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HUMAN CLONING AND EMBRYONIC STEM CELL RESEARCH AFTER SEOUL; EXAMINATION EXPLOITATION, FRAUD AND ETHICAL PROBLEMS IN THE RESEARCH

HEARING

BEFORE THE

SUBCOMMITTEE ON CRIMINAL JUSTICE, DRUG POLICY, AND HUMAN RESOURCES

OF THE

COMMITTEE ON GOVERNMENT REFORM

HOUSE OF REPRESENTATIVES

ONE HUNDRED NINTH CONGRESS

SECOND SESSION

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HUMAN CLONING AND EMBRYONIC STEM CELL RESEARCH AFTER SEOUL; EXAMINATION EXPLOITATION, FRAUD AND ETHICAL PROBLEMS IN THE RESEARCH

TUESDAY, MARCH 7, 2006

HOUSE OF REPRESENTATIVES,
SUBCOMMITTEE ON CRIMINAL JUSTICE, DRUG POLICY,
AND HUMAN RESOURCES,
COMMITTEE ON GOVERNMENT REFORM,
Washington, DC.

The subcommittee met, pursuant to notice, at 2:05 p.m., in room 2247, Rayburn House Office Building, Hon. Mark E. Souder (chairman of the subcommittee) presiding.

Present: Representatives Souder, McHenry, Foxx, Schmidt, Waxman, Cummings, Watson, Ruppersberger, and Norton.

Staff present: Marc Wheat, staff director and chief counsel; Michelle Gress, counsel; Malia Holst, clerk; Sarah Despres, Tony Haywood, and Naomi Seiler, minority counsels; Earley Green, minority chief clerk; and Teresa Coufal, minority assistant clerk.

Mr. SOUDER. The committee will come to order.

Good afternoon, and I thank you all for being here. We are here to examine the controversial research areas of human cloning and embryonic stem cell research in light of the massive scientific scandal in Seoul, South Korea. The scandal revealed that cloning research widely acclaimed by proponents of human cloning and embryonic stem cell research was a fraud. The scandal also brought to light the disturbing fact that women were paid large sums of money, and female assistants were coerced to donate, if that is the word, their eggs for stem cell and cloning research in violation of the Helsinki agreement.

Embryonic stem cell research and human cloning have been intense political and societal issues for several years now. Embryonic stem cell research requires the destruction of living human embryos to harvest their stem cells, and research cloning involves the deliberate creation of cloned human embryos for sole purpose of destroying them to obtain their stem cells.

Proponents of these research areas promise they will result in therapies and cures for a range of maladies and diseases, although there has been little hard, empirical evidence to support these claims. In fact, there are currently ho human clinical trials or therapeutic applications using human embryonic stem cells.

And here I will quote British stem cell expert Professor Lord Winston. "One of the problems is that in order to persuade the pub-

lic that we must do this work, we often go rather too far in promising what we might achieve. I am not entirely convinced that embryonic stem cells will, in my lifetime, and possibly anybody's lifetime, for that matter, be holding quite the promise that we desperately hope they will."

In contrast to the lack of any therapeutic applications using embryonic stem cells, adult stem cells have provided therapeutic benefits to human patients for at least 67 diseases and conditions. Nonetheless, even in the absence of therapeutic applications for embryonic stem cells, scientists have been very clear that they seek to use stem cells from cloned human embryos as research tools.

Various critics of research cloning and embryonic stem cell research have raised a myriad of objections to the research: The research necessarily requires the destruction of living human embryos, and in the case of cloning, the special creation of embryos to be destroyed for their stem cells. The research necessarily requires a large number of eggs, likely leading to the exploitation of women in order to obtain their eggs for research. Advocates of research cloning/embryonic stem cell research have created unjustified hype of the research that is not supported by current science, but plays on the hopes of suffering patients.

These criticisms were borne out through the cloning research conducted by Dr. Hwang, whose two groundbreaking papers were retracted in January by the peer review journal that initially published them. In addition to admitting that he deliberately fabricated data, Hwang has also admitted the had lied about the circumstances under which he obtained eggs for his research, and that in fact he had used eggs from junior scientists in his laboratory, a violation of the Helsinki declaration, as well as from paid donors.

Skeptics of cloning and embryonic stem cell research consistently warned that the sheer volume of eggs needed to pursue this line of research would make it untenable, and virtually invite ethical lapses by feeling the temptation to exploit women for their eggs. Hwang's research proves these fears. He initially claimed that he had used only 185 eggs from female donors, which the scientific community agreed was astonishingly low. But investigators now believe that more than 2,200 eggs were obtained from 199 women.

Some donors who have since reported they were in desperate need of money when they were offered and paid more than $1,400 for their eggs. And according to the South Korean National Bioethics Committee, the women had not been properly informed about the risks to their health; 15 to 20 percent of those women developed ovarian hyperstimulation syndrome.

This scientific scandal is not an isolated incident of fabrication, without real application to U.S. research efforts. Rather, it highlights the serious inherent political problems with research cloning and embryonic stem cell research, including but not limited to exploitation, fraud, and coercion. The incident is a siren warning against proceeding in these research areas without most cautiously examining the societal costs necessarily associated with it. It would be quite disingenuous to say otherwise.

Dr. Hwang was not a rogue scientist operating on the fringes of his field with no oversight. He operated in an environment that

proponents of cloning and embryonic stem cell research would like to see adopted in the United States.

Dr. Hwang enjoyed the full support of his Government, which vigorously promoted his research and funded it with tens of millions of dollars. Dr. Hwang also enjoyed enormous popular support and had agreed to conduct his research under accepted ethical protocols. Dr. Hwang suspended his research until ethics laws were enacted by the South Korean Government to demonstrate his willing compliance with ethical standards. Dr. Hwang's research was conducted with the approval of two separate Institutional Review Boards.

Nonetheless, Dr. Hwang's actions represent the fulfillment of every warning dismissed by proponents of research cloning and embryonic stem cell research. Thousands of eggs were obtained through payments and coercion. Many women suffered terrible side effects after they were not properly informed of the risks. Not a single embryonic stem cell line was obtained for the tens of millions of dollars in Government funds that were invested in research. Anxious patients were misled about the research potential.

As stem cell researcher Ron McKay said about the hype involved with embryonic stem cell research and distortions that are not aggressively corrected by scientists, "To start with, people need a fairy tale. Maybe that's unfair, but they need a story line that's relatively simple to understand."

Our examination today will include an overview of current Federal policies related to these research areas. In particular, we will hear what if any extra protections exist in the United States that would prevent the type of widespread fraud or exploitation apparent in the Hwang research. Also of special interest to the subcommittee are the huge Federal grants that have been awarded to the University of Pittsburgh researcher Gerald Schatten, who was initially a co-author on one of Hwang's fraudulent papers.

We will also hear from scientists, ethicists, women's advocates, and a patient advocate discuss these research areas and the known problems associated with them.

On our first panel today, we have James Battey, Chair of the National Institutes of Health Stem Cell Task force, and Director of the National Institute on Deafness and Other Communication Disorders; Bernard Schwetz, Director of the Office for Human Research Protections; and Chris Pascal, Director of the Office of Research Integrity.

The second panel consists of Dr. Richard Chole, Lindberg professor and chairman, Department of Otolaryngology, Washington University School of Medicine, St. Louis; Judy Norsigian, executive director, Our Bodies Ourselves, co-author of the book, "Our Bodies, Ourselves"; Ms. Diane Beeson, professor emerita, Department of Sociology and Social Services, California State University, East Bay; Mr. Richard Doerflinger, deputy director of secretariat for pro-life activities of the U.S. Conference of Catholic Bishops; Ms. Debra Mathews, assistant director for Science Programs, the Phoebe R. Berman Bioethics Institute; and Mr. Joe Brown, Parkinson's Action Network State coordinator of Texas.

[The prepared statement of Hon. Mark E. Souder follows:]

Subcommittee on Criminal Justice,
Drug Policy and Human Resources

Opening Statement of Chairman Mark Souder

"Human Cloning and Embryonic Stem Cell Research after Seoul: Examining exploitation, fraud and ethical problems in the research"

March 7, 2006

Good afternoon, and thank you all for being here.

We are here to examine the controversial research areas of human cloning and embryonic stem cell research in light of the massive scientific scandal in Seoul, South Korea.

This scandal revealed that cloning research widely acclaimed by proponents of human cloning and embryonic stem cell research was a fraud. The scandal also brought to light the disturbing fact that women were paid large sums of money, and female assistants were coerced, to "donate," if that is the word, their eggs for the stem cell and cloning research, in violation of the Helsinki agreement.[1]

Embryonic stem cell research and human cloning have been intense political and societal issues for several years now. Embryonic stem cell research requires the destruction of living human embryos to harvest their stem cells, and research cloning involves the deliberate creation of cloned human embryos for the sole purpose of destroying them to obtain their stem cells.

Proponents of these research areas promise they will result in therapies and cures for a range of maladies and diseases, although there has been little hard, empirical evidence to support these claims. In fact, there are currently no human clinical trials or therapeutic applications using human embryonic stem cells.

And here I will quote British stem cell expert Professor Lord Winston: "One of the problems is that in order to persuade the public that we must do this work, we often go rather too far in promising what we might achieve… I am not entirely convinced that embryonic stem cells will, in my lifetime, and possibly anybody's lifetime for that matter, be holding quite the promise that we desperately hope they will."[2]

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[1] WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI: Ethical Principles for Medical Research Involving Human Subjects (Adopted by the World Medical Association General Assembly in June, 1964). One of its principles states, "When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship." See http://www.trepan.com/agreement.html (last visited March 6, 2006).
[2] Lecture at Gresham College, June 20, 2005, www.gresham.ac.uk/printtranscript.asp?EventId=347 (last visited March 6, 2006).

In contrast to the lack of any therapeutic applications using embryonic stem cells, adult stem cells have provided therapeutic benefits to human patients for at least 67 diseases and conditions. Nonetheless, even in the absence of therapeutic applications for embryonic stem cells, scientists have been very clear that they seek to use stem cells from cloned human embryos as research tools.

Various critics of research cloning and embryonic stem cell research have raised a myriad of objections to the research:

- The research necessarily requires the destruction of living human embryos (and in the case of cloning, the special creation of embryos to be destroyed for their stem cells).
- The research necessarily requires a large number of eggs, likely leading to the exploitation of women in order to obtain their eggs for research.
- Advocates of research cloning/embryonic stem cell research have created unjustified "hype" of the research that is not supported by current science, but plays on the hopes of suffering patients.

These criticisms were borne out through the cloning research conducted by Dr. Hwang [*pronounced* **wong**], whose two groundbreaking papers were retracted in January by the peer-reviewed journal that initially published them. In addition to admitting that he deliberately fabricated data, Hwang has also admitted that he had lied about the circumstances under which he obtained eggs for his research, and that in fact he had used eggs from junior scientists in his laboratory - a violation of the Helsinki declaration - as well as from paid donors.

Skeptics of cloning and embryonic stem cell research consistently *warned* that the sheer volume of eggs needed to pursue this line of research would make it untenable, and virtually *invite* ethical lapses by fueling the temptation to exploit women for their eggs. Hwang's research proves those fears. He initially claimed that he had used only 185 eggs from female donors, which the scientific community agreed was astonishingly low. But investigators now believe that more than 2,200 eggs were obtained from 119 women.

Some donors who have since reported they were in desperate need of money when they were offered and paid more than $1400 for their eggs. And according to the South Korean National Bioethics Committee, the women had <u>not</u> been properly informed about the risks to their health: 15-20 percent of those women developed ovarian hyperstimulation syndrome.

This scientific scandal is not an isolated incident of fabrication, without real application to U.S. research efforts. Rather, it highlights the serious, inherent potential problems with research cloning and embryonic stem cell research, including but not limited to: exploitation, fraud, and coercion. The incident is a siren warning against proceeding in these research areas without *most cautiously* examining the societal costs necessarily associated with it. It would be quite disingenuous to say otherwise.

Dr. Hwang was not a rogue scientist operating on the fringes of his field with no oversight. He operated in an environment that proponents of cloning and embryonic stem cell research would like to see adopted in the United States:

- Dr. Hwang enjoyed the full support of his government, which vigorously promoted his research and funded it with tens of millions of dollars.
- Dr. Hwang also enjoyed enormous popular support and he had agreed to conduct his research under accepted ethical protocols.
- Dr. Hwang suspended his research until ethics laws were enacted by the South Korean government to demonstrate his willing compliance with ethical standards.
- Dr. Hwang's research was conducted with the approval of two separate Institutional Review Boards.

Nonetheless, Dr. Hwang's actions represent the fulfillment of every warning dismissed by proponents of research cloning and embryonic stem cell research: thousands of eggs were obtained through payments and coercion; many women suffered terrible side-effects after they were not properly informed of the risks; not a single embryonic stem cell line was obtained for the tens of millions of dollars in government funds that were invested in the research; anxious patients were misled about the research potential.

As stem cell researcher Ron McKay said about the hype involved with embryonic stem cell research and distortions that are not aggressively corrected by scientists – quote – "To start with, people need a fairy tale. Maybe that's unfair, but they need a story line that's relatively simple to understand."[3]

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[3] Weiss, R., "Stem Cells An Unlikely Therapy for Alzheimer's," The Washington Post, June 10, 2004, p. A3.

Source: Do No Harm: The Coalition of Americans for Research Ethics
www.stemcellresearch.org

Potential U.S. Patient Populations for Stem Cell-Based Therapies (according to the National Academy of Sciences)[1]

Condition	Number of Patients
Cardiovascular disease	58 million
Autoimmune diseases	30 million
Diabetes	16 million
Osteoporosis	10 million
Cancers	8.2 million
Alzheimer's disease	5.5 million
Parkinson's disease	5.5 million
Burns (severe)	0.3 million
Spinal-cord injuries	0.25 million
Birth Defects	0.15 million

Total patient population = 133.9 million (10% = 13.4 million)

Assume cloning efficiency at 20%; Assume ES extraction/line establishment at 10%; assume conservatively obtaining 10 eggs per donor.

NEEDED: AT LEAST 670 MILLION EGGS,
DONATED BY AT LEAST 67 MILLION WOMEN.

Indiana University Center for Bioethics at IUPUI
http://bioethics.iu.edu/Woo.html

S O U T H K O R E A N S T E M C E L L C O N T R O V E R S Y T I M E L I N E

2004

12 February

Hwang, with colleagues from Seoul National University, claims 30 cloned embryos with one being used to create a stem cell line. Announcement of 242 eggs from 16 volunteers. Published in Science (W. S. Hwang et al. Science 303, 1669-1674; 2004). This article was formally retracted by Science on January 11th, 2006. Read the abstract and the retraction notice.

May
First allegations of inappropriate collection of eggs used in study, as a result of investigations by Nature. Hwang denies, but announces self-imposed suspension of research until new SKorean law comes into effect in 2005.

The Korean Bioethics Association calls for Hwang to answer questions about egg sources and funding. (Note that this is 18 months before the Korean press makes claim of improperly obtained eggs by Hwang's associate.)
Read the news reports in Nature:
Korea's stem-cell stars dogged by suspicion of ethical breach
Stem-cell research: Crunch time for Korea's cloners

2005

January
New South Korean bioethics law comes into effect, and Hwang's research is the first to be approved by the South Korean government.

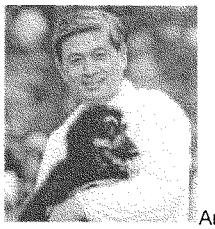
Chin Kyo Hun, a professor emeritus at Seoul National University, told the New York Times that, "The bioethics law had little to do with safeguarding bioethics but everything to do with giving Hwang a legal support,".
(New York Times, January 11th, 2005. Available online.)

View the South Korea Bioethics & Biosafety Act:

May
Announcement of the creation of 11 patient-specific embryonic stem cell lines. Published in Science (W. S. Hwang et al. Science 308, 1777-1783; 2005). This article was formally retracted by Science on January 11th, 2006.

Read the abstract and the retraction notice.

August


Announcement of first dog cloned, Snuppy. Published in Nature (Lee B. C. et al Nature 436, 641; 2005). This research was the one aspect of Hwang's work that was verified in the investigation by Seoul National University.

Read the abstract.

October
Announcement of World Stem Cell Hub, to be headed by Hwang, and involving such stem cell leaders as Gerald Schatten (Hwang's collaborator on the now-retracted papers) and Ian Wilmut (cloned Dolly the sheep).

Announcement by The Korea Times.

10 November

Korean press reports first allege illegally traded ova by a member of Hwang's lab. Gerald Schatten of the University of Pittsburgh and a co-author with Hwang tells Science that no ova were inappropriately obtained.

11 November
Schatten tells Science that he will no longer work with Hwang, and states that he has concerns over consent issues related to the 2004 landmark paper.

12 November
Schatten publicly and formally cuts all ties with Hwang and his lab.

Read report in Nature.

Science makes corrections to a table the 2005 paper after the authors request a change. The change is said to not affect the paper's conclusions.

21 November
Hwang's associate Sun Il Roh (co-author on 2004 paper) admits that 20 of the original 242 eggs were purchased. Roh also claims that Hwang was unaware of this.

"Korean Stem Cell Crisis Deepens"

22 November
A South Korean television network, MBC, airs a story that details suspicions of inappropriate ova sources, including junior members of Hwang's own lab. The main result of this story is backlash at MBC for criticizing a national 'hero', and the station is forced to apologize and loses much in the way of viewership and sponsors.

Story on the backlash.

24 November
Hwang admits to using ova from paid donors as well as members of his lab. He resigns his official posts, but continues as researcher.

Hwang admits lies.
Resigns leadership.

30 November
The Internation Society for Stem Cell Research (ISSCR) announced that it will launch an 'International Embryonic Stem Cell Research Guidelines Task Force'. The guidelines will be released at the ISSCR annual meeting in 2006.

Read ISSCR statement.

1 December
MBC raises new concerns by challenging the authenticity of Hwang's patient-specific stem cells. The station runs its own DNA tests and believes it has evidence to show that the stem cells do not match their parent tissue.

On the same day, the South Korean IRB clears Hwang's name by finding that the eggs were donated appropriately and without coercion, and that the money given was for direct expenses.

4 December
MBC apologizes for certain reporting tactics used in their November exposé.

Hwang contacts Science to alert of errors in the 2005 paper. Four pictures were used redundantly, but Science concludes that the errors do not affect the paper's conclusions.

5 December
University of Pittsburg officials open an inquiry into the 2005 paper.

11 December
Seoul National University (SNU) opens an investigation of Hwang's research, as requested by Hwang.

Statement by SNU.

Hwang enters the University Hospital for treatment for stress and exhaustion.

13 December
Schatten calls on Hwang to retract the 2005 paper on patient-specific stem cells. Schatten claims to have new information leading to "substantial doubts" about the paper's accuracy. Ian Wilmut and 7 other scientists call on Hwang to allow them to independently validate his results with a paternity-type test.

Schatten demands retraction.

15 December
Hwang's associate Roh admits that the 2005 paper was a fabrication, and claims that Hwang told him that there were no cloned embryonic stem cells.

Scientific American removes Hwang as research leader of 2005.

Read Scientific American announcement.

16 December
Hwang and Schatten request retraction of 2005 paper. Science waits for letters from all co-authors before retraction can be made.

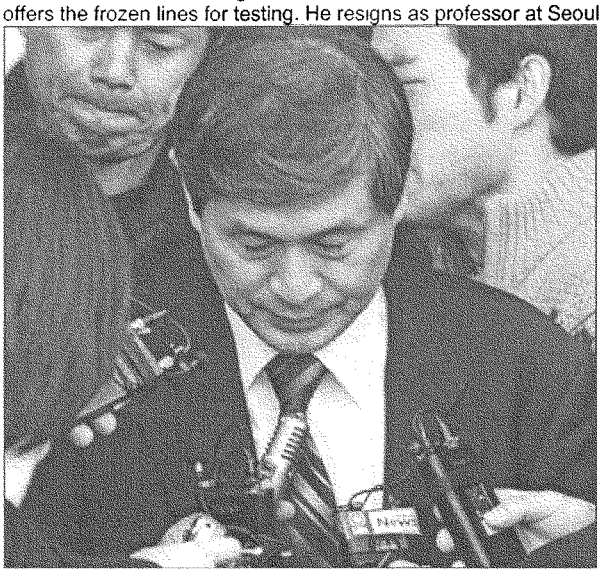
Hwang claims at press conference that the problems were "human errors", but that the patient-specific cells were created.

23 December
Interim report of Seoul National University's investigation indicates that large amounts of the 2005 paper data were fabricated. Only 2 lines led to the 2005 paper, and not 11 as claimed. The investigating panel says that this could only be the result of "deliberate fabrication."

The investigation panel announces that there is no evidence to suggest the existence of any cloned patient-specific stem cells. The panel claims that the 2 remaining lines do not match patient DNA, but instead match DNA of embryos created by IVF – although it was unclear if these last 2 lines were fabricated by Hwang or by his collaborators.

The final report will be released in mid-January and will included the results of investigation of Hwang's earlier achievements such as the first cloned human embryo and the first cloned dog.

SNU interim report. Hwang maintains that the 2 lines were indeed patient-specific, and offers the frozen lines for testing. He resigns as professor at Seoul National University.



Hwang leaves University.

29 December
Science confirms that the 2005 paper will be retracted, and awaits letters from all co-authors.

31 December
Hwang insists that he has proof that he did create cloned patient-specific stem cells, despite the report from the investigatory panel. Hwang claims that he can "replicate the process any time."

Hwang claims that his cells were replaced with other, non-cloned cells by researchers at Mizmedi Hospital in Seoul. "It's certain (stem cells) have been switched...under a detailed plan over quite a long period of time."

Hwang has filed a complaint with South Korean prosecutors, but they will wait until the University investigation is complete before conducting their own inquiry.

Hwang claims switched cells.

2006

4 January
Korean news station MBC airs new program with specific accusations of Hwang coercing junior researchers.

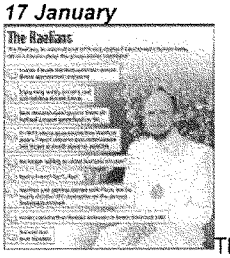
Story.

10 January
Seoul National University releases final report in Hwang investigation, indicating that both the 2004 and 2005 papers regarding human embryonic stem cells were fabricated. The August, 2005 paper results regarding the first cloned dog stands was verified by DNA fingerprinting.

Summary of SNU final report.
Statement by President of SNU.

12 January
Science formally retracts both of Hwang's stem cell papers (2004 and 2005) after being notified by all authors.

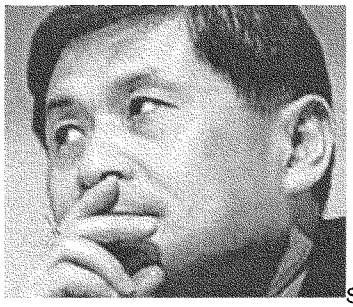
Read retraction letter.

17 January

The Raelians

The Raelians, a UFO-related cult, offer Hwang a job at their Clonaid science/cloning research laboratories.

News report.
Clonaid support for Hwang.
The article, "Timeline of a Controversy" was a valuable resource source for many parts of this site. It contains further reading as well.

9 February

 Seoul National University fired disgraced scientist Hwang Woo-suk and six other professors on his team for their involvement in fabricated stem cell research, a news report said on Thursday, February 9.

More on Stem Cells
The Future of human embryonic stem cell research will certainly be altered by this series of events in South Korea. Many are now speculating on exactly how the changes will play out.

Where now for stem-cell cloners?

To learn more about stem cells...

Government Reports
Report by the National Institutes of Health.

Reports by the President's Council on Bioethics:
Cloning.
Stem Cells.
Alternative sources to stem cells.

Report by the National Bioethics Advisory Commission (NBAC):
Volume 1: Report and Recommendations of the NBAC (Sept 1999).
Volume 2: Commissioned Papers (Jan 2000).
Volume 3: Religious Perspectives (June 2000).

Indiana University
Report by the Indiana University School of Medicine Adult Stem Cell Task Force.
Human Stem Cell Study Group.

US Legislative Measures on Stem Cells
The US congress has considered multiple bills regarding measures to ban cloning, as well as measures to increase embryonic stem cells eligible for cloning. None of these have become law, but one is still under consideration, HR 810.

In addition, many states have passed legislation in the past 4 years both to ban and allow various types of stem cell research. Eight states have even allocated funding to support stem cell research, some including embryonic stem cells.

International Stem Cell Developments
Twenty-one countries now have legislation that is permissive toward embryonic stem cell research. These include:

Australia	The Netherlands
Belgium	Singapore
Brazil	South Africa
China	South Korea
Finland	Spain

France	Sweden
Canada	Switzerland
India	Taiwan
Israel	Thailand
Japan	The United Kingdom
New Zealand	

To see a map highlighting these countries, as well as links to read the various legislative measures, see mbbnet. Several treaty proposals regarding a ban on human cloning have been introduced to the United Nations, the most recent in 2004. None have yet been accepted.

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Mr. SOUDER. I will now yield to the ranking member, Mr. Elijah Cummings, for his opening statement.

Mr. CUMMINGS. Thank you very much, Mr. Chairman.

Just yesterday a disgraced researcher, Dr. Hwang Woo Suk, admitted to prosecutors in South Korea that he had directed a subordinate at the World Stem Cell Hub to fabricate research results. This was the first admission by Dr. Hwang of his personal involvement in fabricating claims made by his research team in two landmark papers on embryonic stem cell research published in the journal Science.

An investigative team at Seoul National University already had determined that Hwang's claims that he had developed 11 patient-specific stem cell lines were in fact false. Dr. Hwang also acknowledged that donated eggs used in the research were coerced from junior members of his research team, and that some donors had been paid large sums of money.

Throughout the investigation, however, Dr. Hwang acknowledged no personal involvement in the scientific fraud. The fraud, exploitation, and coercion for which Dr. Hwang has now admitted personal responsibility have earned him a resounding international rebuke, including from Seoul National University where he was employed.

We can only hope that Dr. Hwang's humiliation will serve to deter other scientists who might contemplate seeking glory through reporting fraudulent research, exploiting employees, and coercing women to donate their eggs without informed consent.

In a sense, this case offers a measure of vindication to the broader scientific community, demonstrating that it is difficult at best to fool one's peers for very long. Ultimately, the very nature of scientific research tends to ensure that the truth about claims of major scientific advances will surface.

In this very high profile case, questions have been raised as to whether the claims of Dr. Hwang's teams should have been verified in advance by the publishing journal. In any case, it was mere months before questions about Dr. Hwang's methods and results began to be called into question publicly. In fact, it is almost startling how quickly many of Dr. Hwang's claims have been thoroughly debunked, including yesterday through his own admission of scientific fraud.

But the case of Dr. Hwang is no cause for celebration, even if opponents of embryonic stem cell research seem to have difficulty containing their glee. Opponents of the research have been eager to portray the Korean scandal as proof that not only is this field a research uniquely prone to ethical pitfalls, but that the research itself is inherently bogus, offering nothing more than false hope to patients.

Mr. Chairman, I join the mainstream of the United States and the international scientific community in drawing a different lesson and conclusion. This research, which will go forward with or without the U.S. funding and oversight, needs the oversight that the broader U.S. oversight would bring. Our own National Institutes of Health is, without question, the entity best equipped to ensure that embryonic stem cell research proceedings with scientific integrity and in a way that ensures that women who donate their eggs are

protected from coercion, exploitation, and undisclosed risk of adverse health effects.

In the absence of strong Federal leadership, several States, including California and Maryland, have taken steps toward adopting guidelines for conducting embryonic stem cell research. The National Academy of Sciences has adopted guidelines as well.

But accountability for U.S. research will come with substantial support for this research, and that support will also help to ensure that important lines of research that offer relatively less profit potential are pursued.

In closing, Mr. Chairman, it is important that we recognize that fraud and ethical misconduct are hardly unique to science, and that scientific fraud is not unique to embryonic stem cell research. Our goal therefore should not be to use this controversy as a justification to impede the search for important new knowledge that could yield therapies and cures for many major diseases. Rather, our objective should be to ensure that as research in this important field inevitably proceeds in and beyond the United States, it does so with the benefit of strict Federal guidelines and a rigorous oversight.

With that, Mr. Chairman, I thank our witnesses for appearing today, and I yield back.

[The prepared statement of Hon. Elijah E. Cummings follows:]

Representative Elijah E. Cummings, D-MD7
Ranking Minority Member
Subcommittee on Criminal Justice, Drug Policy and Human Resources
Committee on Government Reform
U.S. House of Representatives
109th Congress

Hearing on "Human Cloning and Embryonic Stem Cell Research After Seoul: Examining Exploitation, Fraud and Ethical Problems in the Research"

March 7, 2006

Mr. Chairman,

Just yesterday, disgraced researcher Dr. Hwang Woo Suk ("WONG WOO SOOK") admitted to prosecutors in South Korea that that he had directed a subordinate at the World Stem Cell Hub to fabricate research results.

This was the first admission by Dr. Hwang of his personal involvement in fabricating claims made by his research team in two landmark papers on embryonic stem cell research published in the journal *Science*.

An investigative team at Seoul National University already had determined that Hwang's claims that he had developed eleven patient-specific stem cell lines were, in fact, false. Dr. Hwang also acknowledged that donated eggs used in the research were coerced from junior members of his research team and that some donors had been paid large sums of money. Throughout the investigation, however, Hwang acknowledged no personal involvement in scientific fraud. The fraud, exploitation and coercion for which Hwang has now admitted personal responsibility have earned him resounding international rebuke, including from Seoul National University where he was employed. We can only hope that Dr. Hwang's humiliation will serve to deter other scientists who might contemplate seeking glory through reporting fraudulent research, exploiting employees, and coercing women to donate their eggs without informed consent.

In a sense, this case offers a measure of vindication to the broader scientific community, demonstrating that it is difficult, at best, to fool one's peers for very long. Ultimately, the very nature of scientific research tends to ensure that the truth about claims of major scientific advances will surface.

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Opponents of the research have been eager to portray the Korean scandal as proof that not only is this field of research uniquely prone to ethical pitfalls, but that the research itself is inherently bogus, offering nothing more than false hope to patients.

Mr. Chairman, I join the mainstream of the U.S. and international scientific community in drawing a different lesson. This research, which *will* go forward *with or without* U.S. funding and oversight, needs the oversight that broader U.S. funding would bring.

Our own National Institutes of Health is, without question, the entity best-equipped to ensure that embryonic stem cell research proceeds with scientific integrity and in a way that ensures that women who donate eggs are protected from coercion, exploitation, and undisclosed risk of adverse health effects.

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Thank you, Mr. Chairman. I yield back my time.

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Mr. SOUDER. I would like to yield to the vice chairman of the committee, Mr. McHenry.

Mr. MCHENRY. Thank you, Mr. Chairman. Thank you so much for holding this hearing today.

Recent events in South Korea have brought to light and global attention has been brought to the issue of human cloning and embryonic stem cell research. A number of concerns have been raised surrounding this subject here and abroad, including the ethical dilemma of destroying life; fraudulent scientific procedures, as has been mentioned by Ranking Member Cummings, as well as exploitation of women. All these are very serious subject matters that we must address here today in this hearing.

As a part of this discussion, it is important to make the distinction between human embryonic stem cell research and adult stem cell research. Adult stem cells and the research derived from adult stem cells do not destroy human life, and do not take the essence of life from the host being; whereas in embryonic stem cell research, that is the case. Life is taken from that fertilized egg, and that life is destroyed.

Embryonic stem cell research is the purposeful creation of human embryos destined to be destroyed for scientific research, in this case, in the name of stem cell research. Adult stem cells have provided therapeutic benefits and cures to 67 diseases and conditions such as diabetes, damaged heart tissue, strokes, cancers, Parkinson's, and spinal cord injuries, among others. We need to focus in the successes of adult stem cell research, an ethical approach that provides cures and therapies, instead of focusing on this all-too-political, it seems, issue of embryonic stem cell research.

Beyond the fact that there are currently no clinical trials or therapeutic applications using embryonic stem cells, there are a number of complications due to this approach, such as immune rejections and the inability to obtain pure cultures. The fact that this process is so inefficient means an outrageous number of eggs will be required for this approach.

And I would like to hear from our panel today as to their estimates on how many eggs would be required to actually move forward with major cures and major therapies. Some have said that even for a disease that touches 17 million people or 20 million people, you would have to have roughly 850 million eggs harvested, which means if you had 10 women willing to donate their eggs, you would have to have about 85 million women in this country donate their eggs.

It is a staggering sum. And this also goes back to the other issue that is of major substance, and that is the exploitation of women, which has been brought to light with the controversy and the fraud perpetrated out of South Korea.

I would like to welcome our witnesses today. I thank you for taking the time to be here. And this issue today is not simply about South Korean research fraud. It is about the larger issue of stem cell research and what is an ethical, realistic, and moral approach that moves science forward while keeping to ethics in medicine and science.

Thank you all again for being here today. And again, Mr. Chairman, thank you so much for your hosting this meeting today.

[The prepared statement of Hon. Patrick T. McHenry follows:]

GR Subcommittee: "Human Cloning & Embryonic Stem Cell Research after Seoul: Examining exploitation, fraud and ethical problems in research"
March 7, 2006

Statement of Congressman Patrick McHenry

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Mr. SOUDER. Thank you. I will now yield to the distinguished ranking member of the full Committee.

Would you yield to Ms. Norton?

Ms. NORTON. I yield to the ranking member.

Mr. WAXMAN. Well, I thank you both very much for this chance to make an opening statement.

We are going to hear testimony today about the ethical issues around embryonic stem cell research and therapeutic cloning. In particular, we will focus on the scandal in South Korea regarding fraudulent research and abuses of research subjects.

Many opponents of stem cell research would like to use the South Korean experience as a basis for banning embryonic stem cell research. The story of Dr. Hwang's fraudulent research in South Korea is shocking because we rely on scientists to discover the truth, not subvert it. We need to condemn the fraud, figure out what happened, and learn how we can keep it from happening again. And we need to make sure that this research is well-regulated and thoroughly scrutinized.

But banning future stem cell research would be a gross overreaction. Unfortunately, though the vast majority of researchers are honest, fraud sometimes occurs in scientific and medical research. In fact, among Members of Congress, while most are honest, there are some who are not.

In 1983, a cardiology researcher at Harvard was found to have fabricated much of his data. In 1996, it was revealed that reports of a re-implanted ectopic pregnancy by British physicians were fraudulent. And in 2002, it was discovered that a rising star physicist working on carbon-based semiconductors had fabricated most of the data.

The answer to these instances of fraudulent research was not to ban or deny funding for research on heart disease, ectopic pregnancy, and semiconductors. The right answer is to create and uphold high standards of oversight. When doubts emerge, disclosure, investigation, and corrections must happen swiftly and openly. That is the right response whether the fraud involves heart disease or stem cell research.

We are also going to hear questions raised today about the potential benefits to be gained from various types of stem cell research. Those who oppose embryonic stem cell research often claim that because we do not yet know what therapies it will yield, we should not allow it to proceed.

That is a flawed line of reasoning. If we followed this to its logical conclusion, it would mean that the Federal Government should only fund research into cures and therapies that we already know about. The argument also understates that we do know about embryonic stem cells.

Decades of research have established the potential that these cells hold for addressing serious illnesses such as Alzheimer's, Parkinson's, and even cancer. I say potential, not promise, because there are no promises in any form of research. But what scientists have already learned about stem cells indicates great potential, which is an argument for moving ahead.

Opponents of embryonic stem cell research claim that there is still much to learn from adult stem cells and therefore we should

focus our efforts there. It is true that adult stem cells may hold potential, and I fully support researching the possibilities of adult stem cells. But evidence tells us that the potential of adult stem cells may be limited because they are already more specialized than other types of stem cells. We should indeed move forward with research on adult stem cell lines, but this is no argument against pursuing study of other types of stem cells with even more potential.

The third issue we will discuss today is the safety of women who donate oocytes or eggs for stem cell research. Egg donation relates to a specific type of research called somatic cell nucleic transfer [SCNT]. This technique involves removing the nucleus of an unfertilized egg and replacing it with the nucleus of an adult cell.

SCNT has two benefits compared to stem cell research on embryos from a fertility clinic. First, the possible outcome of this research is the production of tissues that are genetic match to the patient, reducing the risk of rejection such as that we have often seen with organ recipients.

Second, the technique holds great potential for studying genetic and other diseases because scientists could potentially develop cells using nuclei from people who have the disease. This would not generally be possible using embryos donated from fertility clinics because researchers cannot select the genes for such cells.

Witnesses today will discuss their concerns about the safety of the women who donate eggs for this research. Some of these concerns are legitimate. The drugs and techniques used are identical to those used by women undergoing fertility treatments, but they are not without risk. And I believe that we need to carefully examine research and monitor safety.

I also agree that we need to think carefully about how egg donors for research should be compensated. We must respect the contribution that these women make, and we must ensure that they participate voluntarily. As with any new field of research, the safety and ethics of human participants are paramount.

What we must not do, however, is become paralyzed into inaction. Stem cell research, including research using embryonic cells, may help cure diseases that cause untold suffering to millions of Americans and hundreds of millions more around the world. With strict scientific and ethical oversight, embryonic stem cell research, including SCNT, should be supported with Federal funds.

Thank you, Mr. Chairman.

[the prepared statement of Hon. Henry A. Waxman follows:]

Opening Statement of
Rep. Henry A. Waxman
Before the Subcommittee on Criminal Justice, Drug Policy, and Human Resources
Hearing on Human Cloning and Embryonic Stem Cell Research after Seoul: Examining exploitation, Fraud and Ethical Problems in the Research

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Opponents of embryonic stem cell research claim that there is still much to learn from adult stem cells and therefore we should focus our efforts there. It is true that adult stem cells may hold potential, and I fully support researching the possibilities of adult stem cells. But evidence tells us that the potential of adult stem cells may be limited because they are already more specialized than other types of stem cells. We should indeed move forward with research on adult stem lines, but this is no argument against pursuing study of other types of stem cells with even more potential.

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Mr. SOUDER. Congresswoman Schmidt.

Ms. SCHMIDT. Thank you. Thank you, Chairman Souder, for holding this important hearing on the abuse in human cloning and embryonic stem cell research.

As a strong supporter of reasonable science, true women's health, and the culture of life, this topic is very dear to my heart. I commend you, Chairman Souder, for bringing these panels of experts together to shed light on the dangerous practices that some researchers are willing to use to advance their agenda. They, with the help of the media, have unfairly raised the hopes of many Americans, who have been led to falsely believe that embryonic stem cell cures are possible in the near future.

While scientists were touting Hwang's research as groundbreaking and necessary for the medical miracles around the corner, Hwang was actually falsifying data and possibly exploiting women for their eggs. How many of these promises were ill-founded?

While it now appears that no scientist has effectively created stem cell lines using cloned embryos, adult stem cell treatments march ahead showing great promise for numerous diseases. The facts have shown that cord blood stem cells and adult stem cells are making great advances in curing diseases today, while clinical trials in embryonic stem cells are still years away.

In the light of this fraud and abuse, and the fact that embryonic stem cell research is just not producing the results that were promised, I am proud to have co-sponsored H.R. 596, the Stem Cell Therapeutic and Research Act of 2005, or the cord blood bill, and H.R. 1359, the Cloning Prohibition Act.

Again, Mr. Chairman, I applaud your leadership on these issues, and I look forward to learning more about them to working with you for a rightful resolution.

Mr. SOUDER. Thank you.

Ms. Norton.

Ms. NORTON. Thank you very much, Mr. Chairman. I want to thank you for focusing the subcommittee on an unusually thorough-going example of the worst kind of scientific fraud because what we have in the Hwang—I hesitate to call it South Korean example because I would hate to think that is characteristic of the science of our friends in South Korea, but it is certainly an example the likes of which I don't think anyone has ever seen before, a massive scientific fraud at every level, fraud that was so good, as it were, if you would forgive the use of the phrase, that even other scientific researchers around the world were fooled by it.

It is a kind of case study in what can happen when nobody is watching very closely, and when scientific research at the cutting edge goes totally and absolutely unregulated. It was very troublesome to see and to count the violations and to see that they ranged from what scientists were doing to violations of individual human rights acknowledged to be important and necessary to the world.

So I welcome laying this matter out in detail, although I must say I was fascinated with what my good friends on the other side focused on. I mean, you would have thought this was not the Congress of the United States that could do something about the issue that we are describing today.

I mean, we are not a television program. Any reasonably literate person or anybody who looks at television has been scandalized by what happened in South Korea. I am pleased we are focusing on this matter not because of any evidence I know of that anything close to it is happening here, but because I have no reason to believe that what happened in South Korea could not or would not happen here, at least to some degree. And I believe it is urgent to move this Congress and this subcommittee from what we cannot do anything about to what we can and must do something about.

This is a national issue, my friends. On a national scientific issue of this kind, the burden is on the Federal Government, first and foremost, to offer leadership and guidance. So if you are really concerned about South Korea, this is the time to focus on remedy, if ever there was.

This much is clear: We cannot legislate against science any more than we can legislate against the weather. But we can ourselves enact reasonable measures in order to make sure that Congress does not—that science does not march ahead in violation of every ethical measure that both science universally has accepted and that are a matter of documented international human rights.

Instead, very frankly, I must say that time after time, I see the Congress trying to stop science. I am embarrassed by the congressional approach to the march of science. It is as if we were still in the 19th century. Science is marching ahead, and it requires deeply analytical, very deep thinking about how to harness science when we know good and well it is marching.

And how do we know it is marching ahead? Well, next door you have heard my good colleague from Maryland talk about what is happening in that State. A Republican Governor, Governor Robert Ehrlich, has proposed spending $20 million on stem cell research in the coming year. That is happening all over the United States. The States are joining the advanced countries of the world, marching ahead to make use of embryonic cell research.

I can only hope that in the countries of our allies, the national legislatures have been more enlightened than to sit by and describe the problem, while parts of their countries march ahead and do whatever they want to do. We could affect how Maryland, how California, and how every other State in the United States goes about this work because we are the Federal Government.

I have every confidence that Mr. Cummings' colleagues in Maryland are going to take up the slack and do the appropriate guidance. I don't think there is a State in the Union that would allow this work to go forward without redoubling their efforts in every way to make sure that what happened in South Korea cannot happen here.

So I don't need to add to the disagreement on the ban on embryonic research. You are not going to change peoples' minds on that. You haven't done it in the States, some of which are governed by Republicans.

But I want to ask this question: Unbelievably, Mr. Chairman, no bill has passed this Congress outlawing, banning, even human cloning. Can we agree on that? Can we get everybody to raise their hands on that? Isn't there any part of this issue where we would be prepared to meet our obligations, instead of going over and over

again the polarizing issue of shall we ban what we can't ban and what our States are telling us we can't ban because we are going ahead and doing it.

So I believe that this hearing is important because perhaps it could lead to more than beating our chests against the obvious. There is no disagreement in the United States of America or among anybody in this Congress that what happened in South Korea should not happen here.

Hearings are for remedies. I will be interested in whether any of the witnesses today are prepared to help this Congress move forward on urgently needed remedies. And I Tim Howard, Mr. Chairman.

Mr. SOUDER. Ms. Foxx.

Ms. FOXX. Thank you, Mr. Chairman. I want to tell you how pleased I am that you are having the hearing today.

I might get the reputation around here for being the person who always brings up the issue of language and how important it is to us. But I hear a lot of very inflammatory terms being used about banning future stem cell research, and legislating against science, and that we are not doing the kinds of things that we should be doing.

We have not at all banned—talked about banning stem cell research in the Congress. We have encouraged stem cell research, adult stem cell research. I am really curious about the word "therapeutic cloning" being used. I don't know how the destruction of human life could ever be called therapeutic.

I think that what you are doing here today is calling attention to what I think is a microcosm of the fraud that has been perpetