stem cell research is unambiguously popular, the premise of this misrepresentation is that majority opinion should act as the moral standard. Of course, in a democracy like ours, decisions are generally made according to the will of the majority. This is a fine guideline, but history is replete with examples where popular opinion proved disastrous as a moral compass. (Consider, for example, the popularity of segregation in 1950s Mississippi and Alabama.) Public figures have a duty not just to follow public opinion but also to lead it, especially on morally fraught questions—a duty, that is, to undertake the hard work of making rigorous arguments to convince minds, and expressing those arguments in a way that moves hearts.

Misrepresentation 8: Opposing embryonic stem cell research means opposing cures for suffering people. One of the tropes of the stem cell debates has been the claim that opposing ES cell research is the equivalent of opposing the potential practical, medical benefits of scientific research—as though the critics of the policy were opposed to cures. President Bush has been accused of "turn[ing] his back on the millions who stand to benefit" from ES cell research, of "putting narrow

ideology ahead of saving lives," and of telling sick people to "drop dead."[84] Opponents of ES cell research have been accused of being "against hope"—a formulation that has even made its way into political advertisements.[85] They have also routinely been called "heartless."[86] The Internet is littered with blog posts and comments from people claiming that opponents of ES cell research want people to "suffer and die."[87]

Surely not all of those who level this sort of charge against the critics of stem cell research seriously believe it; in many cases, the accusation can probably be chalked up to rhetorical excess arising in the midst of heated policy debates and political contests. Ethical argument is replaced by indignation, which in turn gives way to defamation, as these advocates of ES cell research ultimately claim that opponents do not really care for human life.

The sad irony of this line of thought is that the core *agreement* among both advocates and critics of embryonic stem cell research is that we have a fundamental obligation to protect and care for human life. The core *disagreement* is over what sorts of beings constitute human life deserving our care and protection—more specifically, over what the status of a human embryo is, and whether it deserves the protection owed to a mature human being, or no protection at all, or something in between. This question is one on which reasonable, scientifically informed people can disagree. But all of the participants in the public stem cell debates wish to see disease cured by any ethically responsible means.

Misrepresentation 9: Opposition to embryonic stem cell research is a matter of religious ideology. It is true that much of the public opposition in the United States to human embryonic stem cell research has come from religious groups, particularly the Roman Catholic Church, but also from many evangelical groups and from Americans of other faiths. This fact has sometimes been invoked by supporters of ES cell research, with two apparent implications: that the critics of ES cell research hold their views for strictly religious reasons, and that therefore their views are illegitimate.[88]

The notions that religious believers' views on stem cell research are necessarily religious opinions, and that those views should be kept out of public debates, are mistaken and undemocratic. Let us deal with these errors in reverse order.

Citizens who have made moral judgments that have a bearing on public questions have a right to attempt to persuade their fellow citizens to enact policies informed by those moral judgments. The right to partici-

pate in the political process regardless of whether our moral and political judgments are rooted in religious or secular commitments is one of the fundamental tenets of democratic self-government. While the First Amendment prohibits the government from establishing a religion, it does not deny religiously informed moral and political argument a place in the public square.

Some might argue that because religious beliefs are based on faith and revelation, they are inherently private and not open to public analysis and debate—making them subversive to sound democratic deliberation. According to this argument, even if religious views are not strictly illegitimate in public, religion is a "conversation stopper" that harms fruitful public discussion of moral or political issues.

However, in the case of the debates over human embryonic stem cell research, religious believers who oppose the research do so on grounds that are publicly intelligible, and are at least as accessible to reasoned debate as are the grounds on which supporters of embryonic stem cell research endorse the destruction of embryos. Those who oppose the destruction of human embryos argue that they are a form of human life; that human life is valuable, has certain rights, and is owed our respect; and that we therefore should not deliberately destroy human embryos for our own purposes, however noble those purposes may be. Each of these claims may be controversial, and clearly there is widespread disagreement on the moral status of the human embryo, but the argument against destroying human embryos need not depend on any theological reasoning or inaccessible faith commitments. The belief that even early human embryos are a form of human life is a straightforward interpretation of the biological facts, and while some philosophers may dispute the claim that all human life is unconditionally valuable, it is a perfectly intelligible moral position. Indeed, it is one of the great ironies of the stem cell debates that the opponents of embryo-destroying research have tended to emphasize scientific, rational knowledge concerning the nature of the embryo, while the supporters of such research have tended to rely on emotional appeals to our desire for medical treatments, or to arguments that the "personhood" we value in human life only emerges at some later, typically unspecified stage of development.

Misrepresentation 10: The Bush stem cell funding policy was an illegitimate politicization of science. This has been a prominent claim by public commentators and advocates of embryonic stem cell research—most notably President Obama, who described ending the Bush policy as a step

toward "ensuring…that we make scientific decisions based on facts, not ideology."[89]

In point of fact, there are no participants in the stem cell debates who will deny, if pressed, that public policy must be based on both facts and moral considerations. For instance, in the very same remarks, President Obama noted that he would restrict federal funding for reproductive cloning because it is "profoundly wrong, and has no place in our society, or any society"—moral judgments that are not settled by scientific fact alone. Other aspects of science policy are obviously moral as well: for example, there is universal agreement today that scientific research on human subjects ought to be conducted with informed consent, a principle that arose in part out of the horror at the work of the Nazi doctors and the Tuskegee experiments. Yet, although informed consent is by definition a restriction on scientific autonomy, no credible person would dismiss it as an improper "ideological" imposition. The notion of a purely scientific decision is itself meaningless: it would be impossible, even if we wished to, to decide what we ought or ought not to do based on scientific facts alone, without relying upon principles of some sort. Even the value we place on scientific inquiry and knowledge is itself non-scientific—that is, we value science because we value knowledge and the practical goods that science can bring us; but scientific knowledge is itself neutral as to whether or not we should value it, or for that matter whether we should value the scientific project that provides us with this knowledge. Pretending that we can somehow denude science policy of moral judgment confuses the public understanding about the proper relationship between science, moral judgment, and public policy. It also threatens to erode the foundation for restricting even those forms of research that most people agree violate ethical principles.

As we reflect on the stem cell debates, there are three key points on which all participants should and generally do agree: (1) the advancement of scientific knowledge, as part of our broader search for knowledge and truth, is good for its own sake; (2) scientific research is of enormous value for the medical and practical benefits it has brought and may yet bring; and (3) society in general, and public funding in particular, ought to support scientific research to the greatest extent that is ethically (and fiscally) responsible. The central question in the debates has been, again, whether experimentation on embryonic stem cells obtained by destroying human embryos is ethical—a matter upon which reasonable, scientifically informed people can be expected to disagree. The claim that it is illegitimate for these ethical views to be expressed in public policy represents a

profound misunderstanding of the proper relationship between science and politics. We say more about that relationship in this report's conclusion.

Case Studies from the Stem Cell Debates

The stem cell debates were carried out in scientific journals, bioethics magazines, and the popular press, in classrooms, conference halls, and political campaigns. In this section, we examine a handful of critical incidents and individuals from the stem cell debates, the better to understand the complicated relationship between science, ethics, and political practice.

Scientific Expertise and Policy—Counting the Stem Cell Lines. A key element of President Bush's 2001 funding policy was the existence of established stem cell lines, the use of which Bush believed could be ethically justified on the grounds that the direct act of destroying the embryos had not been incentivized or rewarded by the government. But a considerable controversy developed over the number of stem cell lines that were available, with one critic describing the number of cell lines estimated by the administration as "one of the most flagrant purely scientific deceptions ever perpetrated by a U.S. president on an unsuspecting public."[90] Examining this controversy points to important questions not only about the particular facts at dispute in this controversy, but about how policymakers should act in light of evolving factual knowledge.

Research involving mouse ES cells, which were first derived in 1981,[91] had almost entirely relied on just two lines of ES cells.[92] Proponents of human ES cell research believed that only a handful of stem cell lines would be necessary for the work to progress significantly, with Stanford researcher Irving Weissman telling the *New York Times* that "a finite number [of ES cell lines] would be sufficient.... If we had ten to fifteen cell lines, no one would complain."[93]

At President Bush's request, the National Institutes of Health in 2001 conducted a global survey of stem cell researchers; the agency reported back to the White House that roughly sixty stem cell lines had been established.[94] That was the figure Bush cited in his address on August 9, 2001: "As a result of private research, more than sixty genetically diverse stem cell lines already exist.... Leading scientists tell me research on these sixty lines has great promise that could lead to breakthrough therapies and cures."[95]

However, many of the ES cell lines that had been created were either not viable or not available under intellectual property restrictions. The

number of ES cell lines eligible for federal funding under the Bush policy dipped down to eleven and then rose to a final number of twenty-one.[96]

Although the number of ES cell lines eligible for funding under the Bush policy was in keeping with what researchers like Dr. Weissman had hoped for, they grew dissatisfied. With respect to the eleven cell lines available in 2003, Weissman said, "you are only looking at the genetics of people who go to in vitro fertility clinics—the white, the rich, and the infertile."[97]

(Weissman's comment, of course, reveals dissatisfaction with more than just the *number* of stem cell lines available; his criticism of the *kind* of embryos from which the cells were derived is tied to his longtime support of cloning for biomedical research, since cloning would make it possible to create stem cells that would be genetically identical to patients, allowing researchers to study genetic diseases at a cellular level. In 2002, Dr. Weissman launched a program at Stanford, among the stated aims of which is to clone human embryos for research purposes, and he continues to insist that the government should fund research on stem cell lines derived from cloned embryos.[98])

Although President Bush's estimate of the number of established ES cell lines was based on the NIH survey, his political critics accused him of intentionally lying about the number—as part of a growing narrative that the president and his party were "anti-science." Bush's claim that there were sixty ES cell lines was "a morsel of scientific misinformation so stunning…that one can only wonder what Bush and his handlers were thinking, or whether they were thinking at all," wrote journalist Chris Mooney in his 2005 book *The Republican War on Science*.[99]

Revisiting the scientists' complaints about the number of lines approved under the Bush policy with the perspective of a few more years, it turns out that American researchers have overwhelmingly relied on just two of the twenty-one approved ES cell lines. Studies on a diversity of cell lines do have certain scientific advantages, but most researchers have preferred to work with the well-characterized H1 and H9 cell lines, which have a proven track record of productivity.[100] Even after the new Obama funding policy went into effect, the Bush-approved lines remained by far the most widely used: a survey of the research presented at the 2010 International Society for Stem Cell Research conference found that over three-quarters of studies employed one or more of the cell lines approved under the Bush policy, and only 8 percent of studies used one of the cell lines newly approved under the Obama policy but not under the Bush policy.[101] And while it is still too early to know what effects the Obama funding policy will have, a 2009 article in *Nature Biotechnology* pointed out that the Bush

funding policy may have had the beneficial consequence of establishing "a reproducible yet small number of well-characterized lines [that] are now used as references for the community of stem cell researchers."[102]

One way to understand the controversy over the number of available stem cell lines is as a consequence of the differing aims of democratic government and technical expertise. Policymakers have a responsibility to seek out the best available expertise to inform their decisions. But experts disagree with one another, and their advice can rapidly shift with evolving knowledge. To accuse President Bush of "flagrant deception" for saying that sixty stem cell lines existed is to assume he acted in bad faith, when in truth our knowledge of the facts changed—just as the evolving factual landscape led scientists like Dr. Weissman to revise their views about the number of ES cell lines "sufficient" to advance the field. Moreover, and perhaps more importantly, these accusations of dishonesty ignore the broader issue that the Bush stem cell policy was primarily shaped not as a technical response to specific claims about a number of available stem cell lines, but as a considered effort to advance stem cell science within responsible ethical constraints.

Politics Distorting the Science—Ron Reagan and the Future of Medicine. During the 2004 political season, stem cell research became a major issue. Scientists organized and mobilized politically to a degree not seen since the 1964 presidential election;[103] candidates for office gave speeches and purchased advertisements criticizing their opponents' views on stem cell research; and the research became the focus of a major ballot initiative in California. We have already mentioned several misrepresentations that arose during the 2004 presidential campaign, including the repeated characterization of the Bush funding policy as a "ban" and Senator Edwards's remarks about an imminent cure for paralysis.

The episode that epitomized the grossly misleading tactics employed in the stem cell debates occurred at the Democratic National Convention in July 2004. One convention speaker after another invoked the promise of stem cells and decried the supposed ban on research; the phrase "stem cell" was uttered twenty times, making it one of the policy topics most mentioned from the podium.[104] Then, on July 27, just fifteen minutes after the keynote address by then-state senator Barack Obama, Ron Reagan, the son of the late President Ronald Reagan, rose to give a primetime speech advocating human embryonic stem cell research.

Reagan began by disavowing that he was delivering a political speech—although he was at a party convention, surrounded by throngs of cheering

partisans, speaking on a subject that the Democratic Party had sought to use as a "wedge issue."[105] His talk certainly had all the trappings of a political speech, including policy recommendations and a stirring peroration promising voters that the Democratic ticket would ensure progress.

Given the attention Reagan's speech enjoyed, with ample news coverage and a live television audience of millions,[106] it is worth looking closely at the way his remarks irresponsibly distorted the scientific facts—both in what he said and what he did not.

First, Mr. Reagan wildly exaggerated both the promise and the imminence of treatments derived from ES cells. Although the science was still very young and unsettled, he claimed that ES cell-derived treatments for Parkinson's disease would be available "ten or so years from now," and described ES cell therapy as "what may be the greatest medical breakthrough in our or any lifetime"—apparently greater even than vaccination and antibiotics, which have saved hundreds of millions of lives.[107]

Second, Reagan never explicitly stated that human ES cells are derived from human embryos that are destroyed in the process. Only attentive listeners already familiar with the science would have recognized that when Reagan spoke of "these cells" and "these undifferentiated cells multiplying in a tissue culture" he was referring not to the ES cells but to embryos themselves. In this way, Reagan avoided acknowledging that the embryo is a human organism—only conceding that "these cells could theoretically have the potential, under very different circumstances" to develop into recognizably human beings. Nor did he ever explain that creating ES cells requires the destruction of human embryos; he referred only to "interfering with the development" of embryos.

Third, he also eschewed the word "cloning," even though he gave a two-sentence description of the SCNT therapeutic cloning procedure. The artifact resulting from that procedure is a cloned human embryo, a genetic near-duplicate of another human being. (Reagan also alluded to the cloning process by saying that ES cells are "created using the material of our own bodies"—a misleading turn of phrase that suggests that ES cells are, like adult stem cells, *only* made from our bodies and do not entail the destruction of distinct organisms.)

Finally, Reagan was silent on what it would take for his vision of ES cell-based regenerative medicine—"your own personal biological repair kit standing by at the hospital"—to become a reality. For even just 1 percent of the American population to have such "repair kits" awaiting them in hospitals, the nation would first have to launch a massive project to harvest millions of eggs from women, a painful and sometimes quite dangerous

procedure. Given the necessary scale, it would surely be impossible to rely only on donated eggs, as Mr. Reagan claimed. Furthermore, we would also have to establish a vast cloning program to create the embryos from which the personalized ES cells could be collected. No wonder Reagan left these facts unsaid: to even contemplate these practical requirements of his vision would surely make the average voter blanch.

Ron Reagan's rhetoric, and the moral and political logic of his speech, reveal the way that scientific progressivism is rooted in charity—in this case, the compassionate desire to ease suffering and find cures. But if unrestrained by other moral and political goods, the impulse for scientific progress can ultimately pervert both science and compassion: and so we witness an advocate for scientific research misleading millions about science, and calling for cures that require egg-harvesting and cloning programs of dystopian dimensions.[108]

Selling Cells—California's Proposition 71. At the same time that stem cell research returned to the national spotlight during the 2004 presidential campaign, it also became a heated issue in California state politics. Proposition 71, a ballot measure called the California Stem Cell Research and Cures Initiative, proposed making stem cell research a constitutional right in the state and establishing an institute for regenerative medicine to fund it. The institute would make $3 billion in grants available to stem cell researchers over ten years, including grants for the creation of new ES cell lines through SCNT—so state taxpayers would underwrite both the creation of human embryos through cloning, and the destruction of those embryos for parts.[109] (For comparison, the NIH now spends roughly $1 billion annually on all forms of stem cell research, with human ES cell research receiving about a tenth of that figure, and none of it directly funding the cloning or destruction of embryos.[110]) The $3 billion would come from general obligation bonds, which would be paid back over thirty years at an estimated total cost to state taxpayers of $6 billion.[111]

Supporters of Proposition 71 framed the vote as a referendum on the stature of science and the need for cures. Funding for stem cell research, they contended, was the scientifically sound policy choice, while opposition to the research resulted from religious ideology or confusion about the scientific facts. Their campaign was well organized and amply funded; it raised and spent $21.6 million to convince California voters, roughly a hundred times more than the campaign against the proposition. The yes-on-71 campaign also had an unambiguous message for voters: funding stem cell research would bring cures to millions of sick Californians.

Written into the language of the proposition was the claim that "about half of California's families have a child or adult who has suffered or will suffer" from a condition that stem cell research will or could potentially treat or cure.[112] Television and radio advertisements, and the campaign's website (CuresForCalifornia.com), made emotional appeals about the urgent need for the cures that stem cells could provide millions of Californians.[113]

Meanwhile, the opponents of Proposition 71 distanced themselves from the question of the moral status of the embryo so as to better court voters in a state that overwhelmingly supports legalized abortion. In fact, they recruited to their cause groups and individuals who supported abortion, and even supported ES cell research, but who opposed the proposition because it supported cloning. (As one prominent feminist critic of Proposition 71 put it, cloning involves "substantial short-term risks to women who would undergo multiple egg extraction" to provide the necessary eggs.[114]) The opponents of Proposition 71 also sought to focus public attention on the myriad other political, economic, and ethical issues raised by the proposal.

On Election Day, the proposition passed by a wide margin (59 percent to 41 percent).[115]

No one should be surprised that the campaign for Proposition 71 relied on exaggerated emotional appeals, such as advertisements featuring a patient with Parkinson's disease saying that "we all are exposed and potentially patients of these diseases," and actor Christopher Reeve saying that by voting yes on Proposition 71, "you could save the life of someone you love."[116] After all, political campaigns aim at persuading citizens, not providing objective scientific analysis. But it is remarkable the extent to which those appeals overwhelmed other concerns, including concerns that usually resonate with voters: the cost to taxpayers, the stewardship of the state's already strained budget, and the lack of fiscal accountability and transparency.[117] That these pocketbook issues were so resoundingly defeated at the polls speaks to the powerful yearning for cures and health.

Ethical Limits and the Stature of Science—The Case of Paul Berg. Stanford University biochemist Paul Berg, a Nobel laureate, was the architect of the famous 1975 Asilomar Conference, at which scientists adopted voluntary guidelines to avoid potentially hazardous outcomes from research involving recombinant DNA technology. During that episode in the history of genetic research, both scientists and regulators acted with restraint: scientists, including Berg himself, refrained from performing new experiments, instead imposing a voluntary moratorium,

while regulators and other public officials gave scientists time to assess the dangers involved in the new genetic engineering techniques. Berg became known as a model of a scientist who understands the need for science to be governed and restrained by ethical boundaries—and so it is worth examining his role in the stem cell debates.

Berg was a prominent opponent of the Bush stem cell policy. In discussing the moral controversy underlying the stem cell debates, he acknowledged the "deeply held religious views" of some that "destruction of the blastocyst is murder."[118] But he ignored the fact that many considered such destruction not to be murder but still to be morally problematic, and he ignored the fact that many people held these views without religious motivation, and even without themselves being religious. He has also dismissed religious views "that [say], 'we dare not sacrifice a life for any purpose.'"[119] Of course, this view is not specifically religious; it is, in fact, widely held. We would never consider it justifiable to sacrifice and vivisect an infant or adult human being, whatever promising medical research might result. His condescending depiction of "confused and even fearful" citizens who "reject the tenets of evolution in favor of the Bible's literal version of creation," and of "social conservatives" who are "actively demonizing scientists conducting research on AIDS and reproductive technologies" smears the serious critics of ES cell research. He crudely conflates opposition to the practice of killing embryos with an opposition to or ignorance of scientific knowledge as such.

Berg's rhetoric broadly illustrates the problematic way that many scientists viewed the relationship between science and politics in the stem cell debates. Berg loosely articulates "the 'social contract' between the public and science," which he describes by speaking longingly of the post-World War II era in which "the federal government enthusiastically embraced untargeted research, what some often refer to as curiosity-driven research," and "the public did not question the value of this research." In apparent contrast to this, Berg says that "what is so troubling about this [stem cell] dispute is that social conservatives and their political representatives are poised to define the boundaries and even the limits of scientific research."[120]

It should instead be troubling that a prominent and decorated scientist, one respected for having helped place ethically-guided restrictions on scientific research, would find it troubling that political representatives might wish to do the same. In a 2002 interview, Berg criticized a proposed cloning ban this way: "If you think about the arrogance of it, you'd say, my God, these 500 guys sitting in Washington—a majority of them—have

said, 'We're not comfortable with this way of doing things. It offends my sensibility,' or whatever."[121] Not only does this statement evince an unwillingness to take seriously the arguments against cloning, it also expresses a clear disdain for representative government and the role that legislation and regulation play in establishing ethical guidelines for scientific research.

Describing embryonic stem cell research, Berg has mourned that the "quality of the science and its potential benefits may no longer be the principal determinant of whether a particular line of research should be permitted."[122] This is a strange sentiment. With respect to whether particular research should be *permitted*, its quality and benefits are not considerations in the first place: certainly the government has no business passing laws prohibiting research simply because it is useless or poorly conducted. However, when it comes to *allocating public funds* for research, government agencies continue to make quality and utility primary determinants for distributing grants, while not funding research that violates ethical guidelines. The dispute, as always, remains what those ethical guidelines ought to be.

Berg worries about the stature of science in American society: "After decades of being heroes, heralded as the driving forces behind the country's progress, the role of scientists in our society is up for grabs."[123] This is an overstatement. Americans continue to regard the men and women of the scientific community with esteem and gratitude for their commitment to uncovering the secrets of nature for the benefit of mankind—and continue to supply public funds that evince that regard. But while we respect the ways that scientists have made us masters and possessors of nature, we must not forget that the responsibility for deciding on ethical limits to (and public financing of) scientific activities in a democracy rests with the public at large, of which scientists (and academic bioethicists) are but a small part. The need for public deliberation on ethically controversial research is an essential part of our nation's social contract with science, not an assault on the legitimate authority of the scientific enterprise.

Lessons of the Stem Cell Debates

Science has an important place in American society, and future scientific advances—especially in biomedicine—promise to profoundly shape American life. While the stem cell debates heightened some political tensions considerably and introduced into the public square a great deal of misrepresentation and confusion, they were also an opportunity to better

understand the relationship between science, ethics, and democratic politics. The lessons we can draw from the stem cell debates may help us address controversies that arise from scientific developments in the future.

Science Informs Ethics. First, the stem cell debates remind us that scientific knowledge contributes to sound ethical analysis. The tantalizing possibility of cures for a wide range of diseases—and the ethical imperative to undertake research in pursuit of these cures—grew out of our scientific knowledge of the pluripotent property of embryonic stem cells, and their promise as a source of cellular and regenerative therapies. Equally important, however, was the contribution of the science of embryology for informing our reasoning about the moral status of the embryo itself. The biological significance of fertilization as the beginning of a human life underlies the moral meaning of human embryonic life for most opponents of ES cell research.

Knowledge of embryology, developmental biology, and cellular biology also contributed to our understanding of the less ethically problematic alternative sources of stem cells. Many proposed alternative sources depended on answers to questions regarding the biological status of particular embryos or embryo-like entities: extracting stem cells from "organismically dead embryos," for example, requires a scientifically accurate definition of embryonic death and a scientifically sound method for determining when an embryo satisfies that definition. Likewise, the Altered Nuclear Transfer proposal depends on having an accurate scientific understanding of the essential features of an embryo, along with a reliable technique for creating entities that lack these features.

Ethics Guides Science. While the ethical positions of both proponents and opponents of ES cell research were informed by scientific knowledge, in neither case was ethical reasoning simply reducible to, or resolvable by means of, scientific facts. While the science shows that the embryo is the beginning of a human life, opposing the destruction of human embryonic life depends on the ethical judgment that all human life is valuable, regardless of size, abilities, or age. Likewise, while there were good scientific reasons for supposing that ES cell research could allow for medical therapies in the future, the value that we place on relieving suffering and treating disease played an important role in assessing the ethical value of the research that held the hope of achieving these ends. Indeed, given the scientific uncertainty regarding the actual promise of the field, the value we place on pursuing medical research to relieve suffering may have

played a comparatively large role in inspiring the hope of many embryonic stem cell advocates. And so we find that ethical values shape the priorities of and set limits on the scientific enterprise.

Modern science has had charitable aims since its beginnings, when Francis Bacon argued that the "end of knowledge" is "the glory of the Creator and the relief of man's estate."[124] The pursuit of new biomedical technology—including stem cell research—is one of the most impressive manifestations of this beneficent impulse. But notwithstanding the charitable aims of modern science, ethical reflection is still needed to evaluate how particular scientific advances will contribute to or diminish human flourishing. While many of the forms of therapy promised by stem cell research would be morally laudable efforts to relieve suffering and treat disease, some potential applications of stem cells to reproductive technology or the modification or enhancement of human beings raise their own ethical questions.

In addition, ethics must place limits on what scientists do while carrying out their research. For example, they must not perform cruel or degrading experiments on human beings, regardless of the potential scientific or practical value of such experiments. Even though the scientific project is animated by broadly charitable intentions, scientists and advocates for scientific research still must reflect on the ethical implications of their experiments before carrying them out. As human beings with consciences and powers of moral reasoning, scientists are naturally equipped to consider whether the conduct of their research is cruel, inhumane, or unethical, and they are likewise capable of restraining their activities in the light of such ethical reflection. Of course, this ability does not mean that scientists are the sole moral arbiters of their own work, nor that their opinion on this point is the final word. Given the public place of science and the public consequences of unethical scientific activities, we all have a role in our democracy in deliberating about the ethics of scientific conduct and the aims that science ought to pursue.

We all share in the hope that modern biomedical research will relieve the suffering of people with serious illnesses or injuries, but we must not forget that science needs ethical boundaries, even in pursuit of a compelling cause. For there is an inherent danger in our quest for cures: it always contains a sense of immediate imperative born of desperation. This is a wholly understandable disposition, but it means that the argument from suffering must always be tempered by a more dispassionate perspective on the promise of science and the broader range of human priorities. Absent this balance, the curative quest on its own knows no bottom, and no end

to what it might justify if we make it our highest goal. The dangers of this imbalanced impulse were in evidence in many of the arguments in favor of unrestricted embryonic stem cell research that appealed to the persuasive power of sentiment, while ignoring or distorting broader ethical, practical, and scientific concerns. Ethical reflection about and boundaries on science are thus especially necessary when research is conducted in pursuit of compelling causes like the relief of suffering and the treatment of serious illness.

Science Informs Politics. To make informed decisions about both the potential and ethical implications of stem cell research, policymakers required accurate, objective scientific advice. As with any case where scientists are seeking government funding, policymakers needed to assess how valuable the research would be for the public interest. That is, they needed accurate, objective scientific advice about the potential of stem cell science to contribute to promising biomedical advances in order to fairly assess what place this research should have among our many public priorities. Exaggerated claims—such as the notion that ES cell research will provide cures for over 100 million Americans—distort the science so as to make the research seem far more valuable than a more sober assessment of its potential would suggest. Stem cell science is still at an early stage, and while it is clearly a promising field, the extent of its ability to deliver on this promise remains uncertain. Furthermore, it is one promising field among many that are calling for public resources. Nevertheless, while accurately assessing the potential of an emerging scientific field is always difficult, policymakers facing the stem cell issue in 2001 needed to make decisions based on the limited knowledge available when the science was still in its earliest stages. In the years since, just as scientific knowledge informed our reasoning on the moral status of the embryo, it also helped policymakers and the public judge how to fund and govern the research.

Politics Governs Science. Scientific research requires many things from the government, including money, support, and regulation. Scientists carrying out research on embryonic stem cells sought funding from the federal government, implicitly arguing that the potential of their work to provide medical therapies made it worthy of public support. Policymakers were called upon to make a difficult decision regarding the funding of research that promised great medical benefits but also raised troubling ethical concerns. This conflict over values made the stem cell question one that required a political resolution; it was not a technical problem that

could be settled by scientific expertise. Because the political controversy over the research was rooted in ethical concerns over the moral status of the embryo, policymakers could not make their decision by deferring to scientific expertise, as scientific expertise could only *inform* the moral question, not *resolve* it. A policy that provided unconditional support to embryonic stem cell research would favor scientific research and ignore or reject ethical concerns regarding the destruction of the embryo, but such a policy would not be based simply on scientific facts any more than a policy that restricted support for the research in light of ethical concerns.

When President Obama overturned the Bush stem cell research policy in 2009, he framed his decision as "an important step in advancing the cause of science in America."[125] Insofar as the new policy expanded the range of scientific activities that would be supported by the government to include practices that many Americans find unethical, the policy does advance the cause of scientific research in America, although at a cost to the ethical treatment of early human life.

Strangely, however, President Obama went on to say that "Promoting science isn't just about providing resources; it's also about protecting free and open inquiry. It's about letting scientists…do their jobs, free from manipulation or coercion and listening to what they tell us, even when it's inconvenient. Especially when it's inconvenient."[126] The president seems in these remarks to be comparing the stem cell debates to other debates about the relationship between science and politics; the word "inconvenient" is likely an allusion to Al Gore's climate-change movie *An Inconvenient Truth*. But as a description of the stem cell debates, the president's remarks are woefully inapt. The policy debate over ES cell research was *precisely* over the extent to which the government ought to provide resources for that research. But there was no attack on the "free and open inquiry" of stem cell scientists, nor were ES cell researchers subjected to "manipulation or coercion" under the Bush policy, as Obama implied. The idea that we must listen to scientists "even when it's inconvenient" seems particularly bizarre in light of the actual policy debates that occurred concerning embryonic stem cell research. Opponents did not find any of the claims made by scientists "inconvenient," and there is certainly nothing "convenient" about opposing this research. Opponents of ES cell research generally acknowledge that the research has promise; they simply believe that the ethical concerns attendant upon the research, especially involving the destruction of human embryos, should cause us to seek alternatives. Indeed, one might say that the "inconvenient truth" in the stem cell debates—a truth that we cannot and should not hide, either

through terminological sleights of hand or by simply ignoring it—is that the pursuit of much-wanted cures requires the destruction of nascent human lives.

It seems clear that President Obama was attempting to argue that, in the stem cell debate and elsewhere, science ought to be placed above politics. This hierarchy seems to be in keeping with the promise in his inaugural address to "restore science to its rightful place."[127] Such rhetoric trades on an ambiguity we previously noted in the meaning of the term "science." The language Obama used to justify his stem cell policy and obliquely criticize the Bush policy refers more to science as a form of *knowledge* than science as a *practice* carried out by scientists. While government has authority to regulate the activities and practices of science, insofar as those activities can be unethical or dangerous or otherwise contrary to the public interest, the government rarely has business regulating scientific knowledge. Likewise, while the government need not automatically grant funding to scientists who request support for their research, particularly when that research involves practices held to be unethical, policymakers ought to listen to what scientists tell them and recognize the authority scientific knowledge has in our society. The controversy over the Bush policy resulted not from a failure of policymakers to listen to the scientific facts presented to them, but rather from the policy decision not to grant unrestrained federal funding for ethically problematic research.

Debates over ethically contentious scientific research are necessarily political in nature. The fact that society can be sharply divided on the ethical acceptability of a form of scientific research means that there will arise conflicts requiring political resolution. If we simply ignored the ethical concerns of millions of Americans and provided funding for research involving the destruction of human embryos, we would not be putting science in its "rightful place" above politics and ideology. Rather, we would simply be making a political decision to disregard particular ethical concerns.

Instead of asking about the proper place of science, we might ask about the proper place of politics in a society dominated by science. We are profoundly grateful for the many blessings of science, but we believe that the practice of science is and must remain governed by politics, properly understood as the practice by which we regulate the terms on which we live our lives in common. That does not mean that politicians should distort scientific findings; rather, it means that scientific findings should inform policy judgments that also take into account many other crucial

factors. Science does not inherently respect human dignity; it does not of itself show us how best to govern our societies or our selves. Our children should be educated in science, but also raised to respect virtues for which science has no inherent regard. Scientific research should be publicly funded, but only in balance with other goods and never in violation of our fundamental political values. And policy decisions should be informed by science, but only alongside the political, social, and economic concerns that, in our democracy, reflect our efforts to live well and wisely.

The Integrity of Science. In the stem cell debates, scientists desired funding from the government, and public officials needed solid scientific findings to inform their decisions about how best to support and regulate research in the public interest and in accordance with ethical principles. This situation led to something of a conflict of interest for the scientific community: on the one hand, scientists sought support for a promising but controversial area of research; on the other hand, they had a responsibility to provide objective advice to policymakers facing difficult decisions. Furthermore, the debate over embryonic stem cell research was highly complex, involving many interrelated technical, scientific, ethical, and political problems. This daunting complexity made many policymakers and the public at large particularly reliant on expert advice for shaping their thinking on the issue.

Proponents of ES cell research argued that they were defending the integrity of science against unwarranted interference. But as we have shown in this report, the most egregious distortions of scientific knowledge were perpetuated by the advocates, not the critics, of ES cell research. Critics sought to place ethical limits on the conduct of scientific research—ethical limits that were based on a scientifically informed and accurate understanding of the moral meaning of human embryonic life. Advocates of stem cell research sought public support for an ethically problematic area of the scientific enterprise, which led many of them to distort the scientific findings and prospects of the research to strengthen their political case.

The integrity of science was also threatened by the attempt to extend the authority of science beyond purely scientific questions to political debates involving ethical questions of the meaning and significance of human equality—questions that are deeply contested in American society, and that science alone cannot resolve. During the stem cell debates, the interests of science-as-a-practice were sometimes treated with the same elevated respect that we rightly accord to science-as-a-kind-of-knowledge—a respect owed in large measure because the knowledge

science brings is always open to further scrutiny, rational discussion, and, as necessary, revision. Conflating these two distinct senses of science clouded democratic decision-making and risked ultimately diminishing the respect we properly have for scientific knowledge.

Science gives us an incredibly powerful way of knowing the natural world, and offers power over nature that provides us with ever-improving standards of material wellbeing and health. For this, we are all profoundly grateful. But in our gratitude we must not forget that there is more to life than material wellbeing, health, and power, and in our respect for the amazing advances in knowledge that modern science has made, we must not forget that there are moral questions that science alone is unable to answer.

Beyond the Stem Cell Debates

The controversy over embryonic stem cell research has revolved largely around the question of the moral status of the human embryo. However, with the advent of alternatives to ES cell research, including techniques for reprogramming cells and creating embryo-like entities, there is reason to hope that the lifesaving promise of regenerative medicine and cell therapy can be pursued without destroying human embryos. The potential circumvention of the embryonic stem cell controversy by scientific advances shows how conflicts between ethics and science need not always be irreconcilable.

The controversy over ES cell research may ultimately be sidestepped through the development of novel scientific techniques. Or alternatively, it may not—and the tension between our respect for nascent human life and our desire for medically and scientifically promising research may persist, and with it will persist passionately contested democratic debates. Moreover, the very technologies that may allow us to get beyond the ethical issues related to the destruction of human embryos may themselves create new ethical dilemmas. The techniques that provide ethical alternatives to ES cells also provide increasing power over human biology at the reproductive, developmental, and cellular levels. While the use of these techniques to circumvent the destruction of human embryos is praiseworthy, the power to transform and reprogram human cells may contribute to our ability to genetically engineer human beings, or possibly transform adult human tissues into developing human embryos. Moreover, many other potential uses in a wide range of research applications for cells and tissues from developing human life may well become evident. Strange

new possibilities in human reproduction will present themselves, as will new techniques that could blur the boundaries between human and animal life. As science continues to advance, giving us new technological powers over human biology, we will need to remain watchful of both the means by which scientists conduct their research and the ends for which that research is conducted.

The potential resolution of the dilemmas of embryo-destroying research also affords us an opportunity to reconsider moral questions our society has barely begun to confront: those raised by the assisted reproductive technologies that made embryonic stem cell research possible in the first place. Fertility clinics, which help tens of thousands of Americans to have children every year, have also created hundreds of thousands of human embryos that are kept in freezers, donated to other parents, or simply discarded. The practice of creating and discarding embryos threatens to make us callously indifferent toward the creation of human life, transforming human procreation into a technological manufacturing process. We still know very little about how IVF and related technologies affect the health and wellbeing of the children created with their aid, and how they transform the relationship between the generations. As we move beyond questions of the moral status of the embryo, we must begin to turn to broader questions of biotechnology and the moral meaning of human reproduction.

Notes

1. Ad Hoc Group of Consultants to the Advisory Committee to the Director, "Report of the Human Embryo Research Panel," National Institutes of Health, September 1994, available at http://bioethics.georgetown.edu/pcbe/reports/past_commissions/index.html.

2. National Institutes of Health, *69th Meeting of the Advisory Committee to the Director*, meeting transcript, December 1, 1994, 39-40.

3. *Ibid.*, 40.

4. *Ibid.*, 140.

5. Senator Robert Menendez (D.-N.J.) quoted in Dana Milbank, "Of Stem Cells and Heartstrings," *Washington Post*, April 12, 2007, A02, http://www.washingtonpost.com/wp-dyn/content/article/2007/04/11/AR2007041102043.html.

6. Neil A. Campbell and Jane Reece, *Biology*, 7th ed. (San Francisco: Pearson Education, 2005), 418.

7. M. Teresa de la Morena and Richard A. Gatti, "A History of Bone Marrow Transplantation," *Hematology/Oncology Clinics of North America* 25, no. 1 (2011): 1-15.

8. President's Council on Bioethics (PCBE), "Appendix A: Notes on Early Human Development," in *Monitoring Stem Cell Research*, Washington, D.C., 2004.

9. James A. Thomson *et al.*, "Embryonic Stem Cell Lines Derived from Human Blastocysts," Science 282, no. 5391 (1998): 1145-1147.

10. Jacqueline Pfeffer Merrill, "Embryos in Limbo," *The New Atlantis*, no. 24, Spring 2009, 18-28, http://www.thenewatlantis.com/publications/embryos-in-limbo.

11. George W. Bush, "Address to the Nation on Stem Cell Research," August 9, 2001, *Public Papers of the Presidents of the United States: George W. Bush (2001, Book II)*, Washington, D.C., 953-956, http://www.gpo.gov/fdsys/pkg/PPP-2001-book2/pdf/PPP-2001-book2-doc-pg953-2.pdf.

12. Vannevar Bush, *Science, The Endless Frontier: A Report to the President on a Program for Postwar Scientific Research*, Office of Scientific Research and Development, Washington, D.C., July 5, 1945, http://www.nsf.gov/od/lpa/nsf50/vbush1945.htm.

13. Benoit Godin, "The Linear Model of Innovation: The Historical Construction of an Analytical Framework," *Science, Technology & Human Values* 31, no. 6 (2006): 639-667. Of course, Vannevar Bush's ideas can be traced much further back, to the very beginnings of modern science. Francis Bacon, one of the first to articulate the need and propose a shape for the modern scientific project, famously argued that science could provide useful knowledge that would allow the conquest of nature for "the glory of the Creator and the relief of man's estate."

14. The Nuremberg Code was first formulated in August 1947, following the trial of Nazi medical researchers for their war crimes involving unethical human experimentation. The Code, an internationally recognized set of standards, consists of ten directives to protect the rights of human research subjects, including rights to voluntary consent and prohibitions against experiments that are foreseeably likely to result in the injury or death of the subject. The Belmont Report was issued in 1978 in the wake of the revelations about the Tuskegee experiments. The Report was the product of four years of deliberation by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The ethical principles articulated in the Report focus on four areas: "(i) the boundaries between biomedical and behavioral research and the accepted and routine practice of medicine, (ii) the role of assessment of risk-benefit criteria in the determination of the appropriateness of research involving human subjects, (iii) appropriate guidelines for the selection of human subjects for participation in such research, and (iv) the nature and definition of informed consent in various research settings." See *Trials of War Criminals Before the Nuremberg Military Tribunals under Control Council Law No. 10*, vol. 2, Washington, D.C.: U.S. Government Printing Office, 1949, 181-182, reprinted at http://ohsr.od.nih.gov/guidelines/nuremberg.html; *Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research*, National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, DHEW Publication No. (OS) 78-0012, Washington, D.C., 1978, available at http://videocast.nih.gov/pdf/ohrp_belmont_report.pdf.

15. Jay Lefkowitz, "Stem Cells and the President—An Inside Account," *Commentary*,

January 2008, http://www.commentarymagazine.com/article/stem-cells-and-the-president—an-inside-account/; George W. Bush, *Decision Points* (New York: Crown, 2010), 106-125.

16. The work of the President's Council on Bioethics (PCBE), including its reports and the transcripts of all of its meetings, is archived online here: http://bioethics.georgetown.edu/pcbe/.

17. Bush, "Address to the Nation on Stem Cell Research," 954.

18. *Ibid.*

19. The Human Cloning Prohibition Acts of 2001 and 2003 would have prohibited both reproductive and therapeutic cloning, but were not passed. See *Human Cloning Prohibition Act of 2001*, H.R. 2505, 107th Congress (July 16, 2001), http://thomas.loc.gov/cgi-bin/bdquery/z?d107:h.r.02505:; *Human Cloning Prohibition Act of 2003*, H.R. 234, 108th Congress (January 8, 2003), http://thomas.loc.gov/cgi-bin/bdquery/z?d108:h.r.00234:.

20. See, for example, Rick Weiss and Mary Fitzgerald, "Edwards, First Lady at Odds on Stem Cells," *Washington Post*, August 10, 2004, http://www.washingtonpost.com/wp-dyn/articles/A52847-2004Aug9.html.

21. Senator John Kerry, "Democratic Response to the President's Weekly Radio Address," August 7, 2004, transcript available at http://www.foxnews.com/story/0,2933,128325,00.html.

22. Arthur Caplan, "Stem-cell research a pawn in electoral politics," MSNBC.com, October 5, 2004, http://www.msnbc.msn.com/id/6142664/.

23. Arthur Caplan, "The Stem Cell Hype Machine," *Science Progress*, April 18, 2011, http://scienceprogress.org/2011/04/the-stem-cell-hype-machine/.

24. National Institutes of Health, "Stem Cell Research Funding, FY 2002-2010," *Stem Cell Information*, http://stemcells.nih.gov/research/funding/funding.htm.

25. In 2008, the NIH implemented a new methodology for reporting research funding, which the agency used to recalculate funding figures for 2007. The Bush administration total funding figure of $294 million we report here uses this revised 2007 data, found on the new NIH RePORT website, along with the data found on the NIH Stem Cell Research website. NIH, "NIH Stem Cell Research Funding, FY 2002-2010," http://stemcells.nih.gov/research/funding/funding.htm; NIH Research Portfolio Online Reporting Tools (RePORT), http://report.nih.gov/rcdc/categories/.

26. Peter Berkowitz, "The Meaning of Federal Funding," Appendix F in PCBE, *Monitoring Stem Cell Research*, Washington, D.C., 2004, 225-236, http://bioethics.georgetown.edu/pcbe/reports/stemcell/pcbe_final_version_monitoring_stem_cell_research.pdf.

27. Gautam Naik, "Lab-Made Trachea Saves Man," *Wall Street Journal*, July 8, 2011, http://on.wsj.com/pXMnUs; Gero Hutter *et al.*, "Long-Term Control of HIV by *CCR5* Δ32/Δ32 Stem-Cell Transplantation," *The New England Journal of Medicine* 360, no.

7 (2009): 692-698; Kristina Allers *et al.*, "Evidence for the Cure of HIV Infection by CCR5Δ32/Δ32 Stem Cell Transplantation," *Blood* 117, no. 10 (2011): 2791-2799.

28. David A. Prentice, "Adult Stem Cell Research Far Ahead of Embryonic," *Kansas Liberty*, August 2, 2010, http://kansasliberty.com/opinions/kansas-leaders/stem-cells/2010/adult-stem-cell-research-far-ahead-of-embryonic/.

29. Shane Smith, William Neaves, and Steven Teitelbaum, "Adult Stem Cell Treatments for Diseases?," *Science* 313, no. 5876 (2006): 439.

30. David A. Prentice and Gene Tarne, "Treating Diseases with Adult Stem Cells," *Science* 315, no. 5810 (2007): 328.

31. Shane Smith, William Neaves, and Steven Teitelbaum, "Adult Versus Embryonic Stem Cells: Treatments," *Science* 316, no. 5830 (2007): 1422.

32. David A. Prentice and Gene Tarne, "Response," *Science* 316, no. 5830 (2007): 1422-1423.

33. James Benjamin Hurlbut, "Experiments in Democracy: The Science, Politics and Ethics of Human Embryo Research in the United States, 1978-2007" (Ph.D. diss., Harvard University, 2010), 213.

34. Irving L. Weissman *et al.*, *Scientific and Medical Aspects of Human Reproductive Cloning*, National Research Council (Washington, D.C.: National Academy Press, 2002), 6.

35. *Ibid.*, 8-9.

36. Weissman quoted in Hurlbut, "Experiments in Democracy," 220.

37. Weissman *et al.*, *Scientific and Medical Aspects of Human Reproductive Cloning*, xiii.

38. See, for example, Michael West, House of Representatives, Committee on Commerce, Subcommittee on Health and Environment, *Cloning: Legal, Medical, Ethical, and Social Issues: Hearing before the Subcommittee*, 105th Cong., 2nd sess., 1998, 69; Rep. Henry Waxman, Subcommittee on Health and Environment, *Cloning*, 7; Rep. Peter Deutsch, "Human Cloning Prohibition Act of 2001," H.R. 2505, 107th Cong., 1st sess.," *Congressional Record* 147, no. 109 (July 31, 2001): H4924, http://www.gpo.gov/fdsys/pkg/CREC-2001-07-31/pdf/CREC-2001-07-31-house.pdf; Bert Vogelstein, Bruce Alberts, and Kenneth Shine, "Please Don't Call It Cloning!," *Science* 295, no. 5558 (2002): 1237; Bill Tammeus, "It's Easy to Be Misled on Stem Cell Research," *National Catholic Reporter*, June 30, 2010.

39. Paul R. McHugh, "Zygote and 'Clonote'—The Ethical Use of Embryonic Stem Cells," *New England Journal of Medicine* 351, no. 3 (2004): 209-211. See also "Statement of Dr. McHugh" in PCBE, *Human Cloning and Human Dignity*, Washington, D.C., 2002, 286, http://bioethics.georgetown.edu/pcbe/reports/cloningreport/pcbe_cloning_report.pdf. Prior to endorsing the word "clonote," Dr. McHugh suggested the term "synthesized embryo" for the product of SCNT; see PCBE, "Session 1: Human Cloning 4: Proper Use of Language" (meeting transcript), February 13, 2002, http://bioethics.georgetown.edu/pcbe/transcripts/feb02/feb13session1.html; and PCBE, "Session 4: Human Cloning 10: Ethics of Cloning for Biomedical Research," April 25, 2002, http://bioethics.georgetown.edu/pcbe/transcripts/apr02/apr25session4.html. See also Robert

P. George and Patrick Lee, "Acorns and Embryos," *The New Atlantis*, no. 7, Fall 2004–Winter 2005, 90-100, http://www.thenewatlantis.com/publications/acorns-and-embryos.

40. PCBE, "On Terminology," *Human Cloning and Human Dignity*, 37-55.

41. Hurlbut, "Experiments in Democracy," 227-229.

42. *Ibid.*

43. Erika Check, "Stem Cell Conference," *Nature News*, June 24, 2005, http://www.nature.com/news/2005/050620/full/news050620-14.html.

44. Hurlbut, "Experiments in Democracy," 237.

45. *Ibid.*

46. *Ibid.*, 239-240.

47. *Ibid.*, 241-243.

48. *Ibid.* The final form of the voter pamphlet can be found here: Office of the Secretary of State of the State of California, "Text of Proposed Laws: Proposition 71," *Official Voter Information Guide*, 10, 68-73, and 147-155, http://vote2004.sos.ca.gov/voterguide/english.pdf.

49. The journal is available online at http://www.liebertonline.com/cell.

50. Andrew J. French *et al.*, "Development of Human Cloned Blastocysts Following Somatic Cell Nuclear Transfer with Adult Fibroblasts," *Stem Cells* 26, no. 2 (2008): 485-493. While South Korean researcher Hwang Woo Suk avoided using terms like "cloning" or even "embryo" in the papers he published describing the creation of human embryonic stem cells using SCNT, it was later revealed that he had faked his results.

51. PCBE, "On Terminology," *Human Cloning and Human Dignity*, 37-55.

52. Open letter from 205 members of Congress to President Bush, April 28, 2004, quoted in Judith A. Johnson and Erin D. Williams, "Stem Cell Research," Congressional Research Service report, August 10, 2005, http://fpc.state.gov/documents/organization/51131.pdf.

53. "Stem Cell Research and Enhancement Act of 2005," 106th Cong., 1st sess., *Congressional Record* 151 (May 24, 2005): H3809-H3852, http://www.gpo.gov/fdsys/pkg/CREC-2005-05-24/pdf/CREC-2005-05-24-pt1-PgH3809.pdf.

54. Dianne Feinstein, "Checklist for Change," 106th Cong., 2nd sess., *Congressional Record* 152 (June 28, 2006): S6597, http://www.gpo.gov/fdsys/pkg/CREC-2006-06-28/pdf/CREC-2006-06-28-pt1-PgS6592.pdf.

55. Barack Obama, in response to questions from ScienceDebate.org, August 30, 2008, http://www.sciencedebate.org/debate08.html.

56. Jason Owen-Smith and Jennifer McCormick, "An International Gap in Human ES Cell Research," *Nature Biotechnology* 24, no. 4 (2006): 391-392.

57. "Stem Cell Spin," *The New Atlantis*, no. 12, Spring 2006, 112-115, http://www.thenewatlantis.com/publications/stem-cell-spin.

58. Owen-Smith and McCormick, "An International Gap in Human ES Cell Research," 391.

59. Anke Guhr *et al.*, "Current State of Human Embryonic Stem Cell Research: An Overview of Cell Lines and Their Use in Experimental Work," *Stem Cells* 24, no. 10 (2006): 2187-2191.

60. Ned Stafford, "Stem Cell Density Highest in Israel," *The Scientist*, March 21, 2006, http://www.the-scientist.com/news/display/23240/#ixzz1ZAxlnWvN.

61. "US Stem Cell Research in Robust Health," *New Scientist*, July 13, 2011, http://www.newscientist.com/article/mg21128212.800-us-stem-cell-research-in-robust-health.html; Peter Aldhous, "Supplementary Analysis: US Stem Cell Research in Robust Health," *New Scientist*, July 13, 2011, http://www.newscientist.com/article/dn20679-us-stem-cell-research-in-robust-health-supplementary-analysis.html.

62. "US Stem Cell Research in Robust Health," *New Scientist.*

63. *Ibid.*

64. Kerry Sheridan, "Rush for Patents is Choking US Stem Cell Research," Agence France-Presse, January 24, 2011.

65. Paolo Macchiarini *et al.*, "Clinical Transplantation of a Tissue-Engineered Airway," *The Lancet* 372, no. 9655 (2008): 2023-2030.

66. Jocelyn Kaiser, "FDA Lifts Hold on First-Ever Embryonic Stem Cell Trial," *Science Insider*, July 30, 2010, http://news.sciencemag.org/scienceinsider/2010/07/fda-lifts-hold-on-first-ever-embryonic.html; Geron Corp., "Geron to Proceed with First Human Clinical Trial of Embryonic Stem Cell-Based Therapy," press release, July 30, 2010, http://www.geron.com/media/pressview.aspx?id=1229; Advanced Cell Technology, Inc. (ACT), "Advanced Cell Technology Receives FDA Clearance for the First Clinical Trial Using Embryonic Stem Cells to Treat Macular Degeneration," press release, November 22, 2010, http://www.advancedcell.com/news-and-media/press-releases/advanced-cell-technology-receives-fda-clearance-for-the-first-clinical-trial-using-embryonic-stem-cel/index.asp; ACT, "Advanced Cell Technology Receives FDA Clearance for Clinical Trials Using Embryonic Stem Cells to Treat Age-Related Macular Degeneration," press release, January 3, 2011, http://advancedcell.com/news-and-media/press-releases/advanced-cell-technology-receives-fda-clearance-for-clinical-trials-using-embryonic-stem-cells-to-tre/; ACT, "ACT Receives Approval for First Human Embryonic Stem Cell Trial in Europe," press release, September 22, 2011, http://www.advancedcell.com/news-and-media/press-releases/act-receives-approval-for-first-human-embryonic-stem-cell-trial-in-europe/index.asp; Gretchen Vogel, "U.K. Approves Europe's First Embryonic Stem Cell Clinical Trial," *Science Insider*, September 22, 2011, http://news.sciencemag.org/scienceinsider/2011/09/uk-approves-europes-first-embryonic.html.

67. Indeed, stem cell research is sometimes explicitly cast as an international "race." See, for example, Joseph Fuller and Brock Reeve, "Will We Lose in the Stem Cell Race?," *Washington Post*, February 3, 2007, http://www.washingtonpost.com/wp-dyn/content/article/2007/02/02/AR2007020201525.html; "Govt to Back Study on

Nonembryonic Stem Cells," *Yomiuri Shimbun*, November 24, 2007, reprinted by the *Seattle Times* at http://seattletimes.nwsource.com/html/nationworld/2004031141_webjapanstemcells23.html; Robert L. Paarlberg, "The Great Stem Cell Race," *Foreign Policy*, no. 148, May-June 2005, 44-51.

68. "Strong at Home, Respected in the World: The 2004 Democratic National Platform for America," 2004 Democratic National Convention, July 27, 2004, 31, http://www.presidency.ucsb.edu/papers_pdf/29613.pdf.

69. "Barack Obama" (candidate responses to press questions), WashingtonPost.com, n.d., http://projects.washingtonpost.com/2008-presidential-candidates/issues/candidates/barack-obama/.

70. Daniel Perry, "Patients' Voices: The Powerful Sound in the Stem Cell Debate," *Science* 287, no. 5457 (2000): 1423.

71. Centers for Disease Control and Prevention, U.S. Department of Health and Human Services, "Health, United States, 2010: With Special Feature on Death and Dying," Washington, D.C., 2010, 225, http://www.cdc.gov/nchs/data/hus/hus10.pdf.

72. For example, Alan Trounson, now president of the California Institute for Regenerative Medicine, predicted in 2001 that within five years stem cell therapies could offer cures for Parkinson's disease, diabetes, cystic fibrosis, and paralysis; see Louise Milligan, "Stem Cell Cures a Five-Year Prospect," *The Australian*, August 28, 2001. As the years go by, "five years" continues to be a commonly proffered benchmark; see "Stem Cell Spinal Cord Repair 'Within Five Years,'" *Aspen Post*, January 29, 2009, http://aspenpost.net/2009/01/29/post-time-news-stem-cell-spinal-cord-repair-within-five-years/ and Stephen Adams, "Stem Cell Treatment for MS in Five Years?," *The Telegraph*, July 29, 2011, http://www.telegraph.co.uk/health/healthnews/8670550/Stem-cell-treatment-for-MS-in-five-years.html.

73. Steve Connor, "Scientists Guilty of 'Hyping' Benefits of Gene Research," *Independent* (London), September 5, 2005, http://www.independent.co.uk/news/science/scientists-guilty-of-hyping-benefits-of-gene-research-505577.html.

74. See, for example, Charles Krauthammer, "An Edwards Outrage," *Washington Post*, October 15, 2004, http://www.washingtonpost.com/wp-dyn/articles/A34167-2004Oct14.html.

75. Chris Mooney, *The Republican War on Science* (New York: Basic Books, 2005), 193. Mooney goes on to say that "Edwards raised hopes—possibly false ones—for cures for paralysis in the near future. In the process, he certainly abused science."

76. See, for example, Kathy L. Hudson, Joan Scott, and Ruth Faden, "Values in Conflict: Public Attitudes on Embryonic Stem Cell Research," Genetics and Public Policy Center, October 2005, http://www.dnapolicy.org/images/reportpdfs/2005ValuesInConflict.pdf; and the annual Virginia Commonwealth University Life Sciences Surveys, all available at http://www.vcu.edu/lifesci/centers/cen_lse_surveys.html.

77. See, for example, "Checklist for Change," S6597; Alan I. Leshner and James A. Thomson, "Standing in the Way of Stem Cell Research," *Washington Post*, December

3, 2007, http://www.washingtonpost.com/wp-dyn/content/article/2007/12/02/AR2007120201636.html; Editorial, "Mr. Bush's Stem Cell Diversion," *New York Times*, June 21, 2007, http://www.nytimes.com/2007/06/21/opinion/21thu1.html; Jonathan Moreno and Sam Berger, "Taking Stem Cells Seriously," *American Journal of Bioethics* 6, no. 5 (2006), http://bioethics.net/journal/j_articles.php?aid=1004.

78. "The Economist/YouGov poll," *The Economist*, August 5, 2004, http://www.economist.com/media/pdf/YouGovE.pdf.

79. Yuval Levin, "Public Opinion and the Embryo Debates," *The New Atlantis*, no. 20, Spring 2008, 47-62, http://www.thenewatlantis.com/publications/public-opinion-and-the-embryo-debates.

80. *Ibid.*, 49.

81. *Ibid.*, 50-51.

82. *Ibid.*, 51.

83. *Ibid.*, 52.

84. Gov. Bill Richardson, "Statement by Bill Richardson: Bush Turns His Back On Millions with Veto of Stem Cell Bill," June 20, 2007, archived at *The American Presidency Project*, http://www.presidency.ucsb.edu/ws/index.php?pid=94386; "Bush Vetoes Stem-Cell Funding," *Washington Times*, 21 June 2007, http://www.washingtontimes.com/news/2007/jun/21/bush-vetoes-stem-cell-funding/; Bill Press, "With Veto, Bush Tells Sick They Should Drop Dead," *Rome News-Tribune* (syndicated column widely reprinted under similar headlines), July 30, 2006; Arthur Caplan, "Bush to Stem Cell Community: Drop Dead," July 19, 2006, http://www.msnbc.msn.com/id/13935219/ns/health-health_care/t/bush-stem-cell-community-drop-dead/.

85. "House Sustains Bush's Veto of Stem Cell Bill," *FoxNews.com*, July 20, 2006, http://www.foxnews.com/story/0,2933,204375,00.html. See also these campaign commercials on the issue of ES cell research: "Says 'Scott Walker Says He Would Ban Stem Cell Research,'" Politifact Wisconsin Truth-O-Meter, October 10, 2010, http://www.politifact.com/wisconsin/statements/2010/oct/10/tom-barrett/democratic-governor-candidate-tom-barrett-says-opp/; "Perdue's Second Version of Stem Cell Ad, Under the Dome," *Raleigh News & Observer*, September 09, 2008, http://projects.newsobserver.com/under_the_dome/perdues_second_version_of_stem_cell_ad.

86. Ernest Dumas and Max Brantley, "Bush's Heartless Act," *Arkansas Times*, July 27, 2006, http://www.arktimes.com/arkansas/bushs-heartless-act/Content?oid=867798; Matthew Rothschild, "Obama Hits Right Notes on Stem Cell Research; Republicans Heartless," *The Progressive*, March 9, 2009, http://www.progressive.org/node/127183/210.

87. There are far too many examples of this sentiment to cite here, but one that is particularly notable appears on the blog of an NIH-funded stem cell researcher at the University of California, Davis: "Those who oppose ESC research as unethical are in effect telling millions of patients who might be helped by such technology 'sorry, you have the wrong disease, go ahead and suffer and die because current medical tech-

nology can't help you!'" From "News Flash: George W. Bush Deserves Credit For iPS Cells?," Knoepfler Lab Stem Cell Blog, September 12, 2011, http://www.ipscell.com/2011/09/news-flash-george-w-bush-deserves-credit-for-ips-cells/.

88. To offer a few examples: In 2009, Thomas B. Okarma, then the CEO of stem cell company Geron, told CNN that the "religious right" had a long history of opposing medical advances like stem cell research (*Newsroom*, CNN, January 23, 2009); Former Senator John Danforth (R.-Mo.) argued that "calling these blastocysts human life can only be understood as a statement of religious doctrine, and advancing legislation to protect them can only be understood as attempting to enforce religion by resorting to the criminal law.... Opposition to embryonic stem cell research and SCNT is... based solely on a religious belief that life begins before implantation in the uterus.... Legislators considering banning such research should realize that they are being asked to establish one religious point of view and to oppose another" (John Danforth, *Faith and Politics* [New York: Viking Adult, 2006], 93 and 97); Ron Reagan, speaking at the 2004 Democratic National Convention, said that opposition to ES cell research was an "article of faith" and that the "theology of the few" should not "be allowed to forestall the health and well-being of the many" (Ron Reagan, speech at the Democratic National Convention, July 27, 2004, transcript at PresidentialRhetoric.com, http://www.presidentialrhetoric.com/campaign/dncspeeches/reagan.html, video at C-SPAN, http://www.c-spanvideo.org/program/Day2Ev/start/11366/stop/11940); Rick Weiss, a *Washington Post* reporter who later worked at a progressive think tank and in the Obama White House, compared the "religious conservatives" concerned about stem cell research to the oppressive Taliban regime in Afghanistan (Rick Weiss, "Bush Unveils Bioethics Council," *Washington Post*, January 17, 2002, http://www.washingtonpost.com/ac2/wp-dyn/A57155-2002Jan16); and University of Mississippi law professor Larry Pittman, in a law review article arguing that the Bush policy was a violation of the First Amendment, wrote that "Other than his belief in the sanctity of embryos as humans from the moment of conception, there is no logical explanation for the August 9, 2001 ban. Therefore, the ban, premised on the President's efforts to promote religious doctrine regarding the source of and the sanctity of human life, presents substantial Establishment Clause problems" (Larry J. Pittman, "Embryonic Stem Cell Research and Religion: The Ban on Federal Funding as a Violation of the Establishment Clause," *University of Pittsburgh Law Review* 68, no. 138 (2006): 131-190).

89. Barack Obama, "Remarks on Signing an Executive Order Removing Barriers to Responsible Scientific Research Involving Human Stem Cells and a Memorandum on Scientific Integrity," *Public Papers of the Presidents of the United States: Barack Obama (2009, Book I)*, March 9, 2009, Washington, D.C., 201, http://www.gpo.gov/fdsys/pkg/PPP-2009-book1/pdf/PPP-2009-book1-Doc-pg199-2.pdf. Other examples include Nobel Prize laureate Elizabeth Blackburn claiming that in the Bush administration, "scientific research...is being manipulated for political ends" (Elizabeth Blackburn, "Bioethics and the Political Distortion of Biomedical Science," *New England Journal of Medicine* 350, no. 14 [2004]: 379-380); Representative Diana DeGette (D.-Col.) touching on this theme numerous times in her book *Sex, Science, and Stem Cells*, as in the statement "Over time, I realized that the politicization of science by the Republicans and the religious right was at its most insidious over any issue relating to

human reproduction" (Diana DeGette, *Sex, Science, and Stem Cells: Inside the Right Wing Assault on Reason* [Guilford, CT: Lyons Press, 2008], xiv); and Mark Rasenick, director of the Biomedical Neuroscience Training Program at the University of Illinois College of Medicine, writing in the *Chicago Tribune* that "the Bush administration has sought to politicize stem cell research.…Science policy should be driven by science, not politics" (Mark M. Rasenick, "Stem Cells," *Chicago Tribune*, October 28, 2004, http://articles.chicagotribune.com/2004-10-28/news/0410280254_1_stem-cell-embryonic-cells).

90. Mooney, *The Republican War on Science*, 2.

91. Martin J. Evans and Matthew H. Kaufman, "Establishment in Culture of Pluripotent Cells from Mouse Embryos," *Nature* 292, no. 5819 (1981): 154-156; Gail R. Martin, "Isolation of a Pluripotent Cell Line from Early Mouse Embryos Cultured in Medium Conditioned by Teratocarcinoma Stem Cells," *Proceedings of the National Academy of Sciences* 78, no. 12 (1981): 7634-7638.

92. Lefkowitz, "Stem Cells and the President—An Inside Account," 22.

93. David E. Sanger, "Bush Leans Against Support for Stem Cell Research, Aides Say," *New York Times*, June 22, 2001, http://www.nytimes.com/2001/06/22/science/22BUSH.html.

94. George W. Bush, "The President's News Conference in Crawford, Texas," August 24, 2001, *Public Papers of the Presidents of the United States: George W. Bush* (2001, Book II), Washington, D.C., 1023, http://www.gpo.gov/fdsys/pkg/PPP-2001-book2/pdf/PPP-2001-book2-doc-pg1018.pdf; Arshad Mohammed, "Bush's Stem-Cell Decision Gets Mixed Reviews," Reuters, August 10, 2001.

95. George W. Bush, "Address to the Nation on Stem Cell Research," 955.

96. NIH, "NIH Human Embryonic Stem Cell Registry Under Former President Bush," *Stem Cell Information*, http://stemcells.nih.gov/research/registry/eligibilitycriteria.asp.

97. Nicholas Wade, "Specter Asks Bush to Permit More Embryonic Cell Lines," *New York Times*, April 23, 2003, http://www.nytimes.com/2003/04/23/us/specter-asks-bush-to-permit-more-embryonic-cell-lines.html.

98. Paul Elias, "Stanford to Spawn New Stem Cells," Associated Press, December 11, 2002, http://www.wired.com/medtech/health/news/2002/12/56802; Monya Baker, "Irving Weissman: Creating a Standard for Stem Cell Therapies and Culturing the Unorthodox," *Nature Reports Stem Cells*, published online August 13, 2009, http://www.nature.com/stemcells/2009/0908/090813/full/stemcells.2009.107.html; Stanford School of Medicine Institute for Stem Cell Biology and Regenerative Medicine, "Developing New Stem Cell Lines for Study of Genetic Disorders," http://stemcell.stanford.edu/research/new_stem_cell_lines.html.

99. Mooney, *The Republican War on Science*, 2.

100. Christopher T. Scott, Jennifer B. McCormick, and Jason Owen-Smith, "And Then There Were Two: Use of hESC Lines," *Nature Biotechnology* 27, no. 8 (2009): 696-697.

101. Christopher T. Scott *et al.*, "Federal Policy and the Use of Pluripotent Stem Cells,"

Nature Methods 7, no. 11 (2010): 866-867.

102. Christopher T. Scott *et al.*, "And Then There Were Two," 697.

103. "Politicizing Science, Sixties-Style," *The New Atlantis*, no. 7, Fall 2004-Winter 2005, 151, http://www.thenewatlantis.com/publications/politicizing-science-sixties-style.

104. Timothy Noah, "Party of Stem Cells," *Slate*, August 3, 2004, http://www.slate.com/articles/news_and_politics/chatterbox/2004/08/party_of_stem_cells.html.

105. *Ibid.*

106. "Historic TV Ratings: Democratic Conventions," Nielsen Wire (blog), August 27, 2008, http://blog.nielsen.com/nielsenwire/media_entertainment/historical-tv-ratings-democratic-conventions-1960-2004/.

107. Ron Reagan, speech at the Democratic National Convention, July 27, 2004, transcript at PresidentialRhetoric.com, http://www.presidentialrhetoric.com/campaign/dncspeeches/reagan.html, video at C-SPAN, http://www.c-spanvideo.org/program/Day2Ev/start/11366/stop/11940.

108. Gilbert Meilaender, "Stem Cells and the Reagan Legacy," *The New Atlantis*, no. 6, Summer 2004, 19-25, http://www.thenewatlantis.com/publications/stem-cells-and-the-reagan-legacy.

109. Office of the Secretary of State of the State of California, "Text of Proposed Laws: Proposition 71," *Official Voter Information Guide*, 147-155, http://vote2004.sos.ca.gov/voterguide/english.pdf.

110. National Institutes of Health, "Estimates of Funding for Various Research, Condition, and Disease Categories (RCDC)," data last updated March 15, 2011, http://report.nih.gov/rcdc/categories/Default.aspx.

111. Legislative Analyst's Office, report on Proposition 71, July 2004, available in the Internet Archive at http://web.archive.org/web/20110519181519/http://www.lao.ca.gov/ballot/2004/71_11_2004.htm.

112. Office of the Secretary of State, "Text of Proposed Laws: Proposition 71," 147.

113. See CuresForCalifornia.com in the Internet Archive at http://web.archive.org/web/20041030084215/http://www.curesforcalifornia.com/.

114. Judy Norsigian, "Stem Cell Research and Embryo Cloning: Involving Laypersons in the Public Debates," *New England Law Review* 39, no. 3 (2005): 528. See also NoOn71.org in the Internet Archive at http://web.archive.org/web/20041103031021/http://www.noon71.org/.

115. Office of the Secretary of State of the State of California, "State Ballot Measures," November 2, 2004, http://vote2004.sos.ca.gov/Returns/prop/00.htm.

116. "June and Leilani," "Scott and Lenore," "Christopher Reeve—Reeve Foundation" (Yes-on-71 Campaign ads), quoted in Hurlbut, "Experiments in Democracy," 286.

117. Hurlbut, "Experiments in Democracy," 257-295.

118. Paul Berg, "California Speaks Out on Stem Cells," in *States and Stem Cells: The Policy and Economic Implications of State-Funded Stem Cell Research*, ed. Aaron D. Levine (Princeton, N.J.: University, 2006), 21, http://wws.princeton.edu/research/prior-publications/conference-books/stemcell.pdf.

119. Paul Berg, interview by Mark Schwartz, "Paul Berg: Use Cloned Embryonic Stem Cells to Cure Disease," *Stanford Report*, October 2, 2002, http://news.stanford.edu/news/2002/october2/frontiersberg-102.html.

120. Berg, "California Speaks Out on Stem Cells," 20-21.

121. Berg, "Paul Berg."

122. Berg, "California Speaks Out on Stem Cells," 21.

123. *Ibid.*

124. Francis Bacon, *The Advancement of Learning* (1605), Book I, Chapter V, paragraph xi.

125. Barack Obama, "Remarks on Signing…," 200.

126. *Ibid.*

127. Barack Obama, "Inaugural Address," *Public Papers of the Presidents of the United States: Barack Obama (2009, Book I)*, January 20, 2009, Washington, D.C., 2, http://www.gpo.gov/fdsys/pkg/PPP-2009-book1/pdf/PPP-2009-book1-Doc-pg1.pdf.

Appendix A
The Science of Embryonic Stem Cell Research

This appendix provides a brief overview of the following questions: What are embryonic stem cells and how are they obtained? What benefits are expected from the study and use of embryonic stem cells? And what alternative methods are available to procure cells functionally similar or identical to embryonic stem cells, without destroying embryos?

Embryonic Stem Cells: What They Are

A notable feature of the genetic constitution of a living organism is the fact that the same genomic structure, found from cell to cell throughout the organism's body, plays a different functional role in each type of cell, tissue, and organ.[1] Consider the differences between, for example, the cells in the pancreas that are responsible for the production of the hormone insulin—which is necessary for regulating glucose levels in the blood—and the cells of the liver, which are responsible for, among other things, transforming glucose into glycogen in response to insulin produced in the pancreas.[2] Each of these types of cells does different work for the organism and is thus functionally different from the other types. Yet each type of cell (in human beings there are approximately 200 basic types and thousands of subtypes[3]) contains the full genetic complement of more than 20,000 genes; that is, different types of cells contain the same genotype.[4] What accounts for this difference in form and function if it is not due to a difference in genes?

The answer is that there *is* a difference between these cells—not in the genes possessed, but in the genes activated, or expressed.[5] Biologists estimate that most human cells only express about 20 percent of the genes they possess at any one time.[6] In different cell types, different genes are active or inactive, or are expressed at different rates; the resulting pattern of gene expression, in conjunction with other factors such as cell position, determines the nature and function of each cell in the organism's body.[7]

The full differentiation of cells (into, say, liver cells or blood platelets) is the result of a process that begins when an organism is an embryo and continues throughout its life. A human embryo develops two structures

within its first five days: an inner cell mass (ICM) of tightly compacted cells and an outer boundary called the trophoblast.[8] In each structure, cells are relatively unspecialized, or undifferentiated.[9] But in the course of the developing life of the embryo, fetus, and eventually newborn, those initial cells will divide through a process called mitosis and give rise to increasingly specialized families of cells. Generally speaking, cells from the trophoblast will give rise to cells that form part of the placenta (the organic support system of the fetus while it is in the womb), while cells of the ICM will give rise to all of the different cell types of the mature organism.[10]

Stem cells are defined by two properties: first, the capacity for self-renewal, and second, the capacity to produce other cells that are more differentiated.[11] Stem cells vary in their potency—the number of differentiated cell types they can produce. Embryos at the single-celled stage (the stage called the "zygote," or fertilized egg) are *totipotent*—capable of differentiating into any cell type of the ICM or trophoblast.[12] Embryonic cells remain totipotent through the first few stages of cell division, and any totipotent cell is capable of becoming a whole new embryo and producing a developed organism.[13] (This is evident in the phenomenon of twinning: one way twinning can occur is when the two-cell embryo splits apart into two separate totipotent cells, each capable of developing into an adult.[14]) While the cells of the early embryo are totipotent, researchers have not been able to isolate cells from the embryo to grow totipotent stem cells *in vitro*.[15]

Meanwhile, certain cells of the ICM are *pluripotent*—capable of producing all of the differentiated cell types of the mature organism, but not of producing cells of the trophoblast (although researchers have been able to induce embryonic stem cells to produce trophoblast cells under certain conditions).[16]

As the organism develops and matures, the process of cell production remains essential to its survival. In order to keep pace with the organism's growth, and with the continual process of cell death and replacement, new fully-differentiated cells must be produced in different regions of the body. This is the work of somatic stem cells, also known as adult stem cells.[17] Adult stem cells are typically *multipotent*—capable of producing only cell types belonging to particular tissues.[18] Generally speaking, then, stem cells become more restricted in potency over the early development of the organism; put another way, stem cells become more determinate in the types of tissue they will produce, while still maintaining their capacity for self-renewal.

The term "adult stem cells" is somewhat misleading, since these stem cells can be found in children and even fetuses.[19] Adult stem cells have a remarkable ability to renew themselves—a property that allows them to sustain the growth and development of the body—although scientists have had difficulty sustaining adult stem cell self-renewal indefinitely *in vitro*.[20]

Different types of adult stem cells can be extracted from different tissues in the body. Blood-forming stem cells, called hematopoietic, reside in the bone marrow.[21] The marrow is also one of several places where mesenchymal stem cells, which form bone, cartilage, and other types of tissue, can be found.[22] They can also be found in body fat, also called adipose tissue (which requires less invasive procedures to reach).[23] The placenta[24] and the umbilical cord[25] are also rich sources of stem cells that have the potential to develop into a variety of tissue types. Other somatic tissues, including muscles and neural tissue, can be sources of specialized stem cells.[26]

A wide variety of potential therapeutic uses exists for adult stem cells, and their extraction and use generates little if any controversy. But a key practical drawback to the therapeutic applications of adult stem cells is their limited potency: stem cells from a particular tissue region can usually be coaxed only into generating further cells of that tissue type.[27]

Embryonic stem cells, on the other hand, have a much greater capacity. Within the life of a developing organism, pluripotent cells play a foundationally important role: they are the ancestor cells that will give rise to all the different cell types of the mature organism's body. Their open-ended potentiality also makes them extremely attractive for scientific research when extracted from the embryo, especially by contrast with adult stem cells.

How Embryonic Stem Cells Are Obtained

The extraction by scientists of cells from the developing embryo—a process that destroys the source embryo—is typically carried out as follows: An embryo four to five days old is immersed in a chemical solution that dissolves and destroys its trophoblast cells, which allows for the cells of the ICM, called blastomeres, to be extracted.[28] These cells can then be placed in specialized culture conditions designed to enable them to grow as colonies of stem cells.[29] The chains of cultured embryonic stem cells and their progeny are referred to as embryonic stem cell *lines*.

Scientists generally employ three tests to assess the pluripotency of stem cells. The stem cells can be injected into an animal with a compromised immune system in order to see if they develop into teratomas, a special type of relatively benign tumor consisting of cells from all three

germ layers of the embryonic body.[30] Because the different germ layers represent distinct developmental paths, the ability of a cell to differentiate into cells from each of the three layers indicates its ability to form all the cell types of the body, even if the teratoma does not consist of each and every cell type in the body.[31] A second test of pluripotency is the ability of the stem cell to contribute to the development of a chimera—an organism with some cells that are genetically distinct from the rest of the organism.[32] In this test, the stem cells are injected into an early embryo, where they contribute to the development of the fetus and adult organism, resulting in a chimera in which cells originating from the stem cells are found in all of the tissue types in the adult organism's body.[33] In the third test of pluripotency, stem cells are injected into an embryo that has been modified so as to make it capable of developing into placental tissues but not the cells of the embryo itself. When the stem cells are added to this special embryo—called a "tetraploid" embryo because the procedure for creating it involves fusing the two cells of the early embryo, resulting in a cell with four sets of chromosomes—the ability of the stem cells to develop into all of the different cell types of the embryo complements the ability of the tetraploid embryo to develop into the tissues of the placenta, thus allowing for normal embryonic development.[34] This procedure, called the "tetraploid complementation assay," is the most stringent test of pluripotency because it creates an organism that is entirely derived from the stem cells used in the procedure. (It is worth noting that, although scientists use all three of these tests in researching *animal* stem cells, they do not use the chimera formation test or the tetraploid complementation assay on *human* stem cells. For ethical and practical reasons, they rely only on the teratoma formation test, in which human embryonic stem cells are injected into immune-compromised mice.[35])

While research on adult stem cells can be traced back decades—indeed, hematopoietic stem cell transplants have been used to treat persons suffering from bone marrow diseases, including cancer, since the 1950s[36]—the key breakthrough for human ES cell research was achieved in 1998 when University of Wisconsin researcher James Thomson announced that he had derived ES cells from human embryos.[37]

Two related issues at this point are of interest because of the ethical questions to which they give rise. The first concerns the *origin of the embryos* from which ES cells are derived. The most practicable source of ES cells is embryos that have been created in fertility clinics through IVF but are "left over" from attempts to aid infertile couples in conceiving. In IVF, a sperm and an egg cell (oocyte) are joined in a petri dish. The result-

ing embryo is then allowed to grow for several days before it is either implanted in the woman or, if it is not to be used immediately, frozen and stored.[38] An American IVF clinic will typically produce more embryos than are used in each cycle of treatment, in order to have additional embryos available in case some turn out to be unusable or the implantation is unsuccessful. Therefore, some embryos usually remain after an IVF cycle has been successfully initiated; currently, there are several hundred thousand of such "spare" embryos frozen in IVF clinics in the United States.[39] The parents of these embryos may choose to donate them to be used in research if they do not wish to use them in a future IVF cycle.[40] Many supporters of ES cell research see these embryos as the most promising source of ES cells. However, as enticing as this sitting stockpile may be to interested researchers, most of the stored embryos have not been designated by the parents for research; they may be unsure if they wish to try to conceive again in the future, or may be uncomfortable donating their embryos to research for other reasons.[41] Further, even when the parents do consent, there are various logistical barriers to using these embryos for research, including possible degradations experienced in long storage, the hazards of transportation from clinic to laboratory, and reduced viability to begin with (the fertility clinicians will have selected the strongest-seeming embryos for the first round of implantation).

The same IVF procedure of creating embryos for fertility treatment could also be used to create embryos specifically for research purposes.

Another source of embryonic stem cells involves the process known as somatic cell nuclear transfer (SCNT), a kind of cloning. In this approach, which will be discussed further below, an enucleated oocyte (that is, an egg whose nucleus has been removed) is fused with the nucleus of a somatic cell (a cell containing the full complement of genetic material, unlike a gamete cell such as a sperm or egg, which contains only half). The oocyte "reprograms" the nucleus back to a totipotent (undifferentiated) state. This one-celled organism, which is genetically almost identical to the organism that provided the somatic cell, is now effectively a new embryo, and it begins the process of cellular division and growth. The embryo could be implanted in a womb; this is how Dolly, the cloned sheep, was created.[42] Or the embryo could be used as a source of ES cells.[43]

It is worth noting that the cloned embryo and the ES cells that result from SCNT are usually not *completely* genetically identical to the original somatic cell and the organism that provided it. The DNA in the new cells' nuclei would be identical to that in the original cells' nuclei. But DNA is also present outside the nucleus, in the mitochondria. Except in cases

where a female provides both the eggs and the somatic cell for the SCNT procedure, the mitochondrial DNA of the egg used in the SCNT process will be different from that of the donor cell, possibly leading to mitochondrial disorders, which have been observed in cloned mammals.[44]

An alternative version of SCNT that would not require the procurement of egg cells from women is called interspecies SCNT (iSCNT). In this process, the nucleus of a *human* somatic cell is transplanted into an enucleated *animal* oocyte in order to produce embryonic stem cells. Because the nucleus of the animal oocyte has been removed, most of the DNA in the resulting embryo will be human, although the small amounts of mitochondrial DNA present in the cytoplasm of the animal oocyte will be present in the resulting embryo. The organisms created via iSCNT have been dubbed "cybrids"—cytoplasmic hybrids—since they have human DNA placed in the cytoplasm of an animal oocyte. While this technique has been successfully used to clone certain mammals of species that were closely related to one another,[45] attempts to perform iSCNT with human nuclei have been so far unsuccessful. Some scientists have expressed doubts about whether iSCNT can work in humans at all, since SCNT relies on the ability of the oocyte to "reprogram" the genome of the nucleus into an embryonic state, but the somatic cell nucleus must be compatible with the oocyte in order for this "reprogramming" to be successful.[46]

Three other procedures also can, in practice or in theory, produce human embryonic stem cells. First, it is possible to reprogram somatic cells to a pluripotent state by fusing them with existing ES cells.[47] Second, blastomeres can be extracted from living embryos without destroying the embryos. This kind of blastomere extraction is already done now in a practice called preimplantation genetic diagnosis (PGD), which is used by IVF clinics to screen embryos before they are implanted. Blastomere extraction apparently does not always significantly interrupt the embryo's biological functioning, although some embryos are evidently lost as a result of this process, as the rate of successful pregnancies following PGD is lower than with other assisted reproduction technologies, and there is evidence that twins or triplets born following PGD have increased rates of birth defects and infant mortality.[48] Third, dead embryos maintained in culture often contain living cells, which might also provide a source of ES cells in the strict sense.[49]

These latter two procedures highlight the second important issue surrounding embryonic stem cells, namely, the *consequences for the embryo* of ES cell extraction. When blastomeres are extracted from an IVF embryo or an SCNT embryo by dissolving the trophoblast, the resulting stem

cells have been obtained at the cost of the embryo's life. By contrast, when blastomeres are extracted from living embryos without dissolving the trophoblast, or when blastomeres are extracted from dead embryos, the resulting stem cells will not have been obtained by destroying embryos. Although the long-term medical consequences to a living embryo brought to term after blastomere extraction are not yet known, these techniques suggest the possibility of attaining human embryonic stem cells without the destruction of living human embryos.

The Value of Embryonic Stem Cells

Since the first successful extraction of human embryonic stem cells in 1998, the field of ES cell research has been awash in grand expectations. The source of these expectations is the link between ES cells and the field of regenerative medicine.[50] Because ES cells are pluripotent, they have the capacity, in principle, to proceed down almost any path of cell differentiation we might wish, provided only that we know what cues are necessary to induce such differentiation.[51] Knowledge of these cues—which include the proteins that promote or block transcription of DNA into RNA in a cell, known as transcription factors, as well as other physical and chemical factors such as adhesion, pressures, and various other aspects of the cellular environment—could help make it possible to grow tissue cultures of any specific type from ES cell lines, and perhaps even to grow entire organs. Across a range of medical cases, such as neurological damage, heart disease, or the inability of the pancreas to produce insulin, the hope is that stem cell therapies could facilitate the regeneration of damaged tissues or organs, or the cure of diseased tissues and organs, by replacing or supplementing existing tissues and organs with healthy ones.[52] (For a more extensive discussion of the treatment potential of stem cell-derived therapies, see Appendix B.)

However, the possibility of applying stem cell research to regenerative medicine faces a number of hurdles, of which three are especially significant. The first is the tumorigenic (tumor-forming) character of embryonic stem cells.[53] As discussed earlier, ES cells have the characteristic ability to form teratomas, which are a relatively benign form of tumor. But malignant tumors called teratocarcinomas tend to result from ES cells that have an abnormal number of chromosomes, which sometimes occurs when ES cell lines are grown *in vitro*.[54] This trait of ES cells constitutes a further difference between ES cells in an embryonic stem cell line and ES cells in the ICM, where they contribute to the ordinary course of

embryological development instead of forming tumors. The processes causing this transition to tumorigenicity are not well understood. But safe therapies involving ES cells will be difficult to develop unless a way is found to restrain this aspect of their power.

The second hurdle to ES cell therapies concerns the problem of immune rejection. This is the same difficulty intrinsic to any transplant procedure: when an organ from one organism is transplanted into another organism, the recipient's immune system recognizes that the transplant is genetically different and attacks the alien cells.[55] This process can sometimes work in reverse as well, since transplanted immune cells can recognize the new host as alien, resulting in graft-versus-host disease.[56] In either case, similar consequences can be expected where ES cell-derived tissues and organs with a different genetic character are used in regenerative therapies. (By contrast, many adult stem cell therapies can avoid the problem of immune rejection by using stem cells that actually come *from* the recipient, which allows for the transplantation of stem cells that are genetically identical to the patient.)

The problem with immune rejection has led to increasing interest in SCNT (cloning) as a method of obtaining embryonic stem cells. For example, if SCNT-generated embryos were used instead of IVF embryos, the patient's own somatic cells could be used as the source of the cell nucleus inserted into the oocyte and reprogrammed back to a totipotent state.[57] Since the ES cells and any tissues derived from them would be genetically almost identical to the recipient's cells, the problem of immune rejection might be eliminated. (As mentioned above, the SCNT-generated cloned cells would not be *completely* genetically identical to the recipient's cells, because they would retain the mitochondrial DNA of the egg used in the SCNT process.[58])

A third major challenge facing embryonic stem cell therapy involves generating the right kinds of differentiated cells using pluripotent stem cells. While ES cells have the theoretical ability to differentiate into any type of cell in the body, coaxing ES cells to develop into specific, functional cell types in the laboratory will require a thorough understanding of the factors that control stem cell differentiation.[59] While scientists have made progress differentiating ES cells into specific cell types, a recent study published in *Cell Research* found that the differentiated progeny of ES cells tend to express genes associated with early fetal development, raising questions regarding their therapeutic usefulness for adults.[60]

Beyond the possibilities of ES cell-derived regenerative therapies, which are still largely speculative, there lie a number of more immediate scientific

and medical benefits to be gained from the study of ES cells. At the most basic level, ES cells give scientists the opportunity to learn more about cell differentiation and about the factors implicated in gene expression. Such knowledge is additionally helpful in our understanding of the development of the human organism from its zygotic stages on, and will come to be integrated into the broader understanding of genetics and epigenetics.[61]

A second expected benefit comes from the use of ES cells to learn more about the workings and natural histories of genetic diseases. By studying ES cells taken from embryos with particular genetic conditions—often identified through preimplantation genetic diagnosis—scientists can learn more about how deficiencies in gene expression arise, and thus how they might be prevented or cured.[62] ES cells provide a window into genetic disease not easily obtained in any other way.

Finally, stem cell cultures that have been differentiated into particular tissue types may be used to study the effects of certain drugs, or to test for the toxicity of various chemicals.[63] Such options could alleviate the need for at least some animal testing and could also provide a more fine-grained knowledge of the effects of environmental conditions on human biology.[64]

For all these reasons, embryonic stem cells are considered by many researchers to be of critical scientific value and medical importance. However, in order to avoid the ethical worries that arise from destroying or harming embryos, researchers have proposed a number of alternative techniques for procuring pluripotent stem cells that are the functional equivalent of embryonic stem cells—techniques not dependent upon human embryos. While many believe that these alternative approaches can mitigate the ethical concerns, some scientists claim that even the alternative techniques require some research into ES cells, for such cells are said to provide the "gold standard" for understanding pluripotent cells more generally.[65] On this view, ES cell research provides an important gauge for the inquiries of scientists investigating alternatives to ES cells. In the following section we turn to some of the key attempts to find alternatives to embryonic stem cell research.

Alternatives to Embryonic Stem Cells

In this section we look at two of the most prominent methods suggested for obtaining pluripotent stem cells without extracting them from embryos. The first approach is called *altered nuclear transfer* (ANT), or, sometimes, altered nuclear transfer with oocyte-assisted reprogramming

(ANT-OAR).[66] The second approach, developed independently by Shinya Yamanaka in Japan and James Thomson in Wisconsin, is called somatic cell dedifferentiation, but is typically referred to by the name of its product, *induced pluripotent stem cells* (iPS cells).[67]

Both approaches rely upon what we know about the factors affecting gene expression in order to create pluripotent stem cells without ever creating embryos. Recall that in the successful cloning attempt that produced Dolly the sheep, the nucleus of a somatic cell was inserted into an enucleated oocyte, and the resulting new cell was dedifferentiated back to a totipotent, not a pluripotent, state.[68] This is a critical point: had the resulting cell not been totipotent, essentially the equivalent of a zygote, it could not have developed as a complete organism and there would have been no Dolly. Likewise, a human stem cell in any state other than totipotency is not and cannot become a complete human organism. In the ANT procedure, unlike in the SCNT cloning procedure, the nucleus of the cell transferred to the oocyte, or the cytoplasm of the oocyte into which it is transferred, is altered in order to prevent the cell from going through the stage of totipotency that is characteristic of a true embryo. These alterations change the patterns of gene expression to cause the cell to express genes characteristic of pluripotent stem cells, rather than the totipotent cells of the early embryo. Proponents of the procedure argue that none of the three cells involved in the process of ANT—the somatic cell with the altered nucleus, the oocyte, and the new cell—is at any point a zygotic, totipotent cell. Thus, ANT appears to provide pluripotent but non-embryonic stem cells.[69]

Like the ANT approach, the induced pluripotent stem cell approach capitalizes both on the ability of the somatic cell's nucleus to be coaxed into a less differentiated state and on our knowledge of the genes whose forced expression alters a cell's identity. Yamanaka and Thomson determined that by inserting genes for transcription factors associated with pluripotency into somatic cells by means of retroviruses, they were able to induce dedifferentiation in those cells, bringing them back to a stage of pluripotency.[70] The pluripotent stem cells created using this technique appear to have the classic marks of embryonic stem cells: they can be indefinitely maintained in a lab culture, and they are capable of multiple types of differentiation.[71] There are some differences in gene expression patterns between iPS cells and ES cells, but the consequences of these differences are at present unknown.[72]

Induced pluripotent stem cells seem to solve two problems that have bedeviled researchers—one moral and one technical. Unlike cells

produced through SCNT, iPS cells at no point go through a stage of totipotency. Thus, no human embryos are created or destroyed in the formation and use of iPS cells, so that that moral controversy is sidestepped. Additionally, like the embryos produced by SCNT and cells produced by ANT, iPS cell technology seems to offer a solution to the threat of immune rejection, because, in the event that regenerative therapies prove feasible, iPS cells could be dedifferentiated from the somatic cells of the diseased patient himself, and would thus have the same genome as the patient.[73]

The iPS approach has been widely and rapidly adopted by the scientific community: Yamanaka's technique was announced to work on mice in 2006, and only a year later was shown to work with human cells.[74] While, as noted, there are small differences in gene expression between iPS cells and ES cells, scientists studying iPS cells have typically been impressed with the degree to which iPS cells are functionally equivalent to ES cells. For example, Ian Wilmut, the researcher who created Dolly the sheep, announced after Yamanaka's discovery that he was halting his own cloning research, since he viewed the iPS cell approach as having more potential.[75] Some scientists have even used techniques similar to the ones used by Yamanaka and Thomson to attempt to reprogram differentiated adult cells of one sort into differentiated cells of another sort, altogether eliminating the pluripotent or multipotent stage.[76] Reliable techniques for reprogramming cells directly from one cell type to another could offer an alternative to stem cell-based cell therapies, but while research in this area has produced exciting preliminary results, more work will need to be done before these techniques could replace stem cell-based cell therapies.[77]

Moreover, because of the relative ease and non-intrusiveness with which iPS cells can be generated, some of the research possibilities proposed using ES cells might be more readily achieved using iPS cells. The difficulties involved in producing ES cells from IVF embryos, including obtaining the parents' permission, do not apply to iPS cells, which can instead be produced in large numbers and from a highly genetically diverse set of donors with little inconvenience to them.[78] And unlike ES cells produced through SCNT, iPS techniques do not require a supply of human eggs, which can be difficult or even dangerous to procure: the hormonal treatments used in collecting eggs from women can lead to such health-threatening complications as ovarian hyperstimulation syndrome.[79]

Induced pluripotent stem cells thus seem to offer many practical advantages sought by scientific and biomedical researchers. Nevertheless, there are some concerns about the iPS approach. One involves the use of retroviruses to introduce the transcription factors into the somatic cells. The

retroviruses "integrate randomly into the host genome," and even though the integrated viral genes are silenced in the iPS cells, there is a risk that they will reactivate.[80] This worry was particularly acute in the cells reprogrammed using some of the earlier iPS methods, as the transferred genes included some that are known to cause tumors.[81] The viral insertion of these genes can also interfere with the genetic functioning of the cell, perhaps even undermining the original purpose of the iPS cell by disrupting the expression of genes involved in developing desired traits.[82] Other concerns include the possibility of mutations or chromosomal abnormalities that can result from the genetic modifications necessary for inducing pluripotency, including some mutations that may contribute to the development of cancer (as has been documented in the use of retroviruses for gene therapy).[83] Growing iPS cells in culture for extensive periods also increases the likelihood of chromosomal abnormalities, including some that may increase the cells' tumorigenicity.[84] Furthermore, the presence of abnormalities or mutations in the tissue of origin can contribute to the risk of cancer in iPS cells.[85] While it was hoped that the ability of iPS cells to provide patient-specific stem cells would overcome the problems of immune rejection, a recent study published in *Nature* has indicated that tissues formed by iPS cells may still be subject to those problems.[86] The study found that certain iPS cells could trigger an immune response in mice, although more research is required to better understand how iPS cells and tissues derived from iPS cells react with organisms' immune systems.[87] The reprogramming of adult cells into iPS cells is also often incomplete, which can cause iPS cells to retain certain gene expression patterns from their tissue of origin.[88]

Some of these initial worries about iPS cells seem surmountable. Research conducted since the creation of the original iPS cells has shown that the process need not use some of the genes known to cause tumors.[89] Other experiments have used approaches that do not require retroviruses at all: some introduce genes into the cell without integrating DNA into the cell's chromosomes;[90] others directly add the transcription factor proteins, rather than transcription factor genes;[91] and progress has been made in modifying patterns of gene expression through the use of chemical compounds, rather than transcription factors, in order to reprogram cells to a pluripotent state.[92]

Another concern about iPS cells is that early attempts to generate them have not been very efficient: only a small proportion of the cells successfully dedifferentiate, with most studies reporting reprogramming between 0.001 and 1 percent of cells.[93] The techniques that involve less drastic genetic modifications to induce pluripotency tend to be less efficient.[94]

Additionally, there are some safety concerns related to the tendency of iPS cells to form dangerous tumors. The genetic and epigenetic changes necessary for inducing pluripotency share many features of the genetic and epigenetic changes associated with cancer; more research is needed to determine how to induce pluripotency without modifying cells in such a way that will increase the likelihood of cancer.[95]

A final difficulty related to the use of iPS cells is that it may not obviate the need for ES cells; as noted above, some researchers argue that ES cells are still necessary at least to provide a standard against which the success of iPS cells can be measured.[96] One example of a clinically relevant difference between iPS cells and ES cells involves the study of Fragile X syndrome, a developmental disorder caused by an inability to express the FMR1 gene.[97] Scientists who study the disorder have found evidence that the gene is expressed while the embryo's cells are still undifferentiated but is silenced as the embryo develops.[98] In ES cells derived from embryos that have the Fragile X mutation, the FMR1 gene is still expressed.[99] But the gene is *not* reactivated in iPS cells derived from *adult* Fragile X patients—indicating that the reprogramming process does not simply restore the cells to the state of undifferentiated embryonic cells.[100] This has led researchers to question the reliability of iPS cells for modeling the earliest developmental stages of diseases.[101] However, while the iPS cells used in this procedure may not have captured the very earliest stages of development, they were still useful for deriving tissues affected by the disorder, such as neurons.[102] Furthermore, other scientists have created iPS cells that were able to reactivate gene expression in the X chromosome that had been silenced during development, indicating that it may someday be possible to create iPS cells that exhibit the same patterns of gene expression as undifferentiated cells.[103]

Recent work by scientists at the Sanger Institute in the United Kingdom has resulted in a new technique for creating iPS cells that appears to be safer and more efficient, and to produce cells even more useful for research and therapy than human ES cells.[104] Many scientists have observed that mouse ES cells seem to represent a more developmentally immature state than human ES cells; the former have been described as being in a "naïve pluripotent state" while the latter are in a "primed pluripotent state."[105] The new Sanger iPS cells have many of the biological properties typically associated with the naïve state, including the activation in female cells of both X chromosomes, as opposed to the usual inactivation of one X chromosome in all mammalian cells (including human ES cells) past an early stage of embryonic development. Naïve mouse cells have shown more reli-

ability and consistency in their developmental potential than human ES or iPS cells, and some scientists have speculated that creating naïve human pluripotent stem cells will facilitate research on the ability of stem cells to differentiate into various tissues.[106] Further, some have argued that it will be easier to perform genetic engineering techniques, which may facilitate the creation of genetically modified tissues for disease modeling and cellular therapies.[107] Additionally, the Sanger iPS technique could open the door to the creation of human-animal chimeras for research or for cross-species organ transplantation.[108]

In sum, induced pluripotent stem cells are a very promising avenue for procuring pluripotent stem cells without the destruction of human embryos, but a number of difficulties with the procedure still need to be addressed.

Conclusion

In this appendix we have given an account of stem cells, and more particularly, of embryonic stem cells and some techniques for producing cells with similar powers. Stem cells clearly hold great potential for scientific research and, hopefully, for new and improved therapies. In the next appendix, we offer a sketch of the state of the art in therapeutic uses of stem cells.

Notes

1. Neil A. Campbell and Jane Reece, *Biology*, 7th ed. (San Francisco: Pearson Education, 2005), 955.

2. *Ibid.*, 955-956, 418.

3. *Ibid.*, 362.

4. International Human Genome Sequencing Consortium, "Finishing the Euchromatic Sequence of the Human Genome," *Nature* 431, no. 7011 (2004): 931-945. See also Wayne M. Becker *et al.*, *The World of the Cell*, 7th ed. (San Francisco: Pearson Education, 2009), 525.

5. Campbell and Reece, *Biology*, 415.

6. *Ibid.*, 362.

7. *Ibid.*

8. *Ibid.*, 1000.

9. The term "undifferentiated" is perhaps somewhat misleading. While these cells have the capacity to develop into any different cell type in the body, they should not be thought of as simple raw material for human development; just like any "differentiated" adult cell, embryonic cells are fully functional cells, which are responsible for

contributing to embryological development.

10. Campbell and Reece, *Biology*, 979.

11. Douglas A. Melton and Chad Cowen, "'Stemness': Definitions, Criteria, and Standards," in *Essentials of Stem Cell Biology*, 2nd ed., ed. Robert Lanza *et al.* (Burlington, Mass.: Elsevier Academic Press, 2009), xxiii.

12. Campbell and Reece, *Biology*, 418.

13. *Ibid.*; President's Council on Bioethics (PCBE), *Alternative Sources of Pluripotent Stem Cells*, Washington, D.C., 2005, 99.

14. PCBE, *Alternative Sources of Pluripotent Stem Cells*, 29.

15. Melton and Cowen, "'Stemness,'" xxiv.

16. PCBE, "Appendix A—Notes on Early Human Development," in *Monitoring Stem Cell Research*, Washington, D.C., 2004; R. H. Xu *et al.*, "BMP4 Initiates Human Embryonic Stem Cell Differentiation to Trophoblast," *Nature Biotechnology* 20, no. 12 (2002): 1261-1264.

17. Campbell and Reece, *Biology*, 418.

18. *Ibid.*

19. PCBE, *Monitoring Stem Cell Research*, 10.

20. Melton and Cowen, "'Stemness,'" xxiii.

21. Becker *et al.*, *The World of the Cell*, 722.

22. N. Beyer Nardi and L. da Silva Meirelles, "Mesenchymal Stem Cells: Isolation, In Vitro Expansion and Characterization," in *Stem Cells*, ed. Anna M. Wobus and Kenneth Boheler, Handbook of Experimental Pharmacology, vol. 174, no. 0171 (2006): 249-282.

23. For corneal regeneration, see Francisco Arnalich-Montiel *et al.*, "Adipose-Derived Stem Cells Are a Source for Cell Therapy of the Corneal Stroma," *Stem Cells* 26, no. 2 (2008): 570-579; Bruce A. Bunnell *et al.*, "Adipose-Derived Stem Cells: Isolation, Expansion and Differentiation," *Methods* 45, no. 2 (2008): 115-120.

24. Tomoharu Tamagawa, Isamu Ishiwata, and Shigeo Saito, "Establishment and Characterization of a Pluripotent Stem Cell Line Derived from Human Amniotic Membranes and Initiation of Germ Layers *In Vitro*," *Human Cell* 17, no. 3 (2008): 125-130.

25. Carmella van de Ven *et al.*, "The Potential of Umbilical Cord Blood Multipotent Stem Cells for Nonhematopoietic Tissue and Cell Regeneration," *Experimental Hematology* 35, no. 12 (2007): 1753-1765.

26. Helmut Gulbins *et al.*, "Cell Transplantation—A Potential Therapy for Cardiac Repair in the Future?," *Heart Surgery Forum* 5, no. 4 (2002): E28-34.

27. Christine Mummery *et al.*, *Stem Cells: Scientific Facts and Fiction* (London: Academic Press, 2011), 50.

28. David Solter and Barbara B. Knowles, "Immunosurgery of Mouse Blastocyst," *Proceedings of the National Academy of Sciences* (*PNAS*) 72, no. 12 (1975): 5099-5102.

29. James A. Thomson *et al.*, "Embryonic Stem Cell Lines Derived from Human Blastocysts," *Science* 282, no. 5391 (1998): 1145-1147. For the first successful derivation of embryonic stem cells in the mouse, see Martin J. Evans and Matthew H. Kaufman, "Establishment in Culture of Pluripotential Cells from Mouse Embryos," *Nature* 292, no. 5819 (1981): 154-156.

30. Franz-Joseph Müller *et al.*, "A Call to Standardize Teratoma Assays Used to Define Human Pluripotent Cell Lines," *Cell Stem Cell* 6, no. 5 (2010): 412-414.

31. Ali H. Brivanlou *et al.*, "Setting Standards for Human Embryonic Stem Cells," *Science* 300, no. 5621 (2003): 913-916.

32. Allan Bradley *et al.*, "Formation of Germ-Line Chimaeras from Embryo-Derived Teratocarcinoma Cell Lines," *Nature* 309, no. 5965 (1984): 255-256.

33. Austin G. Smith, "Embryo-Derived Stem Cells: Of Mice and Men," *Annual Review of Cell and Developmental Biology* 17, no. 1 (2001): 435-462.

34. *Ibid.*

35. Thomson *et al.*, "Embryonic Stem Cell Lines Derived from Human Blastocysts," 1145-1147.

36. M. Teresa de la Morena and Richard A. Gatti, "A History of Bone Marrow Transplantation," *Hematology/Oncology Clinics of North America* 25, no. 1 (2011): 1-15.

37. Thomson *et al.*, "Embryonic Stem Cell Lines Derived from Human Blastocysts," 1145-1147.

38. National Bioethics Advisory Commission, Ethical Issues in Human Stem Cell Research (Rockville, Md., 1999), 17.

39. David I. Hoffman *et al.*, "Cryopreserved Embryos in the United States and Their Availability for Research," *Fertility and Sterility* 79, no. 5 (2003): 1063-1069; Jacqueline Pfeffer Merrill, "Embryos in Limbo," *The New Atlantis*, no. 24, Spring 2009, 18-28, http://www.thenewatlantis.com/publications/embryos-in-limbo.

40. Hoffman *et al.*, "Cryopreserved Embryos in the United States and Their Availability for Research," 1063-1069; Merrill, "Embryos in Limbo," 18-28.

41. Hoffman *et al.*, "Cryopreserved Embryos in the United States and Their Availability for Research," 1063-1069; Merrill, "Embryos in Limbo," 18-28.

42. Ian Wilmut *et al.*, "Viable Offspring Derived from Fetal and Adult Mammalian Cells," *Nature* 385, no. 6619 (1997): 810-813.

43. Konrad Hochedlinger and Rudolf Jaenisch, "Nuclear Transplantation, Embryonic Stem Cells, and the Potential for Cell Therapy," *New England Journal of Medicine* 349, no. 3 (2003): 275-286.

44. Douglas C. Wallace, "Diseases of the Mitochondrial DNA," *Annual Review of Biochemistry* 61 (1992): 1175-1212; K. Takeda *et al.*, "Dominant Distribution of

Mitochondrial DNA from Recipient Oocytes in Bovine Embryos and Offspring After Nuclear Transfer," *Journal of Reproduction and Fertility* 116, no. 2 (1999): 253-259. An alternative version of the SCNT procedure, in which the egg nucleus was not removed prior to the fusion of the egg with the nucleus of the somatic cell, created human embryos that contained three sets of chromosomes rather than the typical two. While this procedure did successfully create human ES cell lines, such embryos would be highly unlikely to develop beyond an early stage, and the ES cells that were derived are likewise too abnormal to be useful in research or therapy. Scott Noggle *et al.*, "Human Oocytes Reprogram Somatic Cells to a Pluripotent State," *Nature* 478, no. 7367 (2011): 70-77.

45. Yanxin Li *et al.*, "Cloned Endangered Species Takin (*Budorcas taxicolor*) by Inter-Species Nuclear Transfer and Comparison of the Blastocyst Development with Yak (*Bos grunniens*) and Bovine," *Molecular Reproduction and Development* 73, no. 2 (2006): 189-195.

46. Young Chung *et al.*, "Reprogramming of Human Somatic Cells Using Human and Animal Oocytes," *Cloning and Stem Cells* 11, no. 2 (2009): 213-223.

47. Masako Tada *et al.*, "Nuclear Reprogramming of Somatic Cells by *In Vitro* Hybridization with ES Cells," *Current Biology* 11, no. 19 (2001): 1553-1558.

48. PCBE, *Alternative Sources of Human Pluripotent Stem Cells*, 24-36; W. Verpoest *et al.*, "Cumulative Reproductive Outcome after Preimplantation Genetic Diagnosis: A Report on 1498 Couples," *Human Reproduction* 24, no. 11 (2009): 2951-2959. The consequences of PGD on the health of children born from embryos on which the procedure was performed are described in I. Liebars *et al.*, "Report on a Consecutive Series of 581 Children Born after Blastomere Biopsy for Preimplantation Genetic Diagnosis," *Human Reproduction* 25, no. 1 (2010): 275-282.

49. Donald W. Landry and Howard A. Zucker, "Embryonic Death and the Creation of Human Embryonic Stem Cells," *The Journal of Clinical Investigation* 114, no. 9 (2004): 1184-1186.

50. Thomson *et al.*, "Embryonic Stem Cell Lines Derived from Human Blastocysts," 1145-1147.

51. *Ibid.*

52. Giuseppe Orlando *et al.*, "Regenerative Medicine as Applied to Solid Organ Transplantation: Current Status and Future Challenges," *Transplant International* 24, no. 3 (2011): 223-232.

53. Barak Blum and Nissim Benvenisty, "The Tumorigenicity of Human Embryonic Stem Cells," *Advances in Cancer Research* 100 (2008): 133–158.

54. Nigel G. Kooreman and Joseph C. Wu, "Tumorigenicity of Pluripotent Stem Cells: Biological Insights from Molecular Imaging," *Journal of the Royal Society Interface* 7, no. Suppl 6 (2010): S753-S763; Blum and Benvenisty, "The Tumorigenicity of Human Embryonic Stem Cells," 133-158; Uri Ben-David and Nissim Benvenisty, "The Tumorigenicity of Human Embryonic and Induced Pluripotent Stem Cells," *Nature*

Reviews Cancer 11, no. 4 (2011): 268-277.

55. Douglas A. Hale, "Basic Transplantation Immunology," *Surgical Clinics of North America* 86, no. 5 (2006): 1103-1125. There is a large range of genetic diversity for human leukocyte antigens—the cell-surface proteins that allow the human immune system to recognize the body's cells—which makes it difficult to find stem cells that are compatible with particular patients.

56. Robertson Parkman, Joel Rappeport, and Fred Rosen, "Human Graft Versus Host Disease," *Journal of Investigative Dermatology* 74, no. 5 (1980): 276-279.

57. Ramiro Alberio, Keith H. Campbell, and Andrew D. Johnson, "Reprogramming Somatic Cells into Stem Cells," *Reproduction* 132, no. 5 (2006): 709-720.

58. Wallace, "Diseases of the Mitochondrial DNA," 1175-1212; Takeda *et al.*, "Dominant Distribution of Mitochondrial DNA," 253-259.

59. Shawdee Eshghi and David V. Schaffer, "Engineering Microenvironments to Control Stem Cell Fate and Function," in *StemBook*, ed. Lisa Gerard (Cambridge, Mass.: Harvard Stem Cell Institute, 2008).

60. Michaela Patterson *et al.*, "Defining the Nature of Human Pluripotent Stem Cell Progeny," *Cell Research* (advance online publication, August 16, 2011).

61. Hiener Niemann *et al.*, "Epigenetic Reprogramming in Embryonic and Foetal Development upon Somatic Cell Nuclear Transfer Cloning," *Reproduction* 135, no. 2 (2008): 151-163.

62. Adeleh Taei *et al.*, "Derivation of New Human Embryonic Stem Cell Lines from Preimplantation Genetic Screening and Diagnosis-Analyzed Embryos," *In Vitro Cellular & Developmental Biology—Animal* 46, no. 3-4 (2010): 395-402.

63. Colin W. Pouton and John M. Haynes, "Embryonic Stem Cells as a Source of Models for Drug Discovery," *Nature Reviews Drug Discovery* 6, no. 8 (2007): 605-616; Anna M. Wobus and Peter Löser, "Present State and Future Perspectives of Using Pluripotent Stem Cells in Toxicology Research," *Archives of Toxicology* 85, no. 2 (2011): 79-117.

64. National Cancer Institute, Response to Senator Specter's Inquiry "What Would You Hope to Achieve from Stem Cell Research?," March 25, 1999.

65. Ben-David and Benvenisty, "The Tumorigenicity of Human Embryonic and Induced Pluripotent Stem Cells," 268-277.

66. William B. Hurlbut, "Ethics and Embryonic Stem Cell Research: Altered Nuclear Transfer as a Way Forward," *BioDrugs: Clinical Immunotherapeutics, Biopharmaceuticals and Gene Therapy* 21, no. 2 (2007): 79-83.

67. Kazutoshi Takahashi *et al.*, "Induction of Pluripotent Stem Cells from Adult Human Fibroblasts by Defined Factors," *Cell* 131, no. 5 (2007): 861-872; Junying Yu *et al.*, "Induced Pluripotent Stem Cell Lines Derived from Human Somatic Cells," *Science* 318, no. 5858 (2007): 1917-1920.

68. Wilmut *et al.*, "Viable Offspring Derived from Fetal and Adult Mammalian Cells," 810-813.

69. William B. Hurlbut, Robert P. George, and Markus Grompe, "Seeking Consensus: A Clarification and Defense of Altered Nuclear Transfer," *The Hastings Center Report* 36, no. 5 (2006): 42.

70. Junying Yu *et al.*, "Induced Pluripotent Stem Cell Lines Derived from Human Somatic Cells," 1917-1920; Kazutoshi Takahashi and Shinya Yamanaka, "Induction of Pluripotent Stem Cells from Mouse Embryonic and Adult Fibroblast Cultures by Defined Factors," *Cell* 126, no. 4 (2006): 663-676.

71. Takahashi and Yamanaka, "Induction of Pluripotent Stem Cells from Mouse Embryonic and Adult Fibroblast Cultures by Defined Factors," 663-676.

72. Matthew G. Guenther *et al.*, "Chromatin Structure and Gene Expression Programs of Human Embryonic and Induced Pluripotent Stem Cells," *Cell Stem Cell* 7, no. 2 (2010): 249-257.

73. Shinya Yamanaka, "A Fresh Look at iPS Cells," *Cell* 137, no. 1 (2009): 13-17.

74. Takahashi *et al.*, "Induction of Pluripotent Stem Cells from Adult Human Fibroblasts by Defined Factors," 861-872.

75. Roger Highfield, "Dolly Creator Prof Ian Wilmut Shuns Cloning," *The Telegraph* (U.K.), November 16, 2007, http://www.telegraph.co.uk/science/science-news/3314696/Dolly-creator-Prof-Ian-Wilmut-shuns-cloning.html.

76. Thomas Graf and Tariq Enver, "Forcing Cells to Change Lineages," *Nature* 462, no. 7273 (2009): 587-593; Qiao Zhou *et al.*, "*In Vivo* Reprogramming of Adult Pancreatic Exocrine Cells to β-cells," *Nature* 455, no. 7213 (2008): 627-632. Liang Qiang *et al.*, "Directed Conversion of Alzheimer's Disease Patient Skin Fibroblasts into Functional Neurons," *Cell* 146, no. 3 (2011): 359-371.

77. Vimal Selvaraj *et al.*, "Switching Cell Fate: The Remarkable Rise of Induced Pluripotent Stem Cells and Lineage Reprogramming Technologies," *Trends in Biotechnology* 28, no. 4 (2010): 214-223.

78. However, while iPS cells can be derived from adult tissues, some researchers have found that fetal tissue cells are more readily reprogrammed into iPS cells; see In-Hyun Park *et al.*, "Reprogramming of Human Somatic Cells to Pluripotency with Defined Factors," *Nature* 451 (2008): 141-146. Indeed, the proof-of-principle experiments in mice and humans by Yamanaka and Thomson first used fetal cells to generate iPS cells, although both performed the experiment with cells from adult tissue sources as well for their seminal papers; see Takahashi and Yamanaka, "Induction of Pluripotent Stem Cells from Mouse Embryonic and Adult Fibroblast Cultures by Defined Factors," 663-676, and Junying Yu *et al.*, "Induced Pluripotent Stem Cell Lines Derived from Human Somatic Cells," 1917-1920.

79. Annick Delvigne and Serge Rozenberg, "Epidemiology and Prevention of Ovarian Hyperstimulation Syndrome (OHSS): A Review," *Human Reproduction Update* 8, no. 6 (2002): 559-577.

80. Joanna Hanley, Ghasem Rastegarlari, and Amit C. Nathwani, "An Introduction to Induced Pluripotent Stem Cells," *British Journal Of Haematology* 151, no. 1 (2010):

16-24; Keisuke Okita and Shinya Yamanaka, "Induction of Pluripotency by Defined Factors," *Experimental Cell Research* 316, no. 16 (2010): 2565-2570.

81. Takahashi and Yamanaka, "Induction of Pluripotent Stem Cells from Mouse Embryonic and Adult Fibroblast Cultures by Defined Factors," 663-676; Ben-David and Benvenisty, "The Tumorigenicity of Human Embryonic and Induced Pluripotent Stem Cells," 268-277.

82. Little has been written about this possible problem with respect to iPS cells, but it has been discussed in other fields that use viral vectors. See, for example, Michael Themis *et al.*, "Mutational Effects of Retrovirus Insertion on the Genome of V79 Cells by an Attenuated Retrovirus Vector: Implications for Gene Therapy," *Gene Therapy* 10, no. 19 (2003): 1703–1711.

83. Yoav Mayshar *et al.*, "Identification and Classification of Chromosomal Aberrations in Human Induced Pluripotent Stem Cells," *Cell Stem Cell* 7, no. 4 (2010): 521-531.

84. Ben-David and Benvenisty, "The Tumorigenicity of Human Embryonic and Induced Pluripotent Stem Cells," 268-277.

85. *Ibid.*

86. Tongbiao Zhao *et al.*, "Immunogenicity of Induced Pluripotent Stem Cells," *Nature* 474, no. 7350 (2011): 212-215.

87. Effie Apostolou and Konrad Hochedlinger, "Stem Cells: iPS Cells Under Attack," *Nature* 474, no. 7350 (2011): 165-166.

88. Kazuhiro Sakurada, "Environmental Epigenetic Modifications and Reprogramming-recalcitrant Genes," *Stem Cell Research* 4, no. 3 (2010): 157-164.

89. Masato Nakagawa *et al.*, "Generation of Induced Pluripotent Stem Cells Without Myc from Mouse and Human Fibroblasts," *Nature Biotechnology* 26, no. 1 (2007): 101-106; Saiyong Zhu *et al.*, "Reprogramming of Human Primary Somatic Cells by OCT4 and Chemical Compounds," *Cell Stem Cell* 7, no. 5 (2010): 651-655.

90. Junying Yu *et al.*, "Human Induced Pluripotent Stem Cells Free of Vector and Transgene Sequences," *Science* 324, no. 5928 (2009): 797-801.

91. Keisuke Kaji *et al.*, "Virus-Free Induction of Pluripotency and Subsequent Excision of Reprogramming Factors," *Nature* 458, no. 7239 (2009): 771-775.

92. Justin K. Ichida *et al.*, "A Small-Molecule Inhibitor of Tgf-Beta Signaling Replaces Sox2 in Reprogramming by Inducing Nanog," *Cell Stem Cell* 5, no. 5 (2009): 491-503; Joonghoon Park *et al.*, "Reprogramming of Mouse Fibroblasts to an Intermediate State of Differentiation by Chemical Induction," *Cellular Reprogramming* 13, no. 2 (2011): 121-122.

93. Takahashi and Yamanaka, "Induction of Pluripotent Stem Cells from Mouse Embryonic and Adult Fibroblast Cultures by Defined Factors," 663-676; Cesar A. Sommer and Gustavo Mostoslavsky, "Experimental Approaches for the Generation of Induced Pluripotent Stem Cells," *Stem Cell Research & Therapy* 1, no. 26 (2010): 1-7.

94. Sommer and Mostoslavsky, "Experimental Approaches," 1-7.

95. Ben-David and Benvenisty, "The Tumorigenicity of Human Embryonic and Induced Pluripotent Stem Cells," 268-277.

96. Insoo Hyun *et al.*, "New Advances in iPS Cell Research Do Not Obviate the Need for Human Embryonic Stem Cells," *Cell Stem Cell* 1, no. 4 (2007): 367-368.

97. François Rousseau, Dominique Heitz, and Jean-Louis Mandel, "The Unstable and Methylatable Mutations Causing the Fragile X Syndrome," *Human Mutation* 1, no. 2 (1992): 91-96.

98. James S. Sutcliffe *et al.*, "DNA Methylation Represses FMR-1 Transcription in Fragile X Syndrome," *Human Molecular Genetics* 1, no. 6 (1992): 397-400.

99. Achia Urbach *et al.*, "Differential Modeling of Fragile X Syndrome by Human Embryonic Stem Cells and Induced Pluripotent Stem Cells," *Cell Stem Cell* 6, no. 5 (2010): 407-411.

100. *Ibid.*

101. *Ibid.*

102. *Ibid.*

103. Maria A. Lagarkova *et al.*, "Induction of Pluripotency in Human Endothelial Cells Resets Epigenetic Profile on Genome Scale," *Cell Cycle* 9, no. 5 (2010): 937-946.

104. Wei Wang *et al.*, "Rapid and Efficient Reprogramming of Somatic Cells to Induced Pluripotent Stem Cells by Retinoic Acid Receptor Gamma and Liver Receptor Homolog 1," *PNAS* 108, no. 45 (2011): 18283-18288.

105. Christa Buecker and Niels Geijsen, "Different Flavors of Pluripotency, Molecular Mechanisms, and Practical Implications," *Cell Stem Cell* 7, no. 5 (2010): 559-564.

106. *Ibid.*

107. *Ibid.*

108. *Ibid.*

Appendix B
The Promise of Stem Cell Therapies

There are two general categories of medical applications for stem cells: first, as an actual therapy, and second, as a way to model diseases to help researchers develop treatments. In this appendix, we discuss the therapeutic value of stem cells. A comprehensive analysis of every clinical treatment, study, and potential therapy is beyond the scope of this report. Instead, this sketch is intended to offer a realistic and up-to-date appraisal of this rapidly evolving field.

Many stem cell therapies are based on the regenerative capacities of stem cells to produce a variety of tissues, either in the patient's body or *in vitro*.[1] Other therapies rely on transplanted stem cells, particularly adult mesenchymal stem cells (a type of multipotent stem cell), to provide signals that modify or regulate the activities of nearby cells without actually integrating into the patient's tissues.[2] At present, treatments in regular clinical use are limited to adult stem cells, although clinical trials have begun for deriving induced pluripotent stem (iPS) cells from patients to help researchers study diseases,[3] and the U.S. Food and Drug Administration in 2010 approved the first clinical trials for therapies using human embryonic stem cells.[4] As of this writing, there are two FDA-approved clinical trials using human ES cells underway in the United States, one of which is also being performed in Europe; one additional FDA-approved trial was recently canceled (detailed below).[5]

There are several types of conditions that either are currently being treated with stem cell-based therapies or that hold out the prospect for such therapies in the future. These include autoimmune diseases, neurological disorders, cancers, and infertility. Furthermore, stem cells may be used in regenerative medicine to replace or repair tissues and organs damaged by disease or injury. Below, we discuss each of these categories in turn.

Autoimmune Diseases. Autoimmune diseases occur when the immune system mistakenly attacks tissues that are normally present in the body.[6] Some of the autoimmune diseases that stem cell therapies have been proposed for include multiple sclerosis, rheumatoid arthritis, juvenile idiopathic arthritis, Crohn's disease, type 1 diabetes mellitus, autoimmune cytopenias, systemic lupus erythematosus, and systemic sclerosis.[7]

Clinical trials are now underway involving at least two distinct types of adult stem cell therapies directed at autoimmune diseases. The first is hematopoietic stem cell transplantation (HSCT). It is one of the best understood and most widely practiced forms of stem cell transplantation for restoring tissue function, and has been called the "gold standard" for the field by stem cell scientists.[8] In HSCT, hematopoietic stem cells—multipotent stem cells that produce many types of blood cell—are transplanted into the patient. Over the past decade, this technique has been used to treat a number of autoimmune diseases by first suppressing the patient's immune system with high doses of chemotherapy or radiation and then transplanting the stem cells into the patient in an attempt to restore the immune system to normal function.[9] A subcategory of HSCT involves hematopoietic stem cells that are "autologous"—that is, they come not from donors but are harvested from the patient's own body before the chemotherapy or radiation. Using the patient's own stem cells avoids complications arising from immunological rejection of foreign tissues, as well as the inverse danger of "graft-versus-host disease," wherein transplanted immune system cells attack tissues in the patient's body.[10]

The ability of HSCT to restore the body's blood-forming functions after high-dose chemotherapy has proven useful not only for the treatment of autoimmune diseases, but for many other blood-related disorders,[11] including leukemia (discussed further below). In these cases, the stem cell transplantation does not treat the disease itself, but rather alleviates the potentially severe side effects of high-intensity chemotherapy, allowing for higher doses of chemotherapy than would otherwise be possible.[12] (Advocates of human embryonic stem cell research, arguing against the claim that adult stem cells are a viable alternative to embryonic stem cells, have noted that chemotherapy, not adult stem cells *per se*, is the "primary treatment" in many of the therapies that involve HSCT.[13])

A second category of adult stem cell therapy that holds promise for treating autoimmune diseases is mesenchymal stem cell transplantation (MSCT). This involves transplanting into patients mesenchymal stem cells derived from bone marrow. In contrast to HSCT, which relies on chemotherapy or radiotherapy to suppress the immune system, in MSCT the mesenchymal stem cells themselves seem to suppress autoimmune responses.[14] Several clinical trials are underway to study the prospect of using MSCT therapy in the treatment of multiple sclerosis, Crohn's disease, type 1 diabetes, systemic lupus erythematosus, systemic sclerosis, and Sjögren syndrome.[15] The ability of MSCT to modulate immune responses has also led researchers to believe it may be useful for treating

graft-versus-host disease in transplant patients, and clinical trials are underway to test this ability.[16]

Autologous HSCT therapy has been attempted in patients with multiple sclerosis who have not responded to conventional therapies. The results so far have been mixed: the condition of some younger patients has stabilized, but the condition of other patients has deteriorated after transplantation.[17] MSCT therapy also holds out the prospect of treating multiple sclerosis, both by alleviating the condition through suppressing the autoimmune response and also by helping to heal damaged nerve cells by releasing signals that promote repair and regeneration.[18] It had been hoped that stem cells would allow for the growth of replacements for the oligodendrocytes and myelin sheaths damaged in patients with multiple sclerosis, but the prospects of such direct replacements using cells derived from bone marrow have since dimmed, and concerns about the tendency of embryonic stem cells to produce tumors has precluded clinical trials.[19] There is, however, some evidence that MSCT can promote repair in these tissues by indirect means, such as providing signals to the neural stem cells that are already present in the brain.[20]

Autologous HSCT has also shown promise in clinical trials in treating rheumatoid arthritis[21] and juvenile idiopathic arthritis.[22] And it has brought about remission of Crohn's disease in patients whose condition had not responded to more conventional treatments.[23] Diabetes is another disease that in some forms is caused by autoimmune responses, and several studies have shown these forms responding positively to autologous HSCT. In these cases, the stem cell treatment has been shown to reduce the need for insulin—even, in combination with other therapies, allowing patients to forgo insulin injections.[24]

In a study that began in 2007 but has recently received increased media attention, scientists from Germany used HSCT to treat an HIV patient who was also suffering from acute myeloid leukemia. The treatment relied on finding a donor who possessed a mutation that conferred resistance to the virus. The patient first underwent chemotherapy to treat his leukemia; his immune system was suppressed as a side effect of the chemotherapy. Hematopoietic stem cells from the donor were transplanted to restore the patient's immune system. After the transplant, the patient's immune system cells were replaced by the HIV-immune cells produced by the transplanted stem cells, with complete replacement obtained 61 days after the transplantation. As a result of the treatment, the HIV virus is no longer detectable in the patient, indicating that the patient's HIV infection may have been cured.[25]

Neurological Disorders. One common cause of loss of neural function is stroke. At least one study has shown that autologous MSCT can decrease neurological deficits in stroke patients.[26]

Still, while stem cells seem to offer a promising therapeutic option for stroke patients, several important problems remain unresolved, including choosing the right type of cells to derive from stem cells to use in transplantation, the number of cells to be transplanted, and the challenge of actually delivering stem cells to the damaged areas of the brain.[27] While the optimal method of delivering stem cells to the brain has presented some difficulty, researchers have found that transplanted neural stem cells seem able to migrate towards damaged tissues.[28]

Parkinson's disease has been widely heralded as an area in which embryonic stem cells in particular may hold prospects for treatment. It has been suggested, for example, that neurons derived from ES cells might treat the disease when transplanted into a patient's brain.[29] And one research team has recently shown that transplanted iPS cells can improve the condition of rats with Parkinson's disease.[30]

Alzheimer's disease was long thought not to be a promising candidate for stem cell therapy. However, in a study conducted with rats and mice, transplants of neural stem cells have migrated to damaged regions of the brain and improved synaptic connectivity among neurons by producing brain-derived neurotrophic factor, a compound that stimulates the development of synaptic connections.[31] In a study on rats that had been injured to simulate Alzheimer's disease, neural precursor cells derived *in vitro* from ES cells were shown to improve cognitive functioning in the rats. While the researchers observed that the neural precursor cells differentiated into neuron-like cells *in vivo*, they noted that the therapeutic results of the treatment were likely due not to the replacement of neurons but rather to the release of neurotrophic factors.[32]

Researchers have also used embryonic stem cells to generate what appear to be one of the important cell types that is lost during Alzheimer's disease: basal forebrain cholinergic neurons. This could be useful as a way to study the disease, as well as offering a potential source of neurons for cell-transplantation therapy.[33]

Cancer. A number of applications for stem cell therapies in treating cancer have been found. Hematopoietic stem cells employed through bone marrow transplantations have been used since the 1950s to treat leukemia, a form of cancer that affects the blood and bone marrow.[34] There is growing evidence that HSCT can be an effective treatment for other forms of cancer

as well. Originally, doctors used HSCT in conjunction with high doses of chemotherapy. The aggressive chemotherapy regimen would destroy resistant tumors in the bone marrow, but it could also cause lethal damage to the patient's blood-forming and immune systems, requiring HSCT to restore these systems to their normal functions.[35] Some researchers have raised questions about whether employing autologous HSCT under this strategy achieves better results when treating metastatic breast cancer than conventional chemotherapy without autologous HSCT.[36]

Also, some researchers believe that one of the troublesome effects of HSCT using donor stem cells, the graft-versus-host problem, can actually be harnessed to fight cancer. There is evidence that HSCT using donor stem cells can stimulate an immune response against the cancer cells in the patient's body—a "graft-versus-leukemia" or "graft-versus-tumor" effect.[37] To take advantage of that effect, some researchers have suggested that regimens of highly toxic chemotherapy might be replaced by less aggressive chemotherapy accompanied by HSCT.[38] While this technique was pioneered for the treatment of leukemia, doctors have begun to explore the possibility that there is a more general "graft-versus-cancer" effect, using HSCT to treat "metastatic colon carcinoma, ovarian carcinoma, advanced pancreatic carcinoma, prostate cancer and neuroblastoma."[39]

Reproductive Applications. There is evidence that both ES[40] and iPS[41] cells have the ability to form primordial germ cells—the cells from which gametes (eggs and sperm) are generated. The results of recent experiments in animals have led some researchers in reproductive medicine to suggest that generating sperm from ES cells may be a promising treatment for severe male infertility.[42] But other research has shown the challenges facing such treatments: mice born from stem cell-derived gametes died shortly after birth due to congenital defects.[43] It is worth noting that if gametes created from ES cells are used to create a new organism, that organism will have at least one genetic parent that is a destroyed embryo.

Additionally, the reprogramming techniques that already allow researchers to induce somatic cells into a pluripotent state might someday, at least theoretically, be adapted to reprogram somatic cells to a totipotent stage. This would possibly allow for human cloning without the use of eggs, since totipotent stem cells would be quite similar to embryos that could be implanted in the womb.[44] (Creating embryos in this manner would face considerable technical hurdles, however. The human egg cell is

considerably larger than ordinary human cells, and is specially adapted for becoming an embryo upon fertilization, containing a large volume of cellular and genetic factors that are essential for development. Even if reprogramming were to deliver the right *types* of genetic factors to an adult cell, it is not clear that the reprogrammed cell would be capable of the kind of embryonic development that is characteristic of fertilized egg cells.)

Furthermore, iPS and ES cells could both also be used for creating offspring through a stem cell-based cloning technique called tetraploid complementation. In this procedure, pluripotent stem cells are injected into a modified embryo that provides the placental layer but does not contribute to the development of the embryo itself, which develops directly from the pluripotent stem cells.[45] This allows researchers to create an organism that is genetically identical to a pluripotent stem cell.[46] (The genetic "parent" of an organism created through this procedure will be the single individual from whom the pluripotent stem cells were derived—either a destroyed embryo or an adult organism, depending on whether an ES cell or an iPS cell is used. And the modified "tetraploid" embryo that provides the placental layer will have a novel relationship with the child: it would not contribute to the child genetically but would play an indispensable role in the child's development that is not comparable to any natural biological relationship.)

As mentioned in Appendix A of this report, tetraploid complementation is already regularly used to analyze animal stem cells.[47] It has also been used for nearly twenty years to clone mice for research purposes, often from stem cells that have been genetically modified *in vitro* to produce genetically engineered organisms. While tetraploid complementation has never been performed on primates for practical and ethical reasons, some experts argue that, in principle, it could eventually be performed on humans.[48] The technique was performed on mice years before the controversy surrounding Dolly the cloned sheep, though it has received very little public attention—perhaps because, until recently, the only source of pluripotent stem cells were early-stage embryos, so the procedure could not have been used to clone an *adult* organism. However, with the advent of iPS cell technology, it is now possible to derive pluripotent stem cells from adult organisms, meaning that this procedure could possibly be used to clone mature organisms.[49] Indeed, in 2009, researchers performed a successful tetraploid complementation experiment using iPS cells from mice.[50] However, because it has not been attempted in primates with either embryonic or induced pluripotent stem cells, it is an open question as to whether this technique will ever be able to clone human beings.

Regenerative Medicine: Organ and Tissue Repair and Replacement. One of the most therapeutically promising prospects of stem cell research has been the possibility of repairing or replacing damaged organs and tissues—that is, of replicating the generative process that normally takes place only *in utero*. While ES cells have shown a great deal of potential in this area, owing to their pluripotency—their ability to develop into a wide variety of tissue types—there have been some successes toward using adult stem cells as well. For example, in 2008, adult stem cells were used to create a new trachea for a woman in her early thirties.[51] All the tissue was removed from a trachea procured from a deceased donor, leaving behind a bare scaffolding of cartilage. Scientists then seeded that scaffolding with the woman's own mesenchymal stem cells; the resulting trachea was successfully transplanted into the patient, with no noted complications from tissue rejection. Even more recently, scientists have used stem cells to create an artificial trachea—one with stem cells seeded upon a scaffolding of plastic rather than cartilage.[52] There have also been at least three trials using autologous mesenchymal stem cells to repair damaged cartilage, all of which showed promise.[53]

Additionally, doctors have recently used hematopoietic stem cells to successfully culture human red blood cells *in vitro*, which they used in blood transfusions. The cultured red blood cells were able to survive and mature into fully functioning cells in the patients' bloodstreams, demonstrating the potential of these cells to serve as an alternative to conventional blood donation. In order to cultivate these cells *in vitro*, researchers needed to find the right mix of growth factors that would coax the hematopoietic stem cells to successfully differentiate. While this represents a major breakthrough in stem cell therapy that will surely be beneficial to many patients in need of blood transfusions, the fact that we have only recently been able to use stem cells to regenerate red blood cells is indicative of the challenges facing the development of *in vitro* tissue and organ regeneration.

One of the most common causes of heart failure is ischemic heart disease, which results from damage to heart tissue. Treating ischemic heart disease by repairing this damage represents one of the major goals of regenerative medicine. One trial, involving several research teams, performed transplantations of autologous myoblasts, or muscle stem cells, on patients recovering from heart attacks, but showed results no better than with transplanted placebos.[54] However, another recent study showed a promising treatment of damaged heart muscle with iPS cell transplants.[55] Heart muscle cells derived from human ES cells have also been shown to

have some promise as treatments in animal models.[56] Perhaps the most promising results in this field have come from a recent study of sixteen patients treated with autologous cardiac stem cells. The therapy appeared to regenerate the damaged heart tissue and significantly improve heart function in patients.[57]

Macular degeneration, a condition that can lead to loss of vision, is another disease for which stem cell therapy is thought to hold promise. In November 2010, the FDA granted approval to Advanced Cell Technologies (ACT) to perform a clinical trial assessing the safety of ES cell-derived treatments for Stargardt disease, a form of macular degeneration that affects children,[58] and in January 2011, the FDA approved another ACT clinical trial testing the same treatment for dry age-related macular degeneration, a condition that can lead to blindness in people over the age of 55.[59] On July 14, 2011, the company announced that it had, as part of those clinical trials, transplanted retinal pigment epithelial cells derived from human ES cells into two patients without any safety complications.[60] On September 22, 2011, the U.K. Medicines and Healthcare Products Regulatory Agency approved an ACT clinical trial for treatment of Stargardt disease, marking the first European embryonic stem cell trial.[61]

The holy grail of regenerative medicine is the treatment of spinal cord injuries. No other treatment for these devastating injuries has appeared in recent decades, and the plight of Christopher Reeve attracted a great deal of attention to the possibility that stem cell therapy might someday reverse such injuries. However, treatments by embryonic, adult, and induced pluripotent stem cells have all faced significant technical challenges.[62] The first clinical trial in human beings involving human embryonic stem cells was a study conducted by the Geron Corporation, a biotechnology company; the study was approved by the FDA in January 2009 and it commenced in October 2010.[63] The subject of the study had suffered a spinal cord injury and was injected with oligodendrocyte progenitor cells derived from human embryonic stem cells.[64] However, in November 2011, Geron announced that it was canceling its stem cell program.[65] The company said that, while it will not be enrolling any new patients in the therapy, it will continue to follow currently enrolled patients and to update the FDA and the medical community on their progress.[66] The company reported that the therapy had been "well tolerated with no serious adverse events."[67]

Unapproved Therapies and Stem Cell Tourism. Both adult and embryonic stem cells hold great therapeutic promise, but it is important to

remember that stem cell science and medicine are still new fields, and that much more work will be needed before safe, effective therapies can become widely available. While stem cells offer a powerful therapeutic tool in some circumstances, they also can come with considerable risks. The FDA has been reluctant to license stem cell therapies in the United States because of the insufficient evidence of their safety and efficacy.[68]

Some proponents of adult stem cell therapy have argued that because autologous stem cell transplantations employ the patient's own tissues, they should not be considered "drugs," and should therefore be subject only to the self-regulation of medical practitioners.[69] Many countries, particularly China and various European states, have more permissive policies on adult stem cell treatments than the United States, leading many Americans to go abroad for stem cell therapies not approved by the FDA—a practice known as "stem cell tourism." Experimental stem cell treatments offer hope to patients with serious medical conditions, including patients who have exhausted all conventional therapies, and stem cell clinics often employ direct-to-consumer advertisements that take advantage of the vulnerability and desperation of the ailing.[70] Several high-profile American celebrities have undergone unapproved experimental treatments, sometimes at clinics overseas, which may lend further seeming credibility to these unproven treatments.[71]

But many stem cell scientists and agencies have warned patients of the dangers posed by clinics claiming to offer unproven stem cell therapies for a variety of conditions.[72] One prominent critic, Douglas Sipp of the RIKEN Center for Developmental Biology, has counted more than two hundred clinics around the world "offering some version of stem cells for some type of medical condition for which there's no really good evidence that stem cells would be either safe or effective."[73] "When someone advertises stem cell products for the treatment of conditions like ALS, spinal-cord injury, Down syndrome, autism, or any of the scores of other unfounded claims that have flooded the Internet," Sipp has written, it is "unscientific, deceitful, and predatory" and deserves "serious monitoring and regulatory involvement."[74]

Conclusion

Stem cells play a fundamental role in our biological development and they promise to provide medical science with a powerful tool. Scientists can use pluripotent stem cells to create specific human tissues in the laboratory to serve as models for studying how diseases develop or as platforms

for testing new drugs and treatments. And, as the brief survey above has shown, both multipotent and pluripotent stem cells hold out hope for treatments for many of the conditions that afflict the body.

However, it is important not to overlook the fact that several of the therapies described above are still experimental and may ultimately prove to be ineffective or impractical. It is also important to remember that powerful therapeutic tools have significant costs and difficulties associated with them—not only the financial costs of their development and application, but also the risks associated with their use. The conditioning regimens for HSCT, for instance, can be very painful and dangerous, involving high doses of chemotherapy and total-body irradiation to destroy tumors or other malignant blood conditions. As with other forms of transplantation, stem cell transplants can result in dangerous immune reactions, and avoiding those immune reactions by creating personalized stem cell lines poses numerous practical and technical challenges. Significant hurdles would also have to be surmounted before nuclear transfer (either SCNT or ANT) could ever be a practical medical tool, given the complexities of the procedure and the difficulty of procuring the large number of human egg cells that it requires. Likewise, iPS cell techniques have not yet reached the point where they can reliably produce safe, effective pluripotent stem cells. And transplanted pluripotent cells continue to pose a cancer risk that researchers have barely begun to explore. While the power of stem cells to treat diseases holds great promise, we must remember that many of these therapies remain unproven and may come at a considerable cost.

In the next appendix, we turn to the ethical implications of research and treatment involving stem cells.

Notes

1. Daley George and David T. Scadden, "Prospects for Stem Cell Therapy," *Cell* 132, no. 4 (2008): 544–548.

2. *Ibid.*

3. NIH Clinical Trials website, http://clinicaltrials.gov/ct2/results?term=ips+cell (accessed July 30, 2011).

4. Geron, "Geron Receives FDA Clearance to Begin World's First Human Clinical Trial of Embryonic Stem Cell-Based Therapy," press release, January 23, 2009, http://geron.com/media/pressview.aspx?id=1148.

5. Jocelyn Kaiser, "FDA Lifts Hold on First-Ever Embryonic Stem Cell Trial," *Science Insider*, July 30, 2010, http://news.sciencemag.org/scienceinsider/2010/07/fda-lifts-hold-on-first-ever-embryonic.html; Geron, "Geron to Proceed with First Human

Clinical Trial of Embryonic Stem Cell-Based Therapy," press release, July 30, 2010, http://www.geron.com/media/pressview.aspx?id=1229; Advanced Cell Technology, Inc. (ACT), "Advanced Cell Technology Receives FDA Clearance For the First Clinical Trial Using Embryonic Stem Cells to Treat Macular Degeneration," press release, November 22, 2010, http://www.advancedcell.com/news-and-media/press-releases/advanced-cell-technology-receives-fda-clearance-for-the-first-clinical-trial-using-embryonic-stem-cel/index.asp; ACT, "Advanced Cell Technology Receives FDA Clearance For Clinical Trials Using Embryonic Stem Cells to Treat Age-Related Macular Degeneration," press release, January 3, 2011, http://advancedcell.com/news-and-media/press-releases/advanced-cell-technology-receives-fda-clearance-for-clinical-trials-using-embryonic-stem-cells-to-tre/; ACT, "ACT Receives Approval for First Human Embryonic Stem Cell Trial in Europe," press release, September 22, 2011, http://www.advancedcell.com/news-and-media/press-releases/act-receives-approval-for-first-human-embryonic-stem-cell-trial-in-europe/index.asp; Gretchen Vogel, "U.K. Approves Europe's First Embryonic Stem Cell Clinical Trial," *Science Insider*, September 22, 2011, http://news.sciencemag.org/scienceinsider/2011/09/uk-approves-europes-first-embryonic.html.

6. Neil A. Campbell and Jane Reece, *Biology*, 7th ed. (San Francisco: Pearson Education, 2005), 917.

7. Daniele Lodi, Tommaso Iannitti, and Beniamino Palmieri, "2011 Stem Cells in Clinical Practice: Applications and Warnings," *Journal of Experimental & Clinical Cancer Research* 30, no. 9 (2011): 1062-1070.

8. Daley and Scadden, "Prospects for Stem Cell-Based Therapy," 544-548.

9. Alan Tyndall and Alois Gratwohl, "Adult Stem Cell Transplantation and Autoimmune Disease," *Current Opinion in Hematology* 16, no. 4 (2009): 285-291.

10. Douglas A. Hale, "Basic Transplantation Immunology," *Surgical Clinics of North America* 86, no. 5 (2006): 1103-1125.

11. Peter A. McSweeney and Rainer Storb, "1998 Hematopoietic Stem Cell Transplantation," in *Encyclopaedia of Immunology*, ed. Peter J. Delves and Ivan M. Roitt (San Diego: Academic Press, 1998), 1062-1070.

12. R. K. Burt *et al.*, "Collection of Hematopoietc Stem Cells from Patients with Autoimmune Diseases," *Bone Marrow Transplantation* 28, no. 1 (2001): 1-12.

13. Shane Smith, William Neaves, and Steven Teitelbaum, "Adult Versus Embryonic Stem Cells: Treatments" *Science* 316, no. 5830 (2007): 1422-1423.

14. Antonio Uccelli, Lorenzo Moretta, and Vito Pistoia, "Immunoregulatory Function of Mesenchymal Stem Cells," *European Journal of Immunology* 36, no. 10 (2006): 2566-2573.

15. Antonio Uccelli and Darwin J. Prockop, "Why Should Mesenchymal Stem Cells (MSCs) Cure Autoimmune Diseases?," *Current Opinion in Immunology* 22, no. 6 (2010): 768-774.

16. Katarina Le Blanc *et al.*, "Mesenchymal Stem Cells Next Term for Treatment of Steroid-Resistant, Severe, Acute Graft-Versus-Host Disease: A Phase II Study," *The Lancet* 371, no. 9624 (2008): 1579-1586.

17. A. S. Fassas *et al.*, "Hematopoietic Stem Cell Transplantation for Multiple Sclerosis: A Retrospective Multicenter Study," *Journal of Neurology* 249, no. 8 (2002): 1088-97.

18. Lianhua Bai *et al.*, "Human Bone Marrow-Derived Mesenchymal Stem Cells Induce Th2-Polarized Immune Response and Promote Endogenous Repair in Animal Models of Multiple Sclerosis," *Glia* 57, no. 11 (2009): 1192-1203; Ezio Gerdoni *et al.*, "Mesenchymal Stem Cells Effectively Modulate Pathogenic Immune Response in Experimental Autoimmune Encephalomyelitis," *Annals of Neurology* 61, no. 3 (2007): 219-227; James R. Munoz *et al.*, "Human Stem/Progenitor Cells from Bone Marrow Promote Neurogenesis of Endogenous Neural Stem Cells in the Hippocampus of Mice," *Proceedings of the National Academy of Sciences* (*PNAS*) 102, no. 50 (2005): 18171-18176.

19. N. Scolding, "Adult Stem Cells and Multiple Sclerosis," *Cell Proliferation* 44 (Supplement s1 to April 2011): 35-38.

20. *Ibid.*

21. John A. Snowden *et al.*, "Autologous Hemopoietic Stem Cell Transplantation in Severe Rheumatoid Arthritis: A Report from the EBMT and ABMTR," *Journal of Rheumatology* 31, no. 3 (2004): 482-488.

22. I. M. de Kleer *et al.*, "Autologous Stem Cell Transplantation for Refractory Juvenile Idiopathic Arthritis: Analysis of Clinical Effects, Mortality, and Transplant Related Morbidity," *Annals of the Rheumatic Diseases* 63, no. 10 (2004): 1318-1326.

23. Yu Oyama *et al.*, "Autologous Hematopoietic Stem Cell Transplantation in Patients with Refractory Crohn's Disease," *Gasteroenterology* 128, no. 3 (2005): 552-563.

24. Julia C. Voltarelli *et al.*, "Autologous Nonmyeloablative Hematopoietic Stem Cell Transplantation in Newly Diagnosed Type 1 Diabetes Mellitus," *Journal of the American Medical Association* 297, no. 14 (2005): 1568-1576.

25. Gero Hutter *et al.*, "Long-Term Control of HIV by *CCR5* Δ32/Δ32 Stem-Cell Transplantation," *The New England Journal of Medicine* 360, no. 7 (2009): 692-698; Kristina Allers *et al.*, "Evidence for the Cure of HIV Infection by CCR5Δ32/Δ32 Stem Cell Transplantation," *Blood* 117, no. 10 (2011): 2791-2799.

26. Oh Young Bang *et al.*, "Autologous Mesenchymal Stem Cell Transplantation in Stroke Patients," *Annals of Neurology* 57, no. 6 (2005): 874-882.

27. Soma Banerjee *et al.*, "Human Stem Cell Therapy in Ischaemic Stroke: A Review," *Age and Aging* 40, no. 1 (2011): 7-13.

28. Raphael Guzman *et al.*, "Long-Term Monitoring of Transplanted Human Neural Stem Cells in Developmental and Pathological Contexts with MRI," *PNAS* 104, no. 24 (2007): 10211-10216.

29. Myung Soo Cho, Dong Youn Hwang, and Dong Wook Kim, "Efficient Derivation of Functional Dopaminergic Neurons from Human Embryonic Stem Cells on a Large Scale," *Nature Protocols* 3, no. 12 (2008): 1888-1894.

30. Marius Wernig *et al.*, "Neurons Derived from Reprogrammed Fibroblasts

Functionally Integrate into the Fetal Brain and Improve Symptoms of Rats with Parkinson's Disease," *PNAS* 105, no. 15 (2008): 5856-5861.

31. Mathew Blurton-Jones *et al.*, "Neural Stem Cells Improve Cognition via BDNF in a Transgenic Model of Alzheimer Disease," *PNAS* 106, no. 32 (2009): 13594-13599.

32. Jun Tang *et al.*, "Embryonic Stem Cell-Derived Neural Precursor Cells Improve Memory Dysfunction in Aβ(1-40) Injured Rats," *Neuroscience Research* 62, no. 2 (2008): 86-96.

33. Christopher J. Bissonnette *et al.*, "The Controlled Generation of Functional Basal Forebrain Cholinergic Neurons from Human Embryonic Stem Cells," *Stem Cells* 29, no. 5 (2011): 802-811.

34. E. Donnall Thomas *et al.*, "Intravenous Infusion of Bone Marrow in Patients Receiving Radiation and Chemotherapy," *The New England Journal of Medicine* 257, no. 11 (1957): 491-496.

35. Keren Osman and Raymond L. Comenzo, "Stem Cell Transplantation," in *Encyclopedia of Cancer*, 2nd ed., ed. Joseph R. Bertino (San Diego: Academic Press, 2002), 1:253-263.

36. Edward A. Stadtmauer *et al.*, "Conventional-Dose Chemotherapy Compared with High-Dose Chemotherapy Plus Autologous Hematopoietic Stem-Cell Transplantation for Metastatic Breast Cancer," *New England Journal of Medicine* 342, no. 15 (2000): 1069-1076.

37. Mary M. Horowitz *et al.*, "Graft-Versus-Leukemia Reactions after Bone Marrow Transplantation," *Blood* 75, no. 3 (1990): 555-562; Cornelius Schmaltz and Marcel R. M. van den Brink, "Graft versus Leukemia and Graft versus Tumor Activity," in *Encyclopedia of Cancer*, 2nd ed., ed. Joseph R. Bertino (San Diego: Academic Press, 2002), 1:325-338.

38. Shimon Slavin *et al.*, "Treatment of Leukemia by Alloreactive Lymphocytes and Nonmyeloablative Stem Cell Transplantation," *Journal of Clinical Immunology* 22, no. 2 (2002): 64-69.

39. Olle Ringden *et al.*, "The Allogeneic Graft-Versus-Cancer Effect," *British Journal of Haematology* 147, no. 5 (2009): 614-633.

40. Amander T. Clark *et al.*, "Spontaneous Differentiation of Germ Cells from Human Embryonic Stem Cells *In Vitro*," *Human Molecular Genetics* 13, no. 7 (2004): 727-739.

41. Sarita Panula *et al.*, "Human Germ Cell Differentiation from Fetal- and Adult-derived Induced Pluripotent Stem Cells," *Human Molecular Genetics* 20, no. 4 (2010): 752-762.

42. Laura Rienzi *et al.*, "What to Do When ICSI Fails," *Systems Biology in Reproductive Medicine* 56, no. 5 (2010): 376-387.

43. Andrew J. Childs, Phillipa T. K. Saunders, and Richard A. Anderson, "Modelling Germ Cell Development *In Vitro*," *Molecular Human Reproduction* 14, no. 9 (2008): 501-511; Bernard A. J. Roelen and Susana M. Chuva de Sousa Lopes, "Of Stem Cells and

Gametes: Similarities and Differences," *Current Medicinal Chemistry* 15, no. 13 (2008): 1249-1256.

44. President's Council on Bioethics, *Alternative Sources of Pluripotent Stem Cells*, Washington, D.C., 2005. See, for example, pp. 5 and 50.

45. András Nagy *et al.*, "Derivation of Completely Cell Culture-Derived Mice from Early-Passage Embryonic Stem Cells," *PNAS* 90, no. 18 (1993): 8424-8428.

46. *Ibid.*

47. Lan Kang *et al.*, "iPS Cells Can Support Full-term Development of Tetraploid Blastocyst-Complemented Embryos," *Cell Stem Cell* 5, no. 2 (2009): 135-138.

48. Hans-Werner Denker, "Human Embryonic Stem Cells: The Real Challenge for Research as Well as for Bioethics Is Still Ahead of Us," *Cells Tissues Organs* 187, no. 4 (2008): 250-256.

49. Lan Kang *et al.*, "iPS Cells Can Support Full-term Development of Tetraploid Blastocyst-Complemented Embryos," 135-138.

50. *Ibid.*

51. Augustinus Bader and Paolo Macchiarini, "Moving Towards *In Situ* Tracheal Regeneration: The Bionic Tissue Engineered Transplantation Approach," *Journal of Cellular and Molecular Medicine* 14, no. 7 (2010): 1877-1889; Paolo Macchiarini *et al.*, "Clinical Transplantation of a Tissue-Engineered Airway," *The Lancet* 372, no. 9655 (2008): 2023-2030.

52. Gautam Naik, "Lab-Made Trachea Saves Man," *Wall Street Journal*, July 8, 2011, http://on.wsj.com/pFq3yJ.

53. Shoichi Wakiani *et al.*, "Human Autologous Culture Expanded Bone Marrow Mesenschymal Cell Transplantation for Repair of Cartilage Defects in Osteoarthritic Knees," *Osteoarthritis and Cartilage* 10, no. 3 (2002): 199-206; Shoichi Wakiani *et al.*, "Repair of Articular Cartilage Defects in the Patello-Femoral Joint with Autologous Culture Expanded Bone Marrow Mesenschymal Cell Transplantation: Three Case Reports Involving Nine Defects in Five Knees," *Journal of Tissue Engineering and Regenerative Medicine* 1, no. 1 (2007): 74-79; Hossein Nejadnik *et al.*, "Autologous Bone Marrow Derived Mesenschymal Stem Cells Versus Autologous Chrondrocyte Implantation: An Observational Cohort Study," *American Journal of Sports Medicine* 38, no. 6 (2010): 1110-1116.

54. Philippe Menasché *et al.*, "The Myoblast Autologous Grafting in Ischemic Cardiomyopathy (MAGIC) Trial: First Randomized Placebo-Controlled Study of Myoblast Transplantation," *Circulation* 117, no. 9 (2008): 1189-2000.

55. Timothy J. Nelson *et al.*, "Repair of Acute Myocardial Infarction by Human Stemness Factors Induced Pluripotent Stem Cells," *Circulation* 120, no. 5 (2009): 408-416.

56. A. Laflamme *et al.*, "Cardiomyocytes Derived from Human Embryonic Stem Cells in Pro-Survival Factors Enhance Function of Infarcted Rat Hearts," *Nature Biotechnology*

25, no. 9 (2007): 1015-1024.

57. Roberto Bolli *et al.*, "Cardiac Stem Cells in Patients with Ischaemic Cardiomyopathy (SCIPIO): Initial Results of a Randomised Phase 1 Trial," *The Lancet*, early online publication, November 14, 2011.

58. Advanced Cell Technology, "Advanced Cell Technology Receives FDA Clearance For the First Clinical Trial Using Embryonic Stem Cells to Treat Macular Degeneration," press release, November 22, 2010, http://www.advancedcell.com/documents/0000/0272/FDA_Approval_Press_Release_Monday.pdf.

59. Advanced Cell Technology, "Advanced Cell Technology Receives FDA Clearance For Clinical Trials Using Embryonic Stem Cells to Treat Age-Related Macular Degeneration," press release, January 3, 2011, http://www.advancedcell.com/news-and-media/press-releases/advanced-cell-technology-receives-fda-clearance-for-clinical-trials-using-embryonic-stem-cells-to-tre/.

60. Advanced Cell Technology, "ACT Announces First Patients Undergo Embryonic Stem Cell Transplantation Treatment for Stargardt's Disease and Macular Degeneration at UCLA's Jules Stein Eye Institute," press release, July 14, 2011, http://www.advancedcell.com/news-and-media/press-releases/act-announces-first-patients-undergo-embryonic-stem-cell-transplantation-treatment-for-stargardts-disease-and-macular-degeneration-at-uclas-jules-stein-eye-institute/index.asp.

61. Rachael Panizzo, "Britain Trials Embryonic Stem Cells as Treatment for Blindness," *BioNews*, September 26, 2011, http://www.bionews.org.uk/page_107183.asp.

62. Enci Mary Kan, Eng-Ang Ling, and J. Lu, "Stem Cell Therapy for Spinal Cord Injury," *Current Medicinal Chemistry* 17, no. 36 (2010): 4492-4510.

63. Geron, "Geron Receives FDA Clearance to Begin World's First Human Clinical Trial of Embryonic Stem Cell-Based Therapy," press release, January 23, 2009, http://geron.com/media/pressview.aspx?id=1148.

64. Geron, "Geron Initiates Clinical Trial of Human Embryonic Stem Cell-Based Therapy," press release, January 23, 2009, http://www.geron.com/media/pressview.aspx?id=1235.

65. Geron, "Geron to Focus on its Novel Cancer Programs," press release, November 14, 2011, http://www.geron.com/media/pressview.aspx?id=1284.

66. *Ibid.*

67. *Ibid.*

68. Eliza Barclay, "Stem-cell Experts Raise Concerns About Medical Tourism," *The Lancet* 373, no. 9667 (2009): 883-884.

69. American Stem Cell Therapy Association, "Physician Group Opposes FDA's Position on Adult Stem Cells," press release, March 26, 2009, PRWeb, http://www.prweb.com/releases/ASCTA/stemcelltherapy/prweb2264534.htm; Zubin Master and David B. Resnik. "Stem-cell Tourism and Scientific Responsibility," *EMBO Reports* 12 (2011): 1-4.

70. Barclay, "Stem-cell Experts Raise Concerns About Medical Tourism," 883-884.

71. Governor Rick Perry of Texas; NFL players Peyton Manning, Terrell Owens, and Jarvis Green; Yankees pitcher Bartolo Colón; golfer John Daly; and musicians Don Ho and Tony Iommi are among the celebrities who have reportedly undergone stem cell treatments unapproved by the FDA. "Doctors Wary of Perry's Stem Cell Treatment," *Boston.com*, August 20, 2011, http://articles.boston.com/2011-08-20/news/29909865_1_cell-treatment-unproven-treatments-governor-rick-perry; Rachael Rettner, "Peyton Manning's Treatment: How Safe Is It?" MSNBC.com, September 21, 2011, http://www.msnbc.msn.com/id/44610314/; Robert Klemko, "Report: Terrell Owens in South Korea for Stem-cell Treatment," *USA Today*, September 20, 2011, http://content.usatoday.com/communities/thehuddle/post/2011/09/report-terrell-owens-in-south-korea-for-stem-cell-treatment/1; Albert Breer, "Green's Stem-cell Success Story Bodes Well for Manning," NFL Network, September 23, 2011, http://www.nfl.com/news/story/09000d5d8227e0ce/article/greens-stemcell-success-story-bodes-well-for-manning; Serge F. Kovaleski, "Pitcher's Treatment Draws Scrutiny," *New York Times*, May 11, 2011, http://www.nytimes.com/2011/05/12/sports/baseball/disputed-treatment-was-used-in-bartolo-colons-comeback.html?pagewanted=all; Dan Baynes, "Golfer Daly to Return Ahead of Schedule After Stem-Cell Surgery," Bloomberg.com, October 13, 2009, http://www.bloomberg.com/apps/news?pid=newsarchive&sid=aaMDdL6Byy9s; "Don Ho Recovering from Stem Cell Procedure," Associated Press, December 6, 2005, http://www.usatoday.com/life/people/2005-12-06-don-ho-stem-cell_x.htm; Tim Masters, "Ionni Says Injured Hand on Mend," BBC News, November 3, 2009, http://news.bbc.co.uk/2/hi/entertainment/8340697.stm.

72. Monya Baker, "Stem Cell Society Condemns Unproven Treatments," *Nature Reports Stem Cells*, June 26, 2008, http://www.nature.com/stemcells/2008/0806/080626/full/stemcells.2008.98.html; International Society for Stem Cell Research, "A Closer Look at Stem Cell Treatments," http://www.closerlookatstemcells.org/Stem_Cell_Treatment.htm; Danielle Nicholson, "Interview with Doug Sipp, Manager at RIKEN CDB, Kobe, Japan," EuroStemCell, August 17, 2011, http://www.eurostemcell.org/commentanalysis/interview-doug-sipp-manager-riken-cdb-kobe-japan.

73. "21st Century Snake Oil," *60 Minutes*, April 18, 2010, available at http://www.youtube.com/watch?v=Rb2NBlmL1es.

74. Doug Sipp, "Stem Cell Pseudoscience: Calling a Spade a Spade," *Stem Cell Treatments Monitor* (blog), September 5, 2011, http://sctmonitor.blogspot.com/2011/09/stem-cell-pseudomedicine-calling-spade.html.

Appendix C

Ethical Considerations Regarding Stem Cell Research

The aim of ethics is to identify principles of right action that can guide us in thinking about what we may do, what we must do, and what we must refrain from doing. Knowledge of these principles is not acquired through the natural sciences, although scientific knowledge can have an important bearing on ethical questions. Ethical reflection focuses on both our doing and our being. In part it attends to "the good"—to what is good for human beings, the goods we seek to realize in our action, and what we must do to flourish and be fulfilled. In part it attends to "the right"—clarifying our duties and obligations. And in part it attends to "character"—to the sort of persons we should be, the virtues we seek to cultivate, and the vices we seek to discourage.

There is a complicated relationship between what we learn through science and how we reflect on ethical, normative matters. Knowledge acquired from the natural sciences helps us think through what we should do and be, but it cannot provide answers to our moral questions, nor does it necessarily provide any special expertise for thinking about them. Our ethical judgments, however, must inform both the kinds of questions we choose to address through science and the methods we adopt in obtaining knowledge of the natural world. Both the ends and the means of science demand ethical scrutiny and ultimately public oversight.

The biomedical applications of stem cell research promise great benefits. But we cannot think about stem cell research simply in terms of the health benefits it might confer. We should also consider how those health benefits will contribute to our flourishing as human beings. We should think about what sorts of virtues and vices the pursuit of those benefits—the actions involved in stem cell research—will encourage. And we should consider how our ethical judgments relating to biomedical research will reflect on and shape our character as persons and as a society. These questions, in turn, require us to think about the human condition, the human good, and the meaning of human dignity.

In this appendix, we offer a brief summary of the moral claims underlying the stem cell debate before examining the ethical problems and questions connected to each of the techniques for obtaining stem cells.

Fundamental Moral Claims

Broadly speaking, there are three moral claims made concerning ES cells by participants in the debate over stem cell research. The first relates to the moral status of human embryos, the second relates to the potential medical therapies that could result from ES cell research, and the third relates to the contributions the research may make to our scientific knowledge.[1]

The question of the moral status of the embryo is the most contested and the most important of these three claims, since the different answers as to what moral status ought to be accorded to embryos each put different limits on what uses of embryos are morally permissible. Many proponents of embryonic stem cell research believe that the early embryo is merely a "clump of cells," lacking the characteristics and properties that define human being and human personhood.[2] The early embryo does not have the appearance of a fully developed human being. It has no face for us to see—indeed, to see the embryo at all, we need a microscope. It has no limbs or organs. It cannot survive on its own. It lacks the integrated development of nerves, muscles, and bones that enable us to move and act in the world. It lacks a central nervous system—and so cannot think, cannot feel pain, and is not self-aware. If the possession of any of those capacities is the defining threshold for a being to merit moral standing, then the embryo can be treated the same way we might treat any other bit of tissue.

Many opponents of embryo destruction argue that it is wrong, or even dangerous, to claim that human dignity and a right to life attach only to those human organisms who fulfill specific criteria. While a developing embryo does not have the manifest capacities of a fully developed human being, many persons who are young, sick, disabled, or developmentally challenged also lack some of these capacities. We may erode our respect for the human dignity and rights of these individuals if we consider it conditional on the possession of specific capacities—capacities we are all prone to lack or lose in the course of a human life.

To counter the claim that the embryo is just a clump of cells deserving no respect, critics of embryonic stem cell research point to the standard position of both traditional and contemporary embryology, which is that a human life begins at fertilization.[3] Fertilization is the clearest moment of discontinuity in life: it is when a new organism, one with a unique genetic identity, exists for the first time. From fertilization and the first stages of cell cleavage, embryos exhibit a highly coordinated pattern of development in preparation for implantation in the uterus, and for further

development into an adult organism. (It is of course this very developmental potential of the human embryo that makes it such an attractive source of cells for research purposes.) Human embryos may appear to lack the characteristics of human beings, but our expanding scientific knowledge of their developmental capacities and underlying structures reveals their intricate and unique power to develop as human beings. Whether created naturally through sexual reproduction, or through IVF or other techniques such as cloning, human embryos are all human beings at a very early stage of development. Being human, regardless of one's capacities or stage of development, confers certain fundamental human rights, which are grounded in the respect we owe to the dignity and wellbeing of our fellow human beings. The most important of these rights—because it is the right necessary to secure all others—is the right to life, which demands that we do not kill other human beings.

Some people believe that the moral status of the embryo falls between the two opposing positions—that the embryo deserves "profound respect"[4] or "serious moral consideration"[5] as an early form of human life, though we need not accord to it the same rights as a fully developed person.[6] Furthermore, some argue that the moral status of human embryos may depend partly on such factors as their state of development, their origins, and the wishes of their parents. In practice, however, these intermediate ethical positions tend to justify policies that differ little from policies that assume the embryo has no special moral status.[7]

For those who see the embryo as no more than a clump of cells with similar moral status to other human tissues, the primary ethical concern with respect to harvesting ES cells from embryos would be obtaining informed consent from embryo donors, such as IVF patients. By contrast, for those who consider the embryo to be a human being with a moral status equal to that of a fully developed person, it is clear that destroying embryos for stem cell research would be a violation of the fundamental duty not to kill, which would override our duty to provide medical treatment.

The second moral claim about stem cells relates to the therapeutic promise of stem cell research—the possibility of relieving the suffering of many people afflicted by degenerative diseases and other conditions. Not only do the medical applications of stem cells offer us considerable potential benefits in terms of human health, but many claim that we are duty-bound to pursue the potential relief of human suffering. Although not everyone believes "the conservation of health…is without doubt *the primary good* and the foundation of all other goods of this life,"[8] nearly everyone would agree that health is *a good*. So there is little dispute that the potential

health benefits of stem cell research make its pursuit an important aim that ought to be carried out as far as is ethically permissible.

The third important moral claim about stem cells has to do with how studying them can contribute to our knowledge of biology. Beyond the foreseeable medical benefits that may come from stem cell therapies, scientific advances made possible by stem cell research may someday allow for as-yet-unforeseen technological and medical breakthroughs. Furthermore, the pursuit of scientific knowledge is often held to be a valuable undertaking that we should encourage for its own sake. Similarly, the freedom of scientific inquiry is a widely held principle that ought not to be constrained in the absence of overriding ethical concerns. But we must also bear in mind that, while advancing our scientific knowledge of biology is a valuable undertaking, the power this knowledge of biological development grants us may be fraught with new ethical dangers as well. Knowledge gained today for the goal of relieving suffering, or of avoiding the technical need to destroy embryos, may be used in the future for ethically questionable purposes, such as projects of human "enhancement." In this respect, our knowledge of nature can never be considered inert, neutral, or merely intrinsically valuable, as it always bears on human questions and pursuits, and, without proper guidance, has as much potential to degrade as to elevate us.

Sources of Stem Cells: An Ethical Analysis

In the following section, we examine the ethical implications of each of the techniques for obtaining stem cells. Some techniques are more problematic than others. These ethical considerations should bear on the actions of scientists and the decisions of policymakers.

Adult Stem Cells. There are a number of types of adult stem cells that can be procured from living, or recently deceased, children or adults and used for therapeutic purposes. This procedure is relatively uncontroversial, and has been carried out for decades for a variety of purposes. Acquiring adult stem cells from donors does raise such ethical issues as proper donor consent, but it does not raise the many novel ethical concerns surrounding the other sources described here. However, "adult stem cells" may also be derived from fetal tissue—the term merely denotes that they are not of embryonic origin, not that they come from fully mature adults. In fact, some kinds of adult stem cells can only be found in fetal tissue, making fetuses a possibly desirable source of tissue for some future therapies. These cells would raise somewhat similar ethical issues as those raised

by embryonic stem cells, though would likely be even more controversial given the later stage of development.

Embryos from IVF Clinics. The standard method of obtaining ES cells involves using cells extracted from the numerous embryos that are created during IVF that are not implanted and are subsequently frozen or discarded. Because the process of extracting these cells requires the destruction of the embryo, the practice is unacceptable to those who believe that human embryos have a moral status comparable to that of recognizably human beings. Even for those who accord the embryo more limited moral status, the large-scale destruction of embryos for research purposes may seem unsettling. Furthermore, obtaining informed consent from the IVF patients for whom the embryos were created represents an important ethical concern.

IVF patients who have had embryos created on their behalf, usually from their own sex cells, must face the difficult decision of the disposition of the unused embryos created during their IVF treatment. Some ethicists and scientists have argued that because these embryos are going to be discarded in any event, it would make practical and ethical sense to derive some benefit from them by using them for medical research or therapy. Others argue that these smallest human organisms deserve respect and protection, and there are programs to assist parents in donating their unused IVF embryos to other couples.[9]

Some IVF embryos go unused not because they are "surplus" but because they are deemed to be in some way deficient. A technique called preimplantation genetic diagnosis (PGD) is carried out by some IVF practitioners to test embryos for genetic conditions prior to implanting them in the patient's uterus. Embryos that are found to have genetic conditions that might reduce their viability or cause them to have an increased susceptibility to genetic diseases are not implanted; they are regarded as defective and are generally discarded.[10] Although it is unlikely that ES cells derived from embryos with genetic abnormalities would be useful in therapies, they are considered useful for the study of genetic disorders, which is one of the major medical applications of stem cell research.[11]

Non-Destructive Embryo Cell Extraction. It is possible to extract from an early stage of the embryo a single cell (blastomere), or a small number of cells, which may be able to generate a line of embryonic stem cells. Beyond the questions related to the feasibility of deriving stem cell lines from one or a very small number of biopsied cells,[12] the ethical questions related to this technique primarily concern its effect on the health of the

embryo and the possible long-term health effects of the procedure on the developing child. While embryo biopsy for PGD is a relatively common practice in IVF clinics, embryos biopsied for PGD tend to have a lower rate of implantation than ordinary IVF embryos,[13] which suggests that the procedure has a risk of killing the embryo. Furthermore, the procedure increases the risk of complications, including infant mortality, for twins and triplets.[14] Additionally, the procedure has only been used on human beings for just over twenty years, so long-term data on the health consequences of embryo biopsy are not available.[15]

Even in cases where embryo biopsy does not result in any noticeable harm to the embryo, the procedure raises ethical issues concerning the treatment of embryos as a means to another's ends. Even if no harm comes to the embryo, it is unjust to use human beings for purposes of no benefit to them without their consent (consent which, of course, the embryo cannot give). It may be argued, however, that this procedure could have benefits for the future child in the form of a line of immunologically compatible pluripotent stem cells that may be useful for future cell therapy. However, it is possible to obtain genetically matched stem cells for a newborn child from the newborn's umbilical cord blood (although it is not clear whether stem cells obtained from cord blood will have the same capacities as embryonic stem cells that could be obtained from embryo biopsy).[16]

An additional line of concern has to do with the possibility that the cells extracted from the early embryo may be totipotent, and therefore capable of developing as independent embryos. There is some uncertainty as to when during embryonic development the totipotency of individually extracted embryonic cells disappears. While there is some evidence that the cells of embryos of some mammalian species retain totipotency until the fifth division (that is, through the sixteen-cell stage),[17] scientists have not been able to isolate individual totipotent stem cells from early human embryos.[18] If it is the case that by the eight-cell stage, when the embryo biopsy would take place, the individual cells are sufficiently differentiated that they are no longer totipotent, then this procedure would avoid concerns over the destruction of early human life. On the other hand, if cells at this stage are still capable of growing as viable independent embryos, then there would be little ethical difference between this procedure and the harvesting of ES cells by destroying living embryos—though concerns over the risk to the blastocyst would remain.[19]

Organismically Dead Embryos. One alternative source of ES cells is embryos that have stopped dividing and can therefore be considered "organ-

ismically dead."[20] Just as many of the cells and organs in a person's body may continue to grow and function for a time after they have died, some of the individual cells in a dead embryo may be capable of further division if placed in a suitable environment. Harvesting ES cells from IVF embryos that have died despite best efforts to sustain their life would allow us to avoid the ethical problems associated with destroying or killing embryos in order to harvest ES cells. The paramount ethical question regarding this procedure is whether we can be certain that the embryos are in fact dead.

Ordinary criteria for organismic death refer to the failure of important organs, such as the brain or heart. The largely undifferentiated embryos discussed in this proposal have not yet developed such organs, so the most obvious criteria for determining whether the embryo has died is the absence of coordinated cell division. Such developmental arrest, if irreversible, can be used as an objective diagnostic criterion for death. Much as studies of irreversible coma have allowed for a definition of brain death in developed humans, studies of IVF embryos allow doctors to determine the duration of arrest beyond which an embryo, having failed to develop further, never resumes the normal path of growth and development and ultimately begins to decompose.[21] Stem cell lines derived from live cells in dead embryos are genetically normal and express the normal markers for ES cells,[22] and several cell lines have been shown to have normal developmental potential.[23]

The harvesting of ES cells from these embryos can be seen as analogous to end-of-life organ donation. One criticism of this analogy comes from the relative indifference of IVF practitioners to the death of embryos, in contrast to the concern of physicians caring for dying patients from whom organs might be harvested. Another concern is that this method might create an incentive for IVF practitioners to create surplus embryos in the hopes that some might be used in research. But proposals for this method include the restriction that it use only embryos created for reproductive purposes that have died despite the best efforts to keep them viable.[24]

Somatic Cell Nuclear Transfer (SCNT). Creating embryos through SCNT is another possible source of ES cells; it allows for the generation of ES cells that may be more safe and efficacious for therapy than ES cells derived from IVF embryos. In 2008, scientists claimed to have successfully created cloned human embryos from adult cells, although they were not able to isolate ES cells from the embryos, which were destroyed shortly after.[25] More recently, scientists in 2011 used a modified version of the SCNT procedure, in which the egg nucleus was not removed prior to adding the somatic cell, so that the resultant embryos and embryonic

stem cells had three sets of chromosomes rather than the normal two.[26] The researchers were then able to create human embryonic stem cell lines using these embryos—the first time human ES cell lines have been created using SCNT. While this experiment represents a major breakthrough, showing that human embryos and ES cell lines can be created through SCNT, the embryos and the ES cell lines were severely genetically abnormal due to the presence of the third set of chromosomes, making them unsuitable for either research or therapy. Because this procedure would create human embryos that are destroyed in order to harvest stem cells, it raises some of the same ethical concerns as other embryo-destroying techniques. Moreover, while it could be argued that the unused embryos created by IVF for reproductive purposes were not created with their destruction in mind, the generation of embryos through SCNT involves the deliberate creation of early human life for the express purpose of destroying and using it. In addition, SCNT raises ethical concerns regarding the exploitation and endangerment of egg donors.

Furthermore, SCNT is a cloning technique: the embryos created will have a genome identical with some donor human being. It thus opens the door not only to cloned embryos but to the birth of cloned human children. This raises vexing questions about the meaning of reproduction, the relationship between the generations, and the defense of human dignity—questions that have largely led to a public consensus in opposition to cloning. Some scientists and commentators eschew the label "cloning" for SCNT, arguing that it wrongly conflates SCNT with "reproductive cloning." But the act of SCNT, at least in theory, would create a cloned embryo that could then be used for the purposes of research, therapy, or reproduction. True, no successful implantation and pregnancy using a cloned human embryo produced through SCNT has been reported and verified to date. But the use of cloning to produce children may someday follow from the use of cloning for biomedical research, especially absent any system regulating or law prohibiting cloning to produce children. (There is no federal law in the United States forbidding human cloning, although a minority of states prohibit it.[27])

Interspecies SCNT. One alternate form of SCNT that would obviate the need for human egg donors is called interspecies SCNT; it involves the transfer of a human nucleus into an enucleated animal oocyte. Some scientists have raised doubts about the technical feasibility of this procedure.[28] But some countries, including the United Kingdom, have funded research on the creation of human-animal "cybrids," or cytoplasmic hybrids, so

named because they result from the use of the interspecies SCNT procedure to combine the cytoplasm of an animal oocyte and the nucleus of a human cell.[29] While the use of interspecies SCNT to obtain pluripotent stem cells would alleviate concerns over the exploitation of egg donors, it remains a form of cloning and raises at least as many ethical concerns regarding reproduction and human dignity as does conventional SCNT.

Altered Nuclear Transfer (ANT). ANT involves the creation of "biological artifacts" through a modified version of the technique of nuclear transfer.[30] In ANT, the starting materials used in the technique (the adult cell nucleus and/or the cytoplasm of the oocyte) are altered before being combined so that the product of the procedure is not capable of establishing the integrated unity that characterizes an embryo. Because these "artifacts" contain pluripotent but not totipotent cells, they are not capable of developing as embryos, and therefore, proponents of this method argue, harvesting stem cells from them does not raise the same ethical issues surrounding the harvesting of stem cells from human embryos. The central ethical question related to this proposal is whether we ought to consider these biological artifacts to be non-organismal and therefore non-human entities, or whether there is a kind of similarity to natural embryos such that they have intrinsic moral value. Proponents of ANT argue that since the modifications made to the nucleus (or the cytoplasm of the egg) to prevent embryogenesis are made *before* it is transferred to the oocyte, and since the artifact created by the procedure has cells that are not totipotent, at no point is the newly created artifact ever an embryo.[31] But if, as some critics contend, ANT actually creates altered but disordered embryos, then it raises questions both about the ethics of destroying human embryos and about the ethics of intentionally creating defective embryos. Also, like SCNT, ANT depends on human egg donors, raising ethical concerns about their possible exploitation and endangerment.[32]

In the version of ANT known as the ANT-Cdx2 procedure, the expression of the gene Cdx2 is preemptively altered. In natural embryogenesis, the expression of Cdx2 is an early indicator of integrated development and orderly cell differentiation, and Cdx2 is an important factor in the formation of the trophectoderm—a structure essential for normal embryonic development and implantation.[33] When Cdx2 is "silenced," or interfered with in such a way that it is not expressed by the cell, it becomes impossible for the "biological artifact" to develop in the manner of a natural embryo. Whether the entity created by the ANT-Cdx2 procedure can be considered a kind of defective embryo, or rather is simply a mass of pluripotent stem cells,

depends on a number of complex philosophical and scientific questions. For instance, the precise role of the Cdx2 gene in embryonic development is still subject to some controversy: while it is clear that Cdx2 is essential for the proper functioning of the trophectoderm and for the specification of the axial body plan in the early embryo,[34] there remains some dispute over the extent to which Cdx2 is responsible for directing the organization of early embryonic cells.[35] Furthermore, some philosophers have raised questions as to whether or not the entities created by procedures like ANT-Cdx2 are sufficiently disorganized to be considered non-embryonic entities.[36] More scientific research in animal models may help to clarify certain issues, such as those related to the precise biological role of genes like Cdx2, including the potential reversibility or irreversibility of the intervention.[37] But to some extent, there are conceptual questions—what do we consider an embryo to be?—that will call for continued debate.

In another version of the procedure, Altered Nuclear Transfer with Oocyte-Assisted Reprogramming (ANT-OAR), rather than silencing or removing from the nucleus the genetic elements that are associated with totipotency, factors associated with pluripotency are *added* to the nucleus. In this way, the procedure aims at directly reprogramming the cell to a pluripotent state. In essence, instead of suppressing some factors required for totipotency, this procedure expresses only the factors required for pluripotency. While the ANT-Cdx2 technique may be thought of as an alternative version of SCNT where the artifact created is not an embryo, ANT-OAR is more similar to other techniques for reprogramming adult cells to a pluripotent state. The moral status of the artifact produced by ANT-OAR would arguably be very similar to an induced pluripotent stem cell, as there is no dispute that the cells produced would never have any of the characteristics of embryos (see below for an ethical analysis of induced pluripotent stem cells).

Regardless of the particular techniques that already exist, ANT is a broad conceptual proposal and is not tied to any specific candidate genes or factors. As knowledge of developmental biology increases, it may be that a number of genes or gene combinations will provide reliable and effective intervention, together with solid evidence for the kind of preemptive alteration envisioned in the ethical argument in support of ANT.

Embryonic Stem Cell Fusion. Researchers have found that fusing an ES cell with an ordinary adult (somatic) cell can transform the adult cell into a cell that will be pluripotent, just like an ES cell.[38] While this procedure does require the use of ES cells, it could allow for the creation of a limitless

number of new pluripotent stem cell lines without using or destroying any more human embryos—since the procedure could, in theory, rely on existing stem cell lines alone. However, this proposal faces difficult technical challenges—namely, the fact that the resulting cells have an abnormal number of chromosomes, which makes them infeasible for clinical use. Still, the knowledge gained through these cell-fusion experiments helped to make possible the creation of induced pluripotent stem cells, discussed below.

Induced Pluripotent Stem (iPS) Cells. Induced pluripotent stem cells are perhaps the most prominent alternative source of stem cells proposed for therapy and research.[39] Derived from many forms of adult cells (although cells derived from fetal tissue have so far been most effective), iPS cells can be easily procured without risk to the donor, and without generating or destroying any human embryos. Unlike ordinary adult stem cells, induced pluripotent stem cells may very well have the same efficacy as embryonic stem cells. And like SCNT-created cells, and in contrast to ES cells extracted from unused IVF embryos, iPS cells derived from a patient's own cells would in principle be fully compatible with the patient's immune system. But unlike SCNT, the procedure for creating iPS cells does not require the generation of embryos, and unlike either SCNT or ANT, the procedure would not require the procurement of human egg cells.

While the use of iPS cells may sidestep many of the questions related to the moral status of the human embryo, other important ethical concerns remain. For instance, pluripotent stem cells can be used in a cloning technique known as "tetraploid complementation" (the technical details of which we describe in Appendix B). The relative ease with which researchers can introduce genetic modifications to embryonic stem cells has made the creation of genetically engineered mice from embryonic stem cells using tetraploid complementation a common practice among molecular biologists.[40] If iPS cell technology can make cells that are equivalent to embryonic stem cells, tetraploid complementation may prove to be an efficient way not only to perform human cloning, but also human genetic engineering.[41] Moreover, creating genetically identical individuals from pluripotent stem cells falls outside a number of current laws that prohibit reproductive cloning but define cloning only in terms of SCNT.[42]

An additional reproductive technology that may be enabled by iPS cells is the generation of sex cells (sperm and eggs) for treating infertility.[43] One advantage of this technique would be that it could reduce the reliance of many infertility-treatment patients on donated sex cells, the use of which raises its own set of ethical concerns.[44] On the other hand,

the development of this technology would raise ethical concerns related to the consequences and risks for embryos and children created using stem cell-derived sex cells. Given the uncertainties surrounding the long-term consequences of reproduction using stem cell-derived sex cells, by employing this technology we are inevitably subjecting future offspring to risks that they obviously had no chance to consent to. Furthermore, research on deriving sex cells from stem cells would require the creation of embryos from the derived sex cells in order to test their functionality.[45] In both its final form as a technology for assisting reproduction and in the process of developing this technology, deriving sex cells from stem cells will essentially involve performing experiments on human organisms without their consent, which is deeply ethically troubling.[46]

Conclusion

A wide range of ethical complications has come to light since interest first arose in the medical applications of stem cells. These problems have chiefly related to the means of procuring stem cells, especially techniques involving the destruction of human embryos. Other ethical problems have included the possibility of human cloning and the potential exploitation of embryo and egg donors, as well as the questions raised by the new alternative techniques for obtaining stem cells.

The ethical acceptability of a particular research technique or medical procedure is not a matter for science alone to decide—it is not only a matter of empirical fact but also of moral judgment. Such moral judgments are not the exclusive domain of scientists or of experts in bioethics. Insofar as these matters impinge on public policy and on questions of the human future, they are deserving of public consideration and they rightly become matters not just of private conscience but of political deliberation. In the next appendix, we turn to matters of public policy and law.

Notes

1. We are indebted to Chapter 3 of the President's Council on Bioethics (PCBE) report *Monitoring Stem Cell Research*, Washington, D.C., 2004, for its analysis of the moral claims related to embryonic stem cell research that helped lay the foundations of our thinking on this question.

2. See, for example, Michael S. Gazzaniga, *The Ethical Brain: The Science of Our Moral Dilemmas*, 2nd ed. (New York: Harper Perennial, 2006).

3. William J. Larsen *et al.*, *Human Embryology*, 3rd ed. (New York: Churchill Livingstone, 2001). See also, Neil A. Campbell and Jane B. Reece, *Biology*, 7th ed. (San

Francisco: Pearson, 2005), 987-1000.

4. Department of Health, Education, and Welfare, Ethics Advisory Board, "Report of the Ethics Advisory Board," *Fed. Reg.* 44 (June 18, 1979): 35,056.

5. National Institutes of Health, *Report of the Human Embryo Research Panel* (Bethesda, Md.: NIH, 1994), available at http://bioethics.georgetown.edu/pcbe/reports/past_commissions/.

6. See, for example, Michael Sandel, "Statement of Professor Sandel," in PCBE, *Human Cloning and Human Dignity: An Ethical Inquiry*, Washington, D.C., 2002, available at http://bioethics.georgetown.edu/pcbe/reports/cloningreport/appendix.html; and Michael J. Sandel, "Embryo Ethics—The Moral Logic of Stem-Cell Research," *New England Journal of Medicine* 351, no. 3 (2004): 207-209.

7. PCBE, *Monitoring Stem Cell Research*, Washington, D.C., 2004, 83-84, available at http://bioethics.georgetown.edu/pcbe/reports/stemcell/pcbe_final_version_monitoring_stem_cell_research.pdf.

8. René Descartes, *Discourse on Method*, trans. Richard Kennington (Newburyport, Mass.: Focus Publishing, 2007), 49 (emphasis added).

9. John Harris, "Stem Cells, Sex and Procreation," *Cambridge Quarterly of Healthcare Ethics* 12, no. 4 (2003): 353-371. See also Jacqueline Pfeffer Merrill, "Embryos in Limbo," *The New Atlantis*, no. 24, Spring 2009, 18-28, http://www.thenewatlantis.com/publications/embryos-in-limbo.

10. For a review of the technical and ethical issues surrounding the practice of PGD, see PCBE, *Reproduction and Responsibility*, Washington, D.C., 2004, Chapter 3, available at http://bioethics.georgetown.edu/pcbe/reports/reproductionandresponsibility/chapter3.html.

11. For a review of the scientific applications of ES cells derived from embryos found to have genetic disorders by PGD, see D. Ben-Yosef, M. Malcov, and R. Eiges, "PGD-Derived Human Embryonic Stem Cell Lines as a Powerful Tool for the Study of Human Genetic Disorders," *Molecular and Cellular Endocrinology* 282, no. 1-2 (2008): 153-158.

12. Scientists from Advanced Cell Technologies have published a protocol for deriving human ES cells from single blastomeres. See Irina Klimanskaya *et al.*, "Derivation of Human Embryonic Stem Cells from Single Blastomeres," *Nature Protocols* 2, no. 8 (2007): 1963-1972.

13. Claire Basille *et al.*, "Preimplantation Genetic Diagnosis: State of the Art," *European Journal of Obstetrics & Gynecology and Reproductive Biology* 145, no. 1 (2009): 9-13.

14. I. Liebaers *et al.*, "Report on a Consecutive Series of 581 Children Born After Blastomere Biopsy for Preimplantation Diagnosis," *Human Reproduction* 25, no. 1 (2009): 275-282.

15. The first human pregnancies using embryos biopsied for PGD were reported in A. H. Handyside *et al.*, "Pregnancies from Biopsied Human Preimplantation Embryos

Sexed by Y-Specific DNA Amplification," *Nature* 344, no. 6268 (1990): 7680-770. See also Liebaers *et al.*, "Report on a Consecutive Series of 581 Children," 275-282.

16. PCBE, *Alternative Sources of Pluripotent Stem Cells*, Washington, D.C., 2005, Section II, available at http://bioethics.georgetown.edu/pcbe/reports/white_paper/alternative_sources_white_paper.pdf.

17. Aneta Swuinska *et al.*, "Blastomeres of the Mouse Embryo Lose Totipotency after the Fifth Cleavage Division: Expression of *Cdx2* and *Oct4* and Developmental Potential of Inner and Outer Blastomeres of 16- and 32-Cell Embryos," *Developmental Biology* 322, no. 1 (2008): 133-144.

18. Douglas A. Melton and Chad Cowen, "'Stemness': Definitions, Criteria, and Standards," in *Essentials of Stem Cell Biology*, 2nd ed., ed. Robert Lanza *et al.* (Burlington, Mass.: Elsevier Academic Press, 2009), xxiii.

19. PCBE, *Alternative Sources of Pluripotent Stem Cells*, 29.

20. For a discussion of the scientific details of this procedure, first proposed by Witherspoon Council chairman Donald W. Landry and his Columbia University colleague Howard A. Zucker, see PCBE, *Alternative Sources of Pluripotent Stem Cells*, 8-23. See also Donald W. Landry and Howard A. Zucker, "Embryonic Death and the Creation of Human Embryonic Stem Cells," *The Journal of Clinical Investigation* 114, no. 9 (2004): 1184-1186.

21. Donald W. Landry *et al.*, "Hypocellularity and Absence of Compaction as Criteria for Embryonic Death," *Regenerative Medicine* 1, no. 3 (2006): 367-371.

22. Svetlana Gavrilov *et al.*, "Derivation of Two New Human Embryonic Stem Cell Lines from Nonviable Human Embryos," *Stem Cells International* 2011, article ID 765378.

23. Xin Zhang *et al.*, "Derivation of Human Embryonic Stem Cells from Developing and Arrested Embryos," *Stem Cells* 24, no. 12 (2006): 2669-2676.

24. PCBE, *Alternative Sources of Pluripotent Stem Cells*, 14.

25. The first successful attempt to clone human embryos using SCNT was reported in Andrew J. French *et al.*, "Development of Human Cloned Blastocysts Following Somatic Cell Nuclear Transfer with Adult Fibroblasts," *Stem Cells* 26, no. 2 (2008): 485-493. While the authors did manage to successfully create a human embryo, they were unable to derive an embryonic stem cell line from it. Previously, Hwang Woo Suk had claimed to have derived patient-specific ES cells from cloned blastocysts, but it was later shown that he had fabricated his results. Hwang Woo Suk *et al.*, "Patient-specific Embryonic Stem Cells Derived from Human SCNT Blastocysts," *Science* 308, no. 5729 (2005): 1777-1783.

26. Scott Noggle *et al.*, "Human Oocytes Reprogram Somatic Cells to a Pluripotent State," *Nature* 478, no. 7367 (2011): 70-77.

27. National Conference of State Legislators, "Human Cloning Laws," http://www.ncsl.org/IssuesResearch/Health/HumanCloningLaws/tabid/14284/Default.aspx.

28. Young Chung *et al.*, "Reprogramming of Human Somatic Cells Using Human and Animal Oocytes," *Cloning and Stem Cells* 11, no. 2 (2009): 213-223. See Appendix A for more details on the technical feasibility of this procedure.

29. United Kingdom, Parliament, Human Fertilization and Embryology Act (2008), c. 22, http://www.legislation.gov.uk/ukpga/2008/22/contents.

30. A detailed review of the scientific issues surrounding ANT appears in Appendix A.

31. PCBE, *Alternative Sources of Pluripotent Stem Cells*, 36-50.

32. William Hurlbut, member of the Witherspoon Council and the author of the ANT proposal, opposes the use of potentially dangerous superovulation techniques to procure human egg cells for the sole and specific objective of obtaining eggs for research purposes, arguing for the use of alternative sources of human egg cells. See William B. Hurlbut, "Framing the Future: Embryonic Stem Cells, Ethics and the Emerging Era of Developmental Biology," *Pediatric Research* 59, no. 4 (2006): 4R-12R.

33. Hathaitip Sritanaudomchai *et al.*, "CDX2 in the Formation of the Trophectoderm Lineage in Primate Embryos," *Developmental Biology* 335 (2009): 179-187.

34. Kallayanee Chawengsaksophak *et al.*, "Cdx2 is essential for axial elongation in mouse development," *Proceedings of the National Academy of Sciences* 101, no. 20 (2004).

35. Guangming Wu *et al.*, "Initiation of Trophectoderm Lineage Specification in Mouse Embryos is Independent of Cdx2," *Development* 137, no. 24 (2010): 4159-4169. According to this paper, Cdx2 has a very important role, but is not absolutely necessary for the differentiation of the trophectoderm, suggesting that Cdx2-deficient embryos do retain some of the important developmental capacities that are characteristic of normal embryos. A 2006 paper published in *Science* claimed that Cdx2 was responsible for specifying trophectoderm cells from the 2-cell stage, but the lead author of the study, Kaushik Deb, was later found to have fabricated data, leading to the retraction of the paper. Kaushik Deb *et al.*, "Cdx2 Gene Expression and Trophectoderm Lineage Specification in Mouse Embryos," *Science* 311, no. 5763 (2006): 992-996.

36. See the 2005 *Communio* debate on ANT, available at http://www.communio-icr.com/ant.htm. See in particular Adrian J. Walker, "Altered Nuclear Transfer: A Philosophical Critique," *Communio* 31, Winter 2004, http://communio-icr.com/articles/PDF/walker31-4.pdf; and David L. Schindler, "*Veritatis Splendor* and the Foundations of Bioethics: Notes Towards an Assessment of Altered Nuclear Transfer and Embryonic (Pluripotent) Stem Cell Research," *Communio* 32, Spring 2005, http://communio-icr.com/articles/PDF/DLS32-1.pdf.

37. In theory, some of the gene-knockdown techniques used for ANT might be reversible through various kinds of "rescue-experiments." A recent paper describing the role of Cdx2 in early cellular differentiation found that by co-injecting both the anti-sense Cdx2 along with synthetic Cdx2 mRNA into the zygote, the embryo would develop normally. It is not clear whether or not an "embryo" with *maternal* Cdx2 knocked down prior to fertilization could be rescued in this way, although it is a very important question that has surprisingly not received much scientific attention. The PCBE White Paper asks whether the procedure is reversible, as does bioethicist Søren Holm in a

2008 article (Søren Holm, "'New Embryos'—New Challenges for the Ethics of Stem Cell Research," *Cells Tissues Organs* 187 (2008): 257-262). Agnieszka Jedrusik *et al.*, "Maternally and Zygotically Provided Cdx2 Have Novel and Critical Roles for Early Development of the Mouse Embryo," *Developmental Biology* 344, no. 1 (2010): 66-78.

38. Chad A. Cowan *et al.*, "Nuclear Reprogramming of Somatic Cells After Fusion with Human Embryonic Stem Cells," *Science* 309, no. 5739 (2005): 1369-1373.

39. A detailed review of the scientific issues surrounding iPS cells appears in Appendix A.

40. Anthony J. F. Griffiths, Susan R. Wessler, Richard C. Lewontin, and Sean B. Carroll, *Introduction to Genetic Analysis* 9th ed. (New York: W. H. Freeman and Company, 2008), 748-750.

41. Hans-Werner Denker, "Human Embryonic Stem Cells: The Real Challenge for Research as Well as for Bioethics Is Still Ahead of Us," *Cells Tissues Organs* 187 (2008): 250-257. Some ethicists have even argued that the ability of embryonic stem cells to be "reconstituted" into viable embryos through the tetraploid complementation technique shows that the harvesting of embryonic stem cells does not really destroy any embryos, since the technique allows the stem cells to be restored into embryos. Regardless of whether the "reconstituted embryo" would really be the same individual as the original, this technique also requires the destruction of the tetraploid embryo in order to work. See Katrien Devolder and Christopher M. Ward, "Rescuing Human Embryonic Stem Cell Research: The Possibility of Embryo Reconstitution After Stem Cell Derivation," *Metaphilosophy* 38, no. 2-3 (2007): 245-263.

42. Bernard Lo *et al.*, "Cloning Mice and Men: Prohibiting the Use of iPS Cells for Human Reproductive Cloning," *Cell Stem Cell* 6, no. 1 (2010): 16-20.

43. ES cells may also be used to generate sex cells that could then be used to treat infertility, but iPS cells would allow for infertility patients to have sex cells generated that would be genetically equivalent to their own sex cells. Given the relative availability of donated sex cells and embryos, the advantage of generating sex cells from iPS cells would be the ability for a patient to have sex cells that are genetically equivalent to his or her own natural sex cells, rather than relying on donated sex cells.

44. For a review of the ethical concerns raised by creating donor-conceived offspring, see Cheryl Miller, "Donated Generation," *The New Atlantis*, no. 21, Summer 2008, 27-44, http://www.thenewatlantis.com/publications/donated-generation; and Elizabeth Marquardt, Norval D. Glenn, and Karen Clark, *My Daddy's Name Is Donor*, Commission on Parenthood's Future (New York: Institute for American Values, 2010), http://familyscholars.org/my-daddys-name-is-donor-2/.

45. Debra J. H. Matthews *et al.*, "Pluripotent Stem Cell-Derived Gametes: Truth and (Potential) Consequences," *Cell Stem Cell* 5, no. 1 (2009): 11-14.

46. For a discussion of some of the ethical issues surrounding reproductive technologies and iPS cells, see Matthew Hoberg, "The Moral Frontiers of Stem Cell Research," *The Public Discourse*, December 6, 2010, http://www.thepublicdiscourse.com/2010/12/2035; as well as Bernard Lo *et al.* "Cloning Mice and Men: Prohibiting the Use of iPS Cells For Reproductive Cloning," 16-20.

Appendix D
Stem Cell Research Funding: Policy and Law

The central policy question in the United States relating to human embryonic stem cell research has not been its legality. While several state legislatures have addressed measures that would limit or ban human embryonic stem cell research, the central policy focus at the federal level has been whether and how such research would receive federal funding.

No one has a right to receive federal funding. The people, projects, and activities that receive federal taxpayer dollars do so as a matter of explicit policy decisions. In our democratic system, decisions about funding rightly take into account not only material costs and benefits but also moral judgments.[1]

In the stem cell debates, this has meant balancing the public interest in finding new cures and treatments—part of our longstanding public consensus in support of practical scientific research generally—against the profound ethical problems raised by the research.

Policymakers Face the Embryo

The policy debate over funding human embryonic stem cell research was not wholly unprecedented. Scientists began experimenting on human fetal tissue as early as the 1930s; by the 1960s, a handful of non-therapeutic experiments had begun on "previable human fetuses"—still-living fetuses that had been obtained by spontaneous and induced abortions.[2] In the 1970s, researchers became more interested in using fetal tissue for clinical purposes. They hoped that if fetal tissue were implanted into the brains of patients with degenerative diseases such as Alzheimer's, Parkinson's, or Huntington's, there might be new growth of some of the brain tissue whose absence or defectiveness had caused the disease. The rapidly rising rate of abortions following the United States Supreme Court's 1973 *Roe v. Wade* decision[3] may have encouraged scientific interest in these possibilities.

During the administrations of Ronald Reagan and George H. W. Bush, no federal funding supported such research, and attempts by Democratic-controlled Congresses to fund it were blocked (although privately

funded fetal-tissue-transplant experiments proceeded). But President Clinton on January 23, 1993—just days after he took office—directed the Department of Health and Human Services (HHS) to lift the Bush administration's moratorium on fetal-tissue research. On June 10, 1993, the Democratic-controlled Congress passed the National Institutes of Health Revitalization Act, which permitted federal funding for research on fetal transplantation, provided that the tissues came from miscarried or aborted fetuses that were donated with the mother's consent.[4] The act also included provisions intended to prevent the purchasing or commercialization of fetal tissue.

The lifting of the moratorium opened the door for government funding of research on *ex utero* embryos created by IVF, although research on embryos *in utero* was still prohibited under federal regulations for the protection of human subjects.

On February 2, 1994, the NIH established the Human Embryo Research Panel (HERP) as an ethics advisory body to provide recommendations on human embryonic research. In a report published September 27, 1994, the panel recommended funding research on human embryos created either for fertility treatments or specifically for the purposes of research.[5] But there was widespread public unease over the research, including a voluminous negative public response submitted to the panel; so, just hours after the HERP report was released, President Clinton rejected part of its recommendations, saying, "I do not believe that federal funds should be used to support the creation of human embryos for research purposes, and I have directed that NIH not allocate any resources for such research."[6]

In the wake of this controversy, and following the 1994 election that brought Republican majorities to the House and Senate, Congress passed the Dickey-Wicker Amendment in 1995, named for its authors, Representatives Jay Dickey (R.-Ark.) and Roger Wicker (R.-Miss.). The amendment—a rider on the annual appropriations bill for HHS, which funds the NIH—prohibited federal funding for research that involves the creation or destruction of human embryos. The original amendment forbade funding for:

> (1) the creation of a human embryo or embryos for research purposes; [and]
>
> (2) research in which a human embryo or embryos are destroyed, discarded, or knowingly subjected to risk of injury or death greater than that allowed for research on fetuses in utero under 45 CFR 46.208(a)(2)

> and 42 U.S.C. 289g(b) [federal statutes relating to the protection of human subjects and fetuses specifically].
>
> For purposes of this section, the phrase "human embryo or embryos" shall include any organism, not protected as a human subject under 45 CFR 46 as of the date of enactment of this Act, that is derived by fertilization, parthenogenesis, cloning, or any other means from one or more human gametes.[7]

Ever since 1995, under presidents and congressional majorities of both parties, the Dickey-Wicker Amendment has been included in the annual appropriations legislation with largely the same language and purpose; it remains in effect to the present day. (The only non-trivial change to the language of the amendment appeared starting in 1997, when the definition of embryos was expanded to include organisms "derived…from one or more…human diploid cells"—a change presumably prompted by the announcement of the creation of Dolly the cloned sheep in early 1997.[8])

In January 1999, two months after the announcement in *Science* that James Thomson had (using private funding) derived human ES cells, Harriet Rabb, the lead legal counsel for HHS, issued a memo advising the director of the NIH that the Dickey-Wicker ban on federal funding for embryo-destructive research would not apply to pluripotent stem cell lines "because such cells are not a human embryo within the statutory definition."[9] The Rabb memo thus drew an implicit distinction between the destruction of human embryos and the research that relies on the products of that destruction; federal funding for the former remained illegal, but funding for the latter was deemed permissible. This distinction would become central to the federal stem cell policies that followed.

Later that year, on September 7, 1999, the National Bioethics Advisory Commission (NBAC) published a report recommending that federal funding be permitted for research on embryonic stem cell lines, as well as for the derivation of new stem cell lines from unused embryos.[10] Notably, the NBAC report rejected the Rabb memo's implicit conclusion that research making use of ES cells is ethically distinct from the process that derives them from embryos:

> An ethical problem is presented in trying to separate research in which human ES cells are used from the process of deriving those cells, because doing so diminishes the scientific value of the activities receiving federal support. This division—under which neither biomedical researchers at NIH nor scientists at universities and other research

> institutions who rely on federal support could participate in some aspects of this research—rests on the mistaken notion that derivation and use can be neatly separated without affecting the expansion of scientific knowledge....
>
> Instead, recognizing the close connection in practical and ethical terms between derivation and use of the cells, it would be preferable to enact provisions that apply to funding by all federal agencies....[11]

The NBAC apparently believed that the Rabb memo's recommendation to fund ES cell derivation contradicted the Dickey-Wicker Amendment, since the NBAC felt it necessary to recommend "an exception" to Dickey-Wicker to permit federal funding for "research involving the derivation of human ES cells"[12] from unused IVF embryos.

Three months later, on December 2, 1999, the NIH released draft guidelines for funding research on ES cells. Under the guidelines, research on stem cell lines could be funded provided that their source embryos came from IVF undertaken for reproductive purposes, and that the embryos were voluntarily donated without financial inducement and free of influence or pressure from the researchers who were proposing to derive or make use of the embryonic stem cells.[13] The guidelines went into effect on August 25, 2000, and the NIH began accepting grant proposals from scientists, although no grants were made before the Clinton administration ended.

The Bush Funding Policy

Stem cell research funding was among the first major policy issues confronted by the new Bush administration in 2001. President Bush faced considerable political pressures on both sides of the issue. Eighty Nobel laureates signed a letter dated February 21, 2001, asking the president to fund the research; meanwhile, a Christian IVF-adoption organization challenged the Clinton administration's NIH guidelines in court, arguing that they violated the Dickey-Wicker Amendment. Jay Lefkowitz, the general counsel of the Bush White House's Office of Management and Budget, later recounted that he

> led a team of lawyers in our own evaluation of the Dickey Amendment. We decided that while spending federal dollars on such [ES cell] research might violate the spirit of the amendment, it would not violate the letter. Responsibility for adjudicating the divide between spirit and letter was necessarily the President's as the nation's chief executive officer.[14]

The Bush administration embarked on a months-long process of formulating a new policy, aiming to weigh the ethical and legal concerns against the medical promise held by stem cell research. In his memoirs, President Bush describes a defining moment of his deliberations, during a conversation with bioethicist Leon R. Kass on July 10, 2001. Kass advised the president that because embryos are an early form of human life, "we at least owe them the respect not to manipulate them for our purposes."[15] The president suggested that federal funds could be authorized for already-existing stem cell lines, on the reasoning that since the embryos had already been destroyed, it would make sense to allow the scientists to pursue research using them. There was a lingering concern that this policy might nonetheless tacitly endorse the destruction of embryos. The president's memoirs paraphrase Kass's advice:

> [Kass] said he believed that funding research on already destroyed embryos would be ethical, with two conditions. I must reaffirm the moral principle that had been violated—in this case, the dignity of human life. And I must make clear that federal funds would not be used in the further destruction of embryos. So long as I did both, he said, the policy would pass the ethical test. "If you fund research on lines that have already been developed," he said, "you are not complicit in their destruction."

In an August 9, 2001 speech, President Bush announced that his administration would fund research conducted on human ES cell lines that had already been derived before his policy was announced.[16] Research on ES cell lines established after August 9, 2001 was ineligible for federal support; in this way, the government would avoid creating any incentive for new acts of embryo destruction.

On November 7, 2001, the NIH officially established a registry listing the ES cell lines eligible for funding under the new policy. It also published a set of criteria for federal funding of research on ES cells.[17] Altogether, more than twenty human ES cell lines from across the world would prove available for federal funding under the Bush policy.[18]

In a January 11, 2002 memo, Alex Azar, general counsel for HHS, reported his conclusion that the Bush policy "comports with the plain language" of the Dickey-Wicker Amendment.[19] Azar argued that, while the amendment prohibits federal funding for "research in which a human embryo or embryos are destroyed," the Bush policy was limited to funding research on "a discrete set of stem cell lines with respect to which the life and death decision had been made prior to the announcement of his policy."

The Bush policy created no incentives for the destruction of additional embryos, Azar wrote, and therefore did not provide funding for *research in which* embryos are destroyed. Azar also noted that the legislative history of the most recent reenactment of the Dickey-Wicker Amendment could be taken as a congressional endorsement of the Bush policy. He referred to a House Committee report on the amendment, issued on October 9, 2001, which stated that the amendment's language should not be construed to limit federal support for stem cell research "carried out in accordance with policy outlined by the President."[20]

In his August 9, 2001 speech, President Bush also formed the President's Council on Bioethics, naming Kass as its first chairman and charging it with monitoring stem cell research. The Council's first report, released in July 2002, dealt with human cloning, addressing not only questions concerning cloning to produce children but also the use of cloning for biomedical research. A majority of the members of the Council supported a moratorium on cloning for biomedical research, and many among that majority would also have supported a ban. Among those Council members who disapproved of cloning for biomedical research, the report noted, most believed that "it is immoral to create human embryos for purposes that are foreign to the embryos' own well-being and that necessarily require their destruction."[21] A later Council report on stem cell research, published in January 2004, gave an outline of the moral foundations of the Bush policy—namely "the principle that *public funds* should not be used to encourage or support the destruction of embryos *in the future*," balancing a respect for human life with the importance of relieving suffering.[22] And in May 2005, the Council published a white paper exploring four proposals for creating pluripotent stem cells without destroying embryos.[23]

Further Policy Developments under President Bush

Over the course of his administration, President Bush sought opportunities to expand support for non-embryo-destroying stem cell research. So, for example, in late 2005 he signed into law the Stem Cell Therapeutic and Research Act, which established a program to help increase the amount of bone marrow and cord blood available for transplantation.[24] Meanwhile, some members of Congress from both parties objected to President Bush's ES cell research funding policy, and there were attempts to undo it through legislation. In May 2005, the House of Representatives passed the Stem Cell Research Enhancement Act of 2005, which would have permitted funding on any human ES cell lines derived from IVF embryos that had

been donated with informed consent and without financial inducement. The bill passed the Senate fourteen months later, on July 18, 2006.[25]

President Bush vetoed the bill the next day—his first use of the presidential veto power. In announcing his decision, the president explained that the bill crossed "a moral boundary" in its support for "the taking of innocent human life in the hope of finding medical benefits for others."[26] Several children who had been born after having been adopted as "spare" IVF embryos were present in the White House for the announcement; the president said they served as a reminder "of what is lost when embryos are destroyed in the name of research."[27] That same day, President Bush signed into law another bill, the Fetus Farming Prohibition Act of 2006, which prohibits the solicitation or acceptance of tissue from fetuses gestated specifically for research purposes.[28] Congress attempted to override the Bush policy again the next year. The House and Senate both passed the Stem Cell Research Act of 2007,[29] and on June 20, 2007, President Bush again vetoed the legislation. In justifying his decision, he reaffirmed the moral principle underlying his policy: "destroying human life in the hopes of saving human life is not ethical."[30]

As we discuss elsewhere in this report (see especially Appendices A and C), the arrival of new, less ethically problematic sources of pluripotent stem cells transformed the factual and moral landscape of the stem cell debate. The Bush policy had been intended in part to encourage the development of such alternative sources of stem cells. In his June 20, 2007 announcement, the president lauded these developments, and took steps to further advance that work, issuing an executive order "to ensure that any human pluripotent stem cell lines produced in ways that do not create, destroy, or harm human embryos will be eligible for federal funding."[31] The order directed the NIH to expand funding for research on the "isolation, derivation, production, and testing" of pluripotent stem cells "derived without creating a human embryo for research purposes or destroying, discarding, or subjecting to harm a human embryo or fetus."[32] In recognition of the change, the NIH registry of stem cell lines was renamed from the Human Embryonic Stem Cell Registry to the Human Pluripotent Stem Cell Registry. (The subsequent registry established under the Obama policy reverted to the old name.)[33]

The Obama Funding Policy

On March 9, 2009, President Barack Obama fulfilled a campaign pledge[34] by issuing an executive order revoking President Bush's 2001 stem cell

funding policy as well as Bush's 2007 executive order encouraging research into alternative sources. The new executive order allowed the NIH to support and conduct "human stem cell research, including human embryonic stem cell research, to the extent permitted by law."[35]

The order further directed the NIH to draft guidelines for funding research on stem cells newly derived from human embryos. These new NIH Guidelines on Stem Cell Research, which went into effect on July 7, 2009, provide criteria for NIH funding of stem cell research in accordance with President Obama's executive order.[36] For stem cell lines derived *after* July 7, 2009 to be eligible for funding, they must have been derived from IVF embryos left over and unwanted in fertility clinics. Donors must have been informed ahead of time that the embryos would be used to derive stem cells and that the embryos would be destroyed in the process. Donors also must have been informed that the stem cell line derived from the embryo might be kept indefinitely, and must also confirm that the donation was made without any restrictions or directions regarding the people who may receive medical benefit from the stem cells. Furthermore, donors must have been informed that the research would not be intended to provide them with any direct medical benefit, and that the donors would not receive any financial benefits from any commercial developments that might come from the stem cells. Finally, donors must have been notified whether any information that could identify them would be available to researchers. The Guidelines also stipulate that there should be a "clear separation between the prospective donor(s)'s decision to create human embryos for reproductive purposes and the prospective donor(s)'s decision to donate human embryos for research purposes."[37] To this end, the IVF clinician should not have been the same person as the researcher proposing to derive or utilize stem cells, "unless separation was not practical."[38]

For ES cell lines derived from donated embryos *before* July 7, 2009, if there is documentary evidence proving that the lines meet all the criteria described above, they will be eligible for funding. Alternatively, if full documentation is not available—as it probably would not be for cells derived before the Obama informed-consent rules were published—researchers can submit what documentation they do have to a special NIH working group. The working group will review the materials and recommend the ES cell line be eligible for funding if the embryo donation satisfied "core ethical principles and procedures" for obtaining informed consent. Stem cell lines derived outside the United States must meet the same requirements in order to be eligible for research funding.[39]

The Guidelines also prohibit funding for research in which pluripotent stem cells, either embryonic or induced, are "introduced into non-human primate blastocysts." And no funding is permitted for breeding animals that have had pluripotent human stem cells introduced to them in such a way that they may contribute to the animal's germ line.[40]

As of this writing, there are 136 human embryonic stem cell lines eligible for funding under the new Obama policy.[41] There is not yet any comprehensive data on how many of the ES cell lines newly available for funding under the Obama Guidelines have actually been used, and there is reason to believe that the lawsuit described below may have delayed some research projects by creating an atmosphere of legal and funding uncertainty.[42] In 2010, the NIH spent $125.5 million on funding for embryonic stem cell research, providing grants for 293 projects—not counting the additional $39.7 million in funding provided by the American Recovery and Reinvestment Act.[43]

The Legal Challenge to the Obama Policy

In a lawsuit that has been moving through the federal court system, *Sherley v. Sebelius*, two research scientists argue that President Obama's NIH Guidelines are in violation of the Dickey-Wicker Amendment.

On August 19, 2009, several parties, including two researchers on adult stem cells, an adoption agency, and a Christian medical association, filed a lawsuit in the United States District Court for the District of Columbia seeking to block HHS from implementing the new Guidelines.[44] The case was assigned to Chief Judge Royce Lamberth, an appointee of President Reagan. Judge Lamberth initially dismissed the entire suit, ruling on October 27, 2009 that all of the plaintiffs lacked legal standing to file the suit because they were not materially harmed by the new federal policy.[45] But on June 25, 2010, the U.S. Court of Appeals for the D.C. Circuit overturned Judge Lamberth's decision, concluding that the two stem cell scientists, Dr. James L. Sherley and Dr. Theresa Deisher, had standing, because the new Obama administration policy would divert federal funds away from their research on adult stem cells. The D.C. Circuit returned the case to Judge Lamberth for a decision on the substantive merits of the case.[46]

On August 23, 2010, Judge Lamberth ruled in favor of the plaintiffs and issued a preliminary injunction ordering HHS to cease funding embryonic stem cell research.[47] His analysis turned on the question of whether the wording of the Dickey-Wicker Amendment, which prohibits federal funding of "research *in which* a human embryo or embryos are destroyed,

discarded, or knowingly subjected to risk of injury or death" (emphasis added), is broad enough to include a researcher's work on stem cells derived from embryos if the researcher being funded had not himself participated in the initial phase of embryo destruction. On that point, Judge Lamberth rejected the government's position that HHS funded only one "piece of research"[48]—namely, research using stem cells already derived from embryos—and not the related activities of deriving those stem cells from embryos and destroying the embryos. Judge Lamberth concluded that

> despite defendants' attempt to separate the derivation of ESCs from research on the ESCs, the two cannot be separated. Derivation of ESCs from an embryo is an integral step in conducting ESC research....The Dickey-Wicker Amendment is unambiguous. It prohibits research in which a human embryo is destroyed, discarded, or knowingly subject to risk of injury or death greater than that allowed under applicable regulations. The [Obama administration's NIH] Guidelines violate that prohibition by allowing federal funding of ESC research because ESC research depends upon the destruction of a human embryo.[49]

As some commentators noted,[50] Judge Lamberth's reasoning not only rejected the Obama administration policy for funding embryonic stem cell research, but implicitly also rejected President Bush's funding policy—since Judge Lamberth denies the claim, first articulated in the 1999 Rabb memo, that the embryo-destroying act of deriving embryonic stem cells is separable under the law from the act of using those stem cells for research. However, since the plaintiff scientists did not challenge the funding of the Bush lines in this litigation, a ruling in their favor would enjoin only the Obama Guidelines.

The Obama administration appealed the decision to the D.C. Circuit, which on September 9, 2010 granted an administrative stay on the injunction, permitting the funding of embryonic stem cell research to continue while the appeal was underway. (A few weeks later, on September 28, 2010, the same court issued a slightly different order, a stay pending appeal, for technical reasons.)

Then on April 29, 2011, the D.C. Circuit ruled in favor of the government, voiding Judge Lamberth's injunction.[51] Judge Douglas Ginsburg, writing for himself and Judge Thomas Griffith, filed the opinion for the court, arguing that

> Dickey-Wicker is ambiguous and the NIH seems reasonably to have concluded that, although Dickey-Wicker bars funding for the destruc-

> tive act of deriving an ESC from an embryo, it does not prohibit funding a research project in which an ESC will be used.

In an accompanying dissent, Judge Karen Henderson criticized the majority opinion for its interpretation of Dickey-Wicker, which depended on "breaking the simple noun 'research' into temporal bits," "narrowing the verb phrase 'are destroyed' to an unintended scope," and other acts of "linguistic jujitsu."

The case then returned to the U.S. District Court for the District of Columbia, where the plaintiffs sought a summary judgment on the merits of the case. Judge Lamberth wrote that while he had "initially agreed with plaintiffs' understanding of the Dickey-Wicker Amendment," the higher court's interpretation of Dickey-Wicker as "ambiguous" overrode his own interpretation—and so, after analyzing the other merits of the plaintiffs' case, he denied their motion for summary judgment.[52] On the binding basis of the higher court's interpretation, Judge Lamberth dismissed the case against the government on July 27, 2011. On September 19, 2011, the plaintiffs filed an appeal to the U.S. Court of Appeals for the District of Columbia as part of their stated effort to "exhaust all of our judicial remedies" to the Obama policy.[53]

Although the lawsuit is still pending final resolution in the courts, the NIH has continued to announce grant opportunities and provide funding for research on human ES cell lines eligible under the Obama policy.[54] All told, the NIH is on track to provide $562 million for human ES cell research during the years of the Obama administration (from 2009 through estimates for 2011 and 2012), compared to a total of $294 million during the years of the Bush administration (2002 through 2008).[55]

Notes

1. For more on the balance of funding, democratic politics, and ethical judgment, see Peter Berkowitz, "The Meaning of Federal Funding," Appendix F in President's Council on Bioethics (PCBE), *Monitoring Stem Cell Research*, Washington, D.C., 2004, 225-236, http://bioethics.georgetown.edu/pcbe/reports/stemcell/pcbe_final_version_monitoring_stem_cell_research.pdf.

2. L. Lawn and R. A. McCance, "Ventures with an Artificial Placenta," *Proceedings of the Royal Society of London. Series B, Biological Sciences* 155, no. 961 (1962): 500-509; M. Pavone-Macaluso, Letter to the Editor, "Artificial Placenta," *The Lancet* 280, no. 7256 (1962): 608-609; Björn Westin, Rune Nyberg, and Göran Enhörning, "A Technique for Perfusion of the Previable Human Fetus," *Acta Paeditricia* 47, no. 4 (1958): 339-349.

3. Guttmacher Institute, "Trends in Abortion in the United States, 1973-2008,"

January 2011, http://www.guttmacher.org/presentations/trends.pdf.

4. *National Institutes of Health Revitalization Act I*, Public Law No. 103-43, 107 Stat 122 (1993): §111, http://www.hhs.gov/ohrp/policy/publiclaw103-43.htm.html, also archived at http://www.gpo.gov/fdsys/pkg/STATUTE-107/pdf/STATUTE-107-1-2.pdf.

5. National Institutes of Health (NIH), *Report of the Human Embryo Research Panel*, (Bethesda, Md.: NIH, 1994), archived at http://bioethics.georgetown.edu/pcbe/reports/past_commissions/human_embryo_vol_1.pdf.

6. William J. Clinton, "Statement on Federal Funding of Research on Human Embryos," *Public Papers of the Presidents of the United States: William J. Clinton (1994, Book II)*, December 2, 1994, Washington, D.C., p. 2142, http://www.gpo.gov/fdsys/pkg/PPP-1994-book2/pdf/PPP-1994-book2-doc-pg2142.pdf.

7. *Balanced Budget Downpayment Act I*, Public Law No. 104-99, 110 Stat 26 (1996): §128, http://www.gpo.gov/fdsys/pkg/PLAW-104publ99/pdf/PLAW-104publ99.pdf.

8. *Department of Labor Appropriations Act 1998*, Public Law No. 105-78, 111 Stat 1467 (1997), http://www.gpo.gov/fdsys/pkg/PLAW-105publ78/pdf/PLAW-105publ78.pdf.

9. Letter from HHS General Counsel Harriet Rabb to Harold Varmus, Director, NIH, January 15, 1999.

10. National Bioethics Advisory Commission, *Ethical Issues in Human Stem Cell Research Volume 1: Report and Recommendations of the National Bioethics Advisory Commission*, Washington, D.C., 1999, iv, http://bioethics.georgetown.edu/pcbe/reports/past_commissions/nbac_stemcell1.pdf.

11. *Ibid.*, v.

12. *Ibid.*, iv.

13. NIH, "Guidelines for Research Using Human Pluripotent Stem Cells," *Stem Cell Information*, August 25, 2000, http://stemcells.nih.gov/news/newsArchives/stemcellguidelines.asp.

14. Jay Lefkowitz, "Stem Cells and the President—An Inside Account," *Commentary*, January 2008, http://www.commentarymagazine.com/article/stem-cells-and-the-president%E2%80%94an-inside-account.

15. George W. Bush, *Decision Points* (New York: Crown, 2010), 117.

16. George W. Bush, "Address to the Nation on Stem Cell Research," August 9, 2001, *Public Papers of the Presidents of the United States: George W. Bush (2001, Book II)*, Washington, D.C., pp. 953-956, http://www.gpo.gov/fdsys/pkg/PPP-2001-book2/pdf/PPP-2001-book2-doc-pg953-2.pdf.

17. NIH, "NIH Human Embryonic Stem Cell Registry under Former President Bush," *Stem Cell Information*, http://stemcells.nih.gov/research/registry/eligibilitycriteria.asp.

18. *Ibid.*

19. HHS General Counsel Memorandum, January 11, 2002, Alex M. Azar II to Ruth Kirchstein, Acting Director, NIH, AR 303.

20. Departments of Labor, Health and Human Services, and Education, and Related Agencies Appropriations Bill, 2002, H.R. Rep. No. 107-229, 107th Congress, 1st Session, p. 180, http://www.gpo.gov/fdsys/pkg/CRPT-107hrpt229/pdf/CRPT-107hrpt229.pdf.

21. PCBE, *Human Cloning and Human Dignity: An Ethical Inquiry*, Washington, D.C., 2002, http://bioethics.georgetown.edu/pcbe/reports/cloningreport/recommend.html.

22. PCBE, *Monitoring Stem Cell Research*, Washington, D.C., 2004, http://bioethics.georgetown.edu/pcbe/reports/stemcell/.

23. PCBE, *Alternative Sources of Pluripotent Stem Cells: A White Paper*, Washington, D.C., 2005, http://bioethics.georgetown.edu/pcbe/reports/white_paper/index.html.

24. *Stem Cell Therapeutic and Research Act of 2005*, Public Law No. 109-129, 119 Stat 2550 (2006): §3, http://www.gpo.gov/fdsys/pkg/PLAW-109publ129/pdf/PLAW-109publ129.pdf.

25. *Stem Cell Research Enhancement Act of 2005*, H.R. 810, 109th Congress (July 18, 2006), http://thomas.loc.gov/cgi-bin/bdquery/z?d109:HR00810:.

26. George W. Bush, "Remarks on Signing the Fetus Farming Prohibition Act and Returning Without Approval to the House of Representatives the 'Stem Cell Research Enhancement Act of 2005,'" July 19, 2006, *Weekly Compilation of Presidential Documents* 42, no. 29, Washington, D.C., 1362-1365, http://www.gpo.gov/fdsys/pkg/WCPD-2006-07-24/pdf/WCPD-2006-07-24-Pg1362-3.pdf.

27. *Ibid.*

28. *Fetus Farming Prohibition Act of 2006*, Public Law No. 109-242, 120 Stat 570 (2006), http://www.gpo.gov/fdsys/pkg/PLAW-109publ242/pdf/PLAW-109publ242.pdf.

29. *Stem Cell Research Enhancement Act of 2007*, S. 5, 110th Congress, (June 7, 2007), http://thomas.loc.gov/cgi-bin/bdquery/z?d110:SN00005:.

30. George W. Bush, "Remarks on Returning Without Approval to the Senate the 'Stem Cell Research Enhancement Act of 2007,'" June 20, 2007, *Weekly Compilation of Presidential Documents* 43, no. 25, pp. 831-833, http://www.gpo.gov/fdsys/pkg/WCPD-2007-06-25/pdf/WCPD-2007-06-25-Pg831-2.pdf.

31. *Ibid.*

32. Executive Order no. 13435, "Expanding Approved Stem Cell Lines in Ethically Responsible Ways," *Federal Register* 72, no. 120 (June 22, 2007): 34591, http://edocket.access.gpo.gov/2007/pdf/07-3112.pdf.

33. *Ibid.*; NIH, *NIH Human Embryonic Stem Cell Registry*, http://grants.nih.gov/stem_cells/registry/current.htm.

34. Then-Senator Obama promised on August 30, 2008 to "lift the [Bush] administration's ban on federal funding of research on embryonic stem cell lines created after August 9, 2001 through executive order." ScienceDebate2008, "ScienceDebate2008.com Presents: Presidential Answers to the Top 14 Science Questions Facing America," August 30, 2008, http://www.sciencedebate.org/debate08.html.

35. Executive Order no. 13505, "Removing Barriers to Responsible Scientific Research Involving Human Stem Cells," *Federal Register* 74, no. 46 (March 11, 2009): 10667, http://edocket.access.gpo.gov/2009/pdf/E9-5441.pdf.

36. NIH, "Guidelines on Human Stem Cell Research," effective July 7, 2009, *Stem Cell Information*, http://stemcells.nih.gov/policy/2009guidelines.htm.

37. *Ibid.*

38. *Ibid.*

39. *Ibid.*

40. *Ibid.*

41. NIH, *NIH Human Embryonic Stem Cell Registry*, http://grants.nih.gov/stem_cells/registry/current.htm, accessed November 29, 2011. The registry notes that three of the 136 lines are designated as "currently on hold and should not be used in NIH-funded research."

42. Aaron D. Levine, "Policy Uncertainty and the Conduct of Stem Cell Research," *Cell Stem Cell* 8, no. 2 (2011): 132-135. See also Christopher T. Scott *et al.*, "Federal Policy and the Use of Pluripotent Stem Cells," *Nature Methods* 7, no. 11 (2010): 866-867.

43. *American Recovery and Reinvestment Act of 2009*, Public Law No. 111-5, 123 Stat 115 (2009); NIH, NIH Research Portfolio Online Reporting Tools (RePORT), http://www.report.nih.gov/rcdc/categories/ProjectSearch.aspx?FY=2010&ARRA=N&DCat=Stem%20Cell%20Research%20-%20Embryonic%20-%20Human.

44. Executive Order no. 13505, March 11, 2009.

45. *Sherley v. Sebelius*, 686 F Supp 2d 1 (DDC 2009), available at https://ecf.dcd.uscourts.gov/cgi-bin/show_public_doc?2009cv1575-36.

46. *Sherley v. Sebelius*, 610 F3d 69 (DC App 2010), available at http://www.cadc.uscourts.gov/internet/opinions.nsf/654D067319DDFA2D852578070070585A/$file/09-5374-1251802.pdf.

47. *Sherley v. Sebelius*, 704 F Supp 2d 63 (DDC 2010), available at https://ecf.dcd.uscourts.gov/cgi-bin/show_public_doc?2009cv1575-44.

48. *Ibid.*, p. 10.

49. *Ibid.*, p. 12.

50. See, for example, William Saletan, "Dickey Waiver: A Crazy Judge Throws Out Obama's Stem-Cell Policy—and Bush's," *Slate*, August 25, 2010, http://www.slate.com/id/2264996/.

51. *Sherley v. Sebelius*, 10-5287 (DC App 2011), available at http://www.cadc.uscourts.gov/internet/opinions.nsf/DF210F382F98EBAC852578810051B18C/$file/10-5287-1305585.pdf.

52. *Sherley v. Sebelius*, No 84-1, slip op (DDC 2011), available at https://ecf.dcd.uscourts.gov/cgi-bin/show_public_doc?2009cv1575-84-1. In issuing his decision,

Judge Lamberth regretted that his court had become "a grudging partner in a bout of 'linguistic jujitsu'" regarding the definition of the word "research," but remarked that "such is life for an antepenultimate court."

53. Law of Life Project, "Adult Stem Cell Researchers Ask Federal Court to Reverse Ruling That Existing Federal Law Does Not Ban Federal Funding of Illegal, Unnecessary, and Unethical 'Research' in Which Human Embryos are 'Knowingly Subjected to Risk of Injury or Death,'" press release, September 19, 2011, http://www.christiannewswire.com/news/694317814.html.

54. The NIH announced a grant opportunity involving research on approved human ES cell lines as recently as September 21, 2011. Furthermore, there are a number of human ES cell research projects currently receiving funding from the NIH, with some projects receiving grants starting as recently as September 1, 2011. NIH, "Environmental Influences on Stem Cells in Development, Health, and Disease (R21)," request for applications, http://grants.nih.gov/grants/guide/rfa-files/RFA-ES-11-010.html; NIH RePORTER, "Project Information: 1R01GM094220-01A1," http://projectreporter.nih.gov/project_info_details.cfm?aid=8108690.

55. In 2008, the NIH implemented a new methodology for reporting research funding, which the agency used to recalculate funding figures for 2007. The Bush administration total funding figure of $294 million we report here uses this revised 2007 data, found on the new NIH RePORT website, along with the data found on the NIH Stem Cell Research website. NIH, "NIH Stem Cell Research Funding, FY 2002-2010," http://stemcells.nih.gov/research/funding/funding.htm; NIH Research Portfolio Online Reporting Tools (RePORT), http://report.nih.gov/rcdc/categories/.

Appendix E
Overview of International Human Embryonic Stem Cell Laws

Countries around the world have responded to the ethical problems raised by embryonic stem cell research in a number of ways. Some governments have passed laws prohibiting all research on human embryos, while others have explicitly endorsed and funded ES cell research. Many countries, like the United States, regulate the research through restrictions on government funding, while others license researchers to ensure compliance with the national policy. Here we describe the stem cell policies of several countries and international bodies, both to offer some perspective on the American policy and to indicate some of the policy options that other nations have pursued.

Australia. The laws in Australia relating to human embryonic stem cell research have undergone significant changes over the past decade. In 2002, the Australian Parliament passed the Prohibition of Human Cloning for Reproduction Act, which banned all kinds of human cloning, regardless of the purpose, and also banned all *in vitro* conception for purposes other than "achiev[ing] pregnancy in a particular woman."[1] Parliament also passed the Research Involving Human Embryos Act, which allowed for research on "excess ART embryos" if licensed by the National Health and Medical Research Council (NHMRC).

The cloning ban was loosened with the passage in 2006 of the Prohibition of Human Cloning for Reproduction and the Regulation of Human Embryo Research Amendment Act.[2] The act retained the ban on so-called reproductive cloning, but it allowed SCNT for research purposes, so long as the cloned embryo did not grow beyond fourteen days.[3] Such research is permitted pursuant to the issuance of licenses by the NHMRC.[4] Human-animal hybrid embryos are permitted under the same licensing and similar growth restrictions, while the creation of chimeric embryos is altogether prohibited. (A "hybrid," in Australian law, is an embryo created by combining gametes or genetic material from two different species. A chimeric embryo is "a human embryo into which a cell, or any component part of a cell, of an animal has been introduced.")

Canada. Canadian regulations on human ES cell research are contained in the Updated Guidelines for Human Pluripotent Stem Cell Research,[5] which went into effect in June 2010 and which supersede earlier Guidelines from 2007. The new Guidelines apply to any research involving human pluripotent stem cells that is funded by any of the country's three central science-funding agencies—the Canadian Institutes of Health Research (CIHR), the National Sciences and Engineering Research Council, and the Social Sciences and Humanities Research Council. The Guidelines apply both to the derivation of ES cells from embryos, and to research carried out on established ES cell lines. Also in place is the 2004 Act Respecting Assisted Human Reproduction and Related Research, which was intended to regulate the derivation of ES cells from embryos, though it does not affect pre-existing human ES cell lines.

The guiding principles of current Canadian ES cell research regulations are that: (1) research should have potential health benefits for Canadians; (2) there should be free and informed consent based on full disclosure of all relevant information; (3) there should be respect for privacy and confidentiality; (4) there should be no payment or financial incentives for donating tissues or embryos for stem cell research; (5) there should be no creation of embryos for research purposes; and (6) there should be respect for "individual and community notions of human dignity and physical, spiritual, and cultural integrity."[6] To those ends, stem cell research proposals seeking funding from any of the three Canadian science agencies for established ES cell lines (either created in Canada or imported) must seek approval from the CIHR's Stem Cell Oversight Committee as well as from a local Research Ethics Board.

In order to minimize the need to create new embryonic stem cell lines, the CIHR established a national registry that would make human embryonic stem cell lines derived using government funding available to researchers. By making these cell lines available, the CIHR hopes to encourage researchers to use stem cell lines that have already been derived, rather than relying on donated embryos to create new stem cell lines. The Guidelines also expressly prohibit a number of research practices. Among the prohibited practices are creating human embryos specifically to derive ES cell lines, creating human embryos through SCNT to derive ES cell lines, combining pluripotent human or non-human stem cells with a human embryo, grafting pluripotent human or non-human stem cells to a human fetus, combining pluripotent human stem cells with a non-human embryo, and grafting human pluripotent stem cells to a non-human fetus (although grafting human pluripotent cells to newborn

or adult animals is permitted, provided that the animals are not allowed to breed).

Chile. In 2006, Chile's government enacted a law that "has as its purpose the protection of human life from the moment of conception, its physical and psychic integrity, as well as its diversity and genetic identity with regard to biomedical research and its clinical applications."[7] The law goes on to state that "the cloning of human beings is prohibited, regardless of the purpose sought and the technique used."[8] It also notes, with regard to ES cell research, that "the cultivation of lines or organs will only proceed with the goals of therapeutic diagnosis or scientific research. In no case is it permitted to destroy human embryos in order to obtain their stem cells, which give rise to the aforementioned lines and organs."[9]

China. Chinese ES cell research is governed by the 2003 Ethical Guiding Principles on Human Embryonic Stem Cell Research, the enforcement of which is entrusted to the Ministry of Science and Technology (MOST) and the Ministry of Health.[10] The Guiding Principles are relatively vague, however, and they lack strong mechanisms for enforcement.[11] MOST funding committees bear the responsibility for ensuring that proposed projects comply with the rules stipulated in the Guiding Principles, although these rules do not apply to the minority of research funded by sources other than MOST.[12]

The Guiding Principles specifically allow for ES cells to be derived from "spare" IVF embryos, from embryos created using voluntarily donated gametes or gametes left over from IVF procedures, from fetal cells derived from spontaneous or induced abortion, and from embryos created by SCNT. They also permit research on existing or imported ES cells. Such research is subject to basic requirements of informed consent (as to the "expected aim of the experiment as well as the potential consequences and risks") and to prohibitions on the buying and selling of gametes, fertilized eggs, embryos, and fetal tissues. The growing of embryos *in vitro* beyond fourteen days is also prohibited. Institutions performing research on ES cells must establish an ethics committee consisting of experts in biology, medicine, law, and sociology.

Denmark. The Danish government allows for ES cell research that destroys embryos only in the case of "spare" IVF embryos and only until fourteen days after fertilization. Denmark banned all cloning in 1992 with its Act on a Scientific Ethical Committee System and the Handling

of Biomedical Research Projects. In 1997, regulation concerning research on fertilized ova and germ cells intended for reproduction was transferred to the Act on Medically Assisted Procreation in Connection with Medical Treatment, Diagnosis, and Research.[13] That 1997 law was in turn amended in 2003 to permit research using spare IVF embryos, noting, "Research on fertilized ova and stem cells intended for reproduction is furthermore allowed, if research has the aim to get knowledge, which can improve treatment concerning human diseases."[14]

European Union. Since 1984, the European Union has provided funding for scientific research through a series of "framework programs for research and technological development."[15] From 2002 to 2006, under the Sixth Framework Program, the EU provided funding for research using embryonic stem cells, although it did not finance the actual act of destroying the embryos to derive the stem cells.[16] In 2006, ministers of science from the EU met to discuss the funding policies for the Seventh Framework Program, and upheld their previous stance.[17] Also funded as part of the Sixth Framework Program was a human ES cell registry, which began operations in April 2007 in order to make efficient use of pre-existing ES cell lines.[18] More recently, a legal battle over whether stem cell techniques can be patented may alter the research landscape, as the removal of the legal protections provided by the patent system might greatly dampen incentives for stem cell research in the EU.[19]

While the EU has demonstrated a willingness to provide funding for human ES cell research, the patentability of ES cells and their applications has proven more contentious. On October 18, 2011, the European Court of Justice ruled that German stem cell scientist Oliver Brüstle's patent on neural precursor cells derived from human ES cells violated Article 6 of the European Biopatent Directive, which specifies that "uses of human embryos for industrial or commercial purposes" cannot be patented.[20] (Since the central legal question in the EU case was whether Brüstle's research—and by extension, ES cell research generally—can be considered "uses of human embryos," it bears similarities to the *Sherley v. Sebelius* lawsuit in the United States, described in Appendix D.)

France. French legislation on ES cell research dates back to a 1994 bioethics law that prohibited the creation of embryos for research as well as experimentation on embryos.[21] That law was changed in 2004, with the passage of a law on Research on the Embryo and Embryonic Cells (Law No. 2004-800).[22] The law prohibits the creation of embryos *in*

vitro or through SCNT for the purposes of research, commerce, industry, or therapy.[23] The law also technically forbids "research on the human embryo," but this prohibition comes with various qualifications. For example, if the couple whose genetic material made an embryo wishes to donate it for this purpose, "research can be authorized on the embryo and embryonic cells when they are likely to allow great therapeutic progress."[24] Such research, however, must be authorized by France's Agency of Biomedicine.

While the 2004 law represented a compromise between the interests of medical research and the duty to protect embryonic life, members of the French left and socialist movements have sought to liberalize France's embryo research laws, particularly as they relate to SCNT.[25] In early 2011, the French Parliament considered whether to renew the 2004 law, or to ease the extant restrictions on ES cell research. On July 7, 2011, the French Parliament renewed the law on embryo research, maintaining the country's 2004 compromise on embryonic stem cell research.[26]

Germany. Germany strictly regulates ES cell research. The Stem Cell Act of 2002 "ban[s], as a matter of principle, the importation and utilization of embryonic stem cells," and prevents the derivation of stem cells from embryos in Germany.[27] The Act makes exceptions, however, for the importation of ES cell lines derived before January 1, 2002, provided that these lines were derived from "spare" IVF embryos rather than embryos created for the purpose of research. Research on authorized ES cell lines must serve "eminent research aims" for which the value of other experimental techniques have been exhausted.[28] In 2008, German lawmakers voted to extend the January 1, 2002 cutoff date to May 1, 2007 to keep German scientists internationally competitive.[29] Lawmakers also limited the scope of the Act by eliminating provisions that made it a criminal offence for German scientists to use ES cells in other countries.[30]

The Act is enforced by the Central Ethics Commission on Stem Cell Research, an agency created by the Ministry of Health and consisting of nine experts from the fields of biology, ethics, medicine, and theology. The Commission is charged with evaluating research applications to ensure that they comply with the Act.[31] Unlike many ethical research guidelines in other countries, this legislation contains fairly harsh penal provisions: the importation of stem cells without approval, or "deliberately giving false information" to gain approval, can be punished with fines or up to three years in prison.[32]

Iceland. While Iceland's first regulations, issued in 1997, were a straightforward ban on most embryo research,[33] legislative changes in 2008 considerably liberalized the country's embryonic stem cell policy. Icelandic law now permits licensed researchers to derive stem cell lines from spare IVF embryos, subject to approval from a Bioethics Committee.[34] Licensed researchers may also perform SCNT using donated egg cells and genetic material, if it is "deemed impossible to achieve the same results or acquire the same knowledge by the use of stem-cell lines made using excess embryos or by other means."[35] Reproductive cloning using SCNT is prohibited, however, and the embryos created through SCNT may not be grown for more than fourteen days.[36]

India. The Indian Department of Biotechnology, together with the Indian Council of Medical Research, drafted the nation's stem cell policy in 2007, the Guidelines for Stem Cell Research and Therapy.[37] The Guidelines call for the establishment of a national body for the review of stem cell research proposals, the National Apex Committee for Stem Cell Research and Therapy (NAC-SCRT). This committee was established only recently, with the twelve-member group being formed by the government in March 2011.[38] Institutions conducting stem cell research are also required to establish their own committees for reviewing stem cell research proposals. Scientists conducting research on stem cells must be registered with the NAC-SCRT, and the creation of new stem cell lines must be approved by both the local and national review committees.

The Guidelines divide research on human stem cells into three areas: permissible, restricted, and prohibited. Permissible research includes *in vitro* studies on previously established cell lines from any cell type (including ES cells), *in vivo* studies in animals with established cell lines from any type of stem cells (including ES cells), the establishment of new ES cell lines from "spare" IVF embryos, and clinical trials with minimally manipulated cells. The Guidelines restrict the creation of human embryos by IVF or SCNT for the purpose of deriving an ES cell line: If researchers seek to create ES cell lines specifically for research purposes, they must provide explicit justification for the procedure, establishing that the creation of the embryo is essential for their research. The Guidelines also restrict clinical trials using cells that have undergone major manipulations such as genetic alteration (which would seem to include many iPS cells and ANT-derived stem cells). And the Guidelines restrict various forms of chimera research, such as the introduction of human ES cells into embryonic animals. The Guidelines prohibit germ-line engineering and

human cloning for reproductive purposes, the growing of embryos *in vitro* for longer than fourteen days, transferring SCNT embryos into a uterus, and the breeding of animals that have received human ES cells.

Italy. Along with Germany, Italy has some of the strictest laws in Western Europe regulating human ES cell research. Law 40, which came into effect on March 10, 2004, regulated both embryo research and IVF (Italy had no regulations in place on IVF prior to this law) and banned research on human embryos, including the use of embryos for deriving ES cell lines.[39] In addition, the law limited the number of embryos that could be created during IVF procedures to three, and required that all embryos created by IVF be implanted in the recipient mother—which prevents any supply of "spare" embryos and thus precludes any demand to use them for ES cell research. The creation of human embryos for research purposes is also prohibited. Italian law on embryonic research includes serious penal provisions for forbidden experimentation on embryos, including jail time ranging from ten to twenty years for reproductive cloning.[40]

Japan. In September 2001, the Japanese government issued its Guidelines for Derivation and Utilization of Human Embryonic Stem Cells,[41] which outline the regulations that the Ministry of Education, Culture, Sports, Science, and Technology is responsible for implementing and enforcing. While the Guidelines were theoretically permissive with respect to many ethically controversial stem cell sources, structural regulations regarding the approval and practice of embryo research reportedly encumbered ES cell research.[42] A number of these regulations were relaxed in 2009 by the Council for Science and Technology Policy, a cabinet office chaired by the prime minister and composed of cabinet members, academics, and industrial leaders, following recommendations from its subcommittee, the Expert Panel of Bioethics.[43]

Under the revised Guidelines, ES cells can be derived only from "spare" IVF embryos, and only if the embryos are younger than fourteen days (not counting time spent frozen), were donated with informed consent, and were donated without financial compensation beyond "necessary costs."[44] The Guidelines ban reproductive cloning, but research-oriented SCNT is permitted, although regulatory delays in the approval process have retarded the development of human SCNT research.[45] Prominent Japanese stem cell researcher Norio Nakatsuji has described the relaxation of the rules as ranging "from absurd to excessively strict" and as

"irrational," since researchers seeking to derive new human ES cell lines must go through a two-stage approval process by both an Institutional Review Board and the Ministry, institutions must have the content of their bioethics and technical training courses approved by the Ministry, and word-for-word minutes of local board meetings on approval for work with existing lines must be sent to the Ministry.[46]

Lithuania. Lithuania's human ES cell laws are remarkably strict. The relevant legislation is the Law on Ethics of Biomedical Research, first enacted in 2000 and amended in 2004, which states: "Human embryos may be subjects only of clinical observations (non-invas[ive] investigations). Other clinical investigations involving human embryos and their creation for purposes of biomedical research shall be prohibited. Human embryos may be subjected to such biomedical research where the medical risks for the embryo are not disproportionate to the potential benefits."[47] Likewise, the law states that the "cloning of a human being shall be prohibited."

The Netherlands. In the Netherlands, the Embryos Law of 2002[48] regulates human ES cell research and bans both human reproductive cloning and the creation of hybrids and chimeras.[49] The law makes a distinction between cloning for reproductive purposes and research-oriented SCNT, instituting a five-year moratorium on SCNT.[50] The creation of human embryos for research purposes is illegal under the law.[51] A 2007 reevaluation of the policy by the Dutch cabinet ended with the existing policy being left in place for the foreseeable future.[52]

Norway. In 2003, the Storting, Norway's parliament, passed the fairly restrictive Act Relating to the Application of Biotechnology in Human Medicine.[53] Chapter 3 of the Act states, "It is prohibited to carry out research on fertilized eggs, human embryos, and cell lines derived from fertilized eggs or human embryos."[54] It is also prohibited "to create human embryos by cloning" and to conduct research on cell lines derived from cloned human embryos.[55]

Poland. Poland's Medical Profession Act of 1996 states that "conceived children"—a term that encompasses human embryos—"cannot participate in research experiments."[56] Because this law antedates both the news about Dolly the cloned sheep (1997) and the isolation of human embryonic stem cells (1998), it explicitly mentions neither human cloning nor stem

cell research, but it is nonetheless understood to ban both cloning and the creation of ES cell lines. In 2006, as the European Union was debating whether to fund human ES cell research (see "European Union," above), the Sejm, the lower house of the Polish parliament, passed a resolution declaring that human ES cell research is "inconsistent with Polish law," in that it violates the article in Poland's constitution ensuring "the legal protection of the life of every human being."[57] The resolution went on to state that experimentation on human embryos would violate the Polish penal code and medical ethics code.[58]

Singapore. While Singapore does not have specific legislation on stem cell research, the government has established a Bioethics Advisory Committee (BAC) that has promulgated recommendations on stem cell research and other areas of biomedical research in Singapore that are adhered to by the scientific community.[59] In 2002, the BAC issued a report containing recommendations on stem cell research. The report recommends that researchers should "wherever possible" draw on existing embryonic stem cell lines for research, rather than destroying embryos for research purposes.[60] However, deriving new stem cell lines from spare IVF embryos is permitted as "a suitable alternative source of ES cells."[61] Furthermore, the creation of embryos through SCNT to derive patient-specific ES cell lines should be permitted on a case-by-case basis,[62] although the report does note that future developments in cell reprogramming may make it "unnecessary to resort to using embryos as a source of stem cells."[63] The report recommends "a complete ban" on reproductive cloning.[64]

Further recommendations of the BAC on stem cell research include guidelines for obtaining informed consent from embryo and gamete donors, and prohibitions against the sale of embryos.[65] In 2010, the BAC released a report entitled "Human-Animal Combinations in Stem Cell Research"; it recommends permitting interspecies SCNT, which employs human genetic material and animal egg cells. The creation of human-animal chimeras by injecting human stem cells into animal embryos was also permitted for scientific research, with the caveat that these chimeras should not be allowed to breed.[66]

Slovakia. Slovakia has very strict laws on human ES cell research and human cloning. Slovakia's Law No. 277/1994 on health care forbids performing research on embryos that is not for their own benefit. According to the law, "Research without medical indication is not permitted on human embryos or fetuses."[67] The law also bans all cloning, stating, "Any

intervention seeking to create a human being genetically identical to another human being, whether living or dead, is prohibited."[68] Anyone who violates the prohibition on human cloning is subject to penalties including a possible sentence of up to twelve years in prison.[69]

Slovenia. In Slovenia, the current policy relevant to stem cell research is found in the Law on Biomedically Assisted Fertilization, which was enacted in 2000.[70] In it, the use of embryos created for the purpose of assisted reproductive therapies is allowed for research, so long as they are not suitable for future reproductive purposes.[71] The law also forbids creation of embryos for research and cloning, and *in vitro* growth of human embryos past fourteen days.[72]

South Korea. The most recent South Korean legislation on human ES cell research is the Bioethics and Safety Act, which came into effect on December 6, 2008.[73] The Act prohibits human reproductive cloning and prohibits the production of embryos for non-reproductive purposes. Nonetheless, sources of human ES cells permitted under the act include SCNT, "for the purpose of conducting research aimed at curing rare or currently incurable diseases," and "spare" IVF embryos if they have exceeded a maximum storage period of five years or if researchers receive consent from their parents. Payment for gametes is prohibited as well, although oocyte donors may be reimbursed for costs associated with the procedure.

The 2008 law replaces the Bioethics and Biosafety Act of 2005,[74] which had been criticized for failing to protect not only human embryos, but embryo and egg donors as well.[75] The 2005 law was repealed in large part due to the scandals surrounding South Korean researcher Hwang Woo Suk. In papers published in *Science* in 2004 and 2005, Hwang claimed to have successfully cloned human embryos and derived stem cells from them.[76] These claims made him a national hero—until it was revealed early in 2006 that his results were fabricated and that he had pressured his female subordinates to donate oocytes for his research.[77] Hwang's high-profile fraud and brazen ethical lapses, which had slipped through the cracks of South Korea's biotechnology policy regime and caused a national embarrassment, prompted the 2008 legislation.

Spain. From 1988 until 2003, Spanish law only allowed for studies on "non-viable" embryos.[78] The law was modified in 2003 to permit research using "spare" IVF embryos.[79] In 2006, the government undertook a new

Law on Assisted Reproduction in order to allow for therapeutic options not possible under Laws 35/1988 and 45/2003.[80]

In 2007, the Congress of Deputies, the lower house of the Spanish legislature, approved a new Law on Biomedical Research that allows for research-oriented SCNT.[81] The relevant clause reads, "The use of whatever technique for obtaining human stem cells for therapeutic or research purposes is permitted, insofar as it does not entail the creation of a pre-embryo or an embryo exclusively for this purpose, in the terms defined through this law, including the activation of oocytes through nuclear transfer."[82] In effect, therapeutic cloning has been approved, while reproductive cloning is still banned.

Switzerland. In Switzerland, the framework for human ES cell research and human cloning is laid forth in the 2003 Federal Act on Research Involving Embryonic Stem Cells (StRA). The law forbids numerous practices, among them efforts "to create an embryo for research purposes...[or] to derive stem cells from such an embryo, or to use such cells" in efforts "to create a clone, a chimera, or a hybrid."[83] At the same time, the law forbids the use of spare IVF embryos "for any purpose other than the derivation of embryonic stem cells."[84] After StRA survived a referendum challenge, the Swiss Federal Council, the government's executive branch, issued an ordinance in 2005 implementing the law, which sets forth licensing procedures for researchers seeking permission to derive human ES cells from IVF embryos. Research applications must include, among other standard descriptions, an explanation of "why equivalent insights could not also be gained in a different way, in particular through experiments involving animal embryos."[85]

United Kingdom. The U.K. has liberal regulations for human ES cell research. Permitted sources of ES cell lines under the 2008 Human Fertilization and Embryology Act (HFE Act) include unused IVF embryos, embryos created by IVF specifically for research purposes, embryos created by SCNT, "admixed embryos" including hybrids (created from human and animal gametes), "cytoplasmic hybrids" (created by SCNT using human nuclei and animal oocytes), transgenic human embryos (created by introducing animal DNA into a human cell), chimeric human embryos (created by introducing one or more animal cells into a human embryo), or any other embryos that contain both human and animal DNA, but in which animal DNA is not predominant.[86] Research on embryos that are over fourteen days old is prohibited.[87]

The Human Fertilization and Embryology Authority (HFEA) is responsible for enforcing the regulations of the HFE Act, and for licensing both IVF clinics and scientists carrying out research on human embryos. The HFEA will not grant a license for embryo research unless it is satisfied that the use of embryos is necessary for the research and that the research is relevant to the purposes specified by the HFE Act; these purposes include increasing knowledge about serious medical conditions, developing treatments for serious medical conditions, advancing the treatment of infertility, increasing knowledge about the causes of miscarriage, developing more effective contraception techniques, developing methods for detecting genetic or mitochondrial abnormalities in preimplantation embryos, and increasing knowledge of embryonic development.[88]

In addition, the HFEA requires licensees to deposit a sample of the cell lines they generate in the U.K. Stem Cell Bank.[89] Licensees must have approval from the Steering Committee for the U.K. Stem Cell Bank before conducting secondary research projects on human ES cells.[90]

United Nations. While the U.N. does not have a policy on human embryonic stem cell research *per se*, on March 8, 2005 the General Assembly approved a non-binding Declaration on Human Cloning which called on member states "to prohibit all forms of human cloning inasmuch as they are incompatible with human dignity and the protection of human life."[91] However, the official press release announcing the vote describes the Declaration as "a weak, non-binding political statement" that does not "reflect anything approaching consensus within the Assembly," and thus does not affect the stem cell research of any of its member nations."[92]

Notes

1. Australia, Parliament, *Prohibition of Human Cloning for Reproduction Act 2002*, no. 144, 2002, §12.1, http://www.comlaw.gov.au/Series/C2004A01081.

2. Australia, Parliament, *Prohibition of Human Cloning for Reproduction and the Regulation of Human Embryo Research Amendment Act 2006*, no. 172, 2006, http://www.comlaw.gov.au/Details/C2006A00172.

3. *Prohibition of Human Cloning for Reproduction Act 2002*, §14.

4. *Research Involving Human Embryos Act 2002*, §20.

5. Canadian Institutes of Health Research (CIHR), *Updated Guidelines for Human Pluripotent Stem Cell Research*, 2010, http://www.cihr-irsc.gc.ca/e/42071.html.

6. CIHR, *Updated Guidelines for Human Pluripotent Stem Cell Research*, §4.

7. Chile, Congreso Nacional, *Sobre la investigacion cientifica en el ser humano, su genoma, y prohibe la clonacion humana*, September 22, 2006, no. 20.120, art. 1, Witherspoon Council staff translation, http://www.leychile.cl/Navegar?idNorma=253478 [Spanish].

8. *Ibid.*, art. 5.

9. *Ibid.*, art. 6.

10. People's Republic of China, Ministry of Science and Technology and the Ministry of Health, *Ethical Guiding Principles on Human Embryonic Stem Cell Research*, 2003, http://www.chinaphs.org/bioethics/regulations_&_laws.htm#_Toc113106142.

11. U.K. Stem Cell Initiative, "Global Positions in Stem Cell Research: China," http://www.advisorybodies.doh.gov.uk/uksci/global/china.htm.

12. *Ibid.*

13. Anne Lykkeskov, Project Leader, The Danish Council of Ethics, e-mail correspondence with the staff of the Witherspoon Council, September 9, 2011.

14. Denmark, *Folketinget, Act No. 460/97 on Medically Assisted Procreation in Connection with Medical Treatment, Diagnosis and Research* (1997, amended 2003), §25, unofficial translation.

15. European Commission Community Research and Development Information Services (CORDIS), "What is FP7?" http://cordis.europa.eu/fp7/faq_en.html.

16. Gwennaël Joliff-Botrel and Pascale Perrin, eds., "European Research Projects Involving Stem Cells in the 6th Framework Programme," European Commission Directorate General for Research: Life Sciences, Genomics and Biotechnologies for Health, http://ec.europa.eu/research/fp6/p1/stemcells/pdf/stemcell_eu_research_fp6_en.pdf.

17. Council of the European Union, "Competitiveness (Internal Market, Industry and Research)," press release, July 24, 2006, http://www.consilium.europa.eu/ueDocs/cms_Data/docs/pressData/en/intm/90654.pdf, p. 7. See also CORDIS, "Stem Cell Compromise Allows Approval of FP7 by Council," press release, July 25, 2006, http://cordis.europa.eu/fetch?CALLER=FP7_NEWS&ACTION=D&QM_EN_RCN_A=26062.

18. European Human Embryonic Stem Cell Registry, "About hESCreg," http://www.hescreg.eu/index.php?id=14.

19. Christine Mummery, "Advocate-general's recommendation could undermine European biotechnology sector," EuroStemCell, April 28, 2011, http://www.eurostemcell.org/commentanalysis/advocate-general%E2%80%99s-recommendation-could-undermine-european-biotechnology-sector.

20. "Directive 98/44/EC of the European Parliament and of the Council of 6 July 1998 on the legal protection of biotechnological inventions," OJ L 213, 30.7.1998, §42, http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31998L0044:EN:NOT.

21. France, Parlement, Act No. 94-654, Article L 152-8, http://www.genethique.org/carrefour_infos/textes_officiels/titres_textes/textes/loi_n94654.htm [French].

22. France, Parlement, Act No. 2004-800, http://www.legifrance.gouv.fr/affichTexte.do?cidTexte=JORFTEXT000000441469.

23. France, Code of Public Health, Legislative Part, Part 2, Book 1, Title V, Article L2151, http://www.legifrance.gouv.fr/affichCode.do?idArticle=LEGIARTI000006687452&idSectionTA=LEGISCTA000006171138&cidTexte=LEGITEXT000006072665 [French].

24. *Ibid.*, Article L2151-5.

25. Jean-Yves Nau, "Roger-Gérard Schwartzenberg veut autoriser les recherches sur le clonage thérapeutique," *Le Monde*, May 27, 2005, 10 [French].

26. Nicole Atwill, "France: New Bioethics Law," July 18, 2011, http://www.loc.gov/lawweb/servlet/lloc_news?disp3_l205402748_text; The text of the law is available, in French, at: http://www.loc.gov/lawweb/servlet/lloc_news?disp1_l205402748_France.

27. Germany, *Bundestag, Stem Cell Act of 2002* (Stammzellgesetz), Bundesgesetzblatt [Federal Law Gazette] 2002, Part I, no. 42, p. 2277, June 29, 2002, §1-1, http://www.bmbf.de/pubRD/stammzellgesetz.pdf [German], unofficial translation accessed at http://www.hinxtongroup.org/docs/Germany1.html [English].

28. Stammzellgesetz, §5.

29. Dorothee Bürkle, "Balancing Act: German Stem Cell Research," trans. Jonathan Uhlaner, Goethe Insitut, August 2008, http://www.goethe.de/wis/fut/fuw/ftm/en3610292.htm [English].

30. *Ibid.*

31. Stammzellgesetz, §8-1.

32. *Ibid.*, §13-1.

33. Iceland, The Ministry of Health and Social Security, *Regulation on Artificial Fertilization No. 568/1997*, art. 22, issued September 30, 1997, http://eng.velferdarraduneyti.is/legislation/regulations/nr/17686 [English].

34. Iceland, *Alþingi, Act on Artificial Fertilisation and Use of Human Gametes and Embryos for Stem-Cell Research No 55/1996 (with amendments according to Act 65/2006, Act 27/2008 and Act 54/2008)*, art. 12, trans. Anna Yates, http://eng.velferdarraduneyti.is/acts-of-Parliament/nr/20092 [English, unofficial translation].

35. *Ibid.*, art. 13.

36. *Ibid.*, art. 13.

37. India, Department of Biotechnology and Indian Council of Medical Research, *Guidelines for Stem Cell Research and Therapy*, November 2007, http://www.icmr.nic.in/stem_cell/stem_cell_guidelines.pdf.

38. Kounteya Sinha, "Apex Body to Regulate Stem Cell Research Finally in Place," *The Times of India*, March 19, 2011, http://articles.timesofindia.indiatimes.com/2011-03-19/india/29145715_1_cell-research-cell-lines-human-embryonic-germ-cells.

39. Italy, Parlamento, *Norme in materia di procreazione medicalmente assistita*, Legge 19 Febbraio 2004, n. 40, available at http://www.normattiva.it/uri-res/N2Ls?urn:nir:stato:legge:2004;40 [Italian].

40. Andrea Boggio, "Italy Enacts New Law on Medically Assisted Reproduction," *Human Reproduction* 20, no. 5 (2005): 1153-1157.

41. Japan, Ministry of Education, Culture, Sports, Science and Technology (MEXT), *Guidelines for the Derivation and Utilization of Human Embryonic Stem Cells* (*Hito-ES saibou no jyuritsu oyobi siyou ni kansuru sisin*), enacted September 25, 2001, http://www.lifescience.mext.go.jp/files/pdf/32_88.pdf [Japanese], http://www.lifescience.mext.go.jp/files/pdf/32_90.pdf [English].

42. David Cyranoski, "Japan Relaxes Human Stem-Cell Rules," *Nature* 460, no. 7259 (2009): 1068.

43. Japan, Council on Science and Technology Policy (CSTP), "About CSTP," http://www8.cao.go.jp/cstp/english/policy/about-cstp.pdf; CSTP, "Summary," 83rd session (July 24, 2009), http://www8.cao.go.jp/cstp/english/policy/83cstp.html.

44. Japan, MEXT, *Guidelines on the Derivation and Distribution of Human Embryonic Stem Cells*, Public Notice of MEXT, No. 86 of May 20, 2010, art. 6, 1, i, http://www.lifescience.mext.go.jp/files/pdf/n743_00.pdf, tentative translation; *ibid.*, art. 6, 1, iv; *ibid.*, art. 6, 1, ii; *ibid.*, art. 4.

45. Masahiro Kawkami, Douglas Sipp, and Kazuto Kato, "Regulatory Impacts on Stem Cell Research in Japan," *Cell Stem Cell* 6, no. 5 (2010): 415-418. Cyranoski, "Japan Relaxes Human Stem-Cell Rules."

46. Japan, MEXT, *Guidelines on the Derivation and Distribution of Human Embryonic Stem Cells*, rev. 2010, art. 47, 3, ix.

47. Lithuania, *Seimas*, *Law on Ethics of Biomedical Research*, no. VIII-1679, May 11, 2000, amended July 13, 2004, no. IX-2362, art. 3, §2, http://www3.lrs.lt/pls/inter3/dokpaieska.showdoc_l?p_id=268769 [English, official translation].

48. Netherlands, Staten-Generaal, *Act Containing Rules Relating to the Use of Gametes and Embryos*, July 1, 2002, http://english.minvws.nl/en/folders/ibe/2002/introduction-embryo-act.asp.

49. Netherlands, Staten-Generaal, *Act Containing Rules Relating to the Use of Gametes and Embryos*, Section 24 (f), http://english.minvws.nl/includes/dl/openbestand.asp?File=/images/eng-embryowettekst_tcm20-107819.pdf [English]; *ibid.*, §25.

50. *Ibid.*, §33, 2.

51. *Ibid.*, §24, a.

52. *Die Verdieping Trouw*, "Kweken embryo's voor onderzoek blijft verboden," April 20, 2007, http://www.trouw.nl/tr/nl/4492/Nederland/article/detail/1423180/2007/04/20/Kweken-embryo-s-voor-onderzoek-blijft-verboden.dhtml [Dutch]; Editorial, *NRC*, "The Dutch Stem-Cell Taboo," March 13, 2009, http://vorige.nrc.nl/international/opinion/article2180263.ece/The_Dutch_stem_cell_taboo [English].

53. Norway, Storting, *Act Relating to the Application of Biotechnology in Human Medicine*, no. 100, §3-1, 2003, http://www.regjeringen.no/upload/kilde/hod/red/2005/0081/ddd/pdfv/242718-biotechnology_act_master.pdf [English].

54. *Ibid.*

55. *Ibid.*, §3-2.

56. Poland, National Assembly, *Act on the Medical Profession of December 5th, 1996*, art. 25.3, Witherspoon Council staff translation, http://www.nil.org.pl/xml/nil/tematy/odz/ustawa_o_zaw [Polish].

57. Gudrun Schultz, "Polish Parliament Adopts Resolution Against Human Embryonic Research," *Life Site News*, July 24, 2006, http://www.lifesitenews.com/news/archive/ldn/2006/jul/06072402.

58. *Ibid.*

59. Singapore, Bioethics Advisory Committee, http://www.bioethics-singapore.org.

60. Singapore, Bioethics Advisory Committee, *Ethical, Legal and Social Issues in Human Stem Cell Research, Reproductive and Therapeutic Cloning*, June 2002, http://www.bioethics-singapore.org/uploadfile/60517%20PMHSC%20Research.pdf, 25.

61. *Ibid.*, 26.

62. *Ibid.*, 29.

63. *Ibid.*, 28.

64. *Ibid.*, 31.

65. *Ibid.*, 34.

66. Singapore, Bioethics Advisory Committee, "Human-Animal Combinations in Stem Cell Research," press release, September 22, 2010, http://www.bioethics-singapore.org/uploadhtml/72555%20PMPress%20Release%20for%20Report%20on%20Human-Animal%20Combinations%20in%20Stem%20Cell%20Research%20.html.

67. Slovakia, Health Care Act No. 277/1994, art. 42, 3(c), as quoted in UNESCO, "National Legislation Concerning Human Reproductive and Therapeutic Cloning," Paris, 2004, http://unesdoc.unesco.org/images/0013/001342/134277e.pdf, 13.

68. *Ibid.*, art. 46.

69. Slovakia, *Slovak Penal Code*, art. 246a added in 2003, as quoted in UNESCO, "National Legislation Concerning Human Reproductive and Therapeutic Cloning," Paris, 2004, http://unesdoc.unesco.org/images/0013/001342/134277e.pdf, 14.

70. Slovenia, National Assembly, *Law on Biomedically Assisted Fertilization* (*Zakon o oploditvi z biomedicinsko pomoãjo*), 70 Uradni list RS, št. 70/2000, August 8, 2000, http://www.uradni-list.si/1/objava.jsp?urlid=200070&stevilka=3307 [Slovenian].

71. *Ibid.*, art. 38.

72. *Ibid.*, art. 33; for a good summary of the provisions of the law see Jože Trontelji

and Damjan Korošec, "National Regulations on Ethics and Research in Slovenia," Brussels: European Commission (2003), available at http://www.kme-nmec.si/Docu/JT_Regulations_research.pdf.

73. South Korea, National Assembly, *Bioethics and Safety Act*, no. 9100, June 5, 2008, trans. Young Mo Koo, http://www.cbd-chm.go.kr/english/law/law06001v.jsp?mcd1=6&mcd2=6 [English].

74. National Assembly, *Bioethics and Biosafety Act*, no. 7150, January 29, 2005, trans. Young Mo Koo, http://www.ruhr-uni-bochum.de/kbe/Bioethics&BiosafetyAct-SouthKorea-v1.0.pdf [English].

75. Mhkuta Jhalani, "Protecting Egg Donors and Human Embryos—The Failure of the South Korean Bioethics and Biosafety Act," *Pacific Rim Law and Policy Journal* 17, no. 3 (2008): 707-733.

76. Hwang Woo Suk *et al.*, "Evidence of a Pluripotent Human Embryonic Stem Cell Line Derived from a Cloned Blastocyst" [Retracted January 12, 2006], *Science* 303, no. 5664 (2004): 1669-1674; Hwang Woo Suk *et al.*, "Patient-Specific Embryonic Stem Cells Derived from Human SCNT Blastocysts" [Retracted January 12, 2006], *Science* 308, no. 5729 (2005): 1777-1783.

77. Seoul National University, *Summary of the Final Report on Professor Woo Suk Hwang's Research Allegations by Seoul National University Investigation Committee*, January 10, 2006, available at http://www.nytimes.com/2006/01/09/science/text-clonereport.html [English, university translation]. For *Science*'s investigation, see "Special Online Collection: Hwang *et al.* Controversy—Committee Report, Response, and Background," *Science* website, http://www.sciencemag.org/site/feature/misc/webfeat/hwang2005/. For a description of one of the early exposés on Dr. Hwang, see Kim Tae-gyu, "Hwang Forced Researcher to Donate Eggs," *Korea Times*, January 3, 2006, available in the Internet Archive at http://web.archive.org/web/20060107153538/http://times.hankooki.com/lpage/tech/200601/kt2006010316440911780.htm.

78. Spain, *Cortes Generales, Ley 35/1988 de 22 de noviembre, sobre Técnicas de Reproducción Asistida* [On Techniques of Assisted Reproduction], November 22, 1988, BOE no. 282, 27108, Witherspoon Council staff translation, http://www.boe.es/boe/dias/1988/11/24/pdfs/A33373-33378.pdf [Spanish].

79. Spain, *Cortes Generales, Ley 45/2003 de 21 de noviembre, por la que se Modifica la Ley 35/1988, de 22 de Noviembre, sobre Técnicas de Reproducción* [On Techniques of Assisted Reproduction], November 21, 2003, BOE no. 280, 21241, Witherspoon Council staff translation, http://www.boe.es/boe/dias/2003/11/22/pdfs/A41458-41463.pdf [Spanish].

80. Spain, *Cortes Generales, Ley 14/2006 de 26 de mayo, sobre Técnicas de Reproducción Humana Asistida* [On Techniques of Assisted Human Reproduction], May 26, 2006, BOE no. 126, 19947, Witherspoon Council staff translation, http://www.boe.es/boe/dias/2006/05/27/pdfs/A19947-19956.pdf [Spanish].

81. *El Mundo*, "El Congreso aprueba la Ley de Investigación Biomédica, que regula la clonación terapéutica," June 14, 2007, Witherspoon Council staff translation, http://www.elmundo.es/elmundosalud/2007/06/14/biociencia/1181832966.html [Spanish].

82. Spain, *Cortes Generales, Ley 14/2007 de 3 de julio, de Investigación Biomedical*, July 3, 2007, art. 33, §2, Witherspoon Council staff translation, http://www.boe.es/boe/dias/2007/07/04/pdfs/A28826-28848.pdf [Spanish].

83. Switzerland, The Federal Assembly of the Swiss Confederation, *Loi fédérale relative à la recherché sur les cellules souches embryonnaires* [Federal Act on Research Involving Embryonic Stem Cells], December 19, 2003, 810.31, art. 3, 1, c, http://www.admin.ch/ch/d/as/2005/947.pdf [French, official], http://www.admin.ch/ch/e/rs/c810_31.html [English, unofficial translation].

84. *Ibid.*, art. 3, 2, a.

85. Switzerland, The Swiss Federal Council, *Ordinance on Research Involving Embryonic Stem Cells*, February 2, 2005, 810.311, art. 8, c, http://www.bag.admin.ch/themen/medizin/03301/03361/03410/index.html?lang=en&download=NHzLpZeg7t,lnp6I0NTU042l2Z6ln1ad1IZn4Z2qZpnO2Yuq2Z6gpJCEfIB_f2ym162epYbg2c_JjKbNoKSn6A--[English].

86. United Kingdom, Parliament, *Human Fertilization and Embryology Act* (1990), c. 37, as amended by *Human Fertilization and Embryology Act* (2008), c. 22, http://www.legislation.gov.uk/ukpga/2008/22/contents. U.K. Stem Cell Bank, *Code of Practice*, April 2010, pp. 10-11; *Human Fertilization and Embryology Act* (2008) 3, (3-4); *ibid.*, 4A, http://www.ukstemcellbank.org.uk/guidelines&policies/codeofpracticefortheuseofhumanstemcelllines.cfm.

87. *Human Fertilization and Embryology Act* (2008), 4A.

88. *Ibid.*, Schedule 2, 3A.

89. *Code of Practice*, pp. 17-18.

90. *Code of Practice*, p. 12.

91. United Nations General Assembly, *Resolution 280*, Fifty-ninth session (March 23, 2005), UN Doc A/RES/59/280, *United Nations Declaration on Human Cloning*, http://daccess-dds-ny.un.org/doc/UNDOC/GEN/N04/493/06/PDF/N0449306.pdf?OpenElement.

92. *Ibid.*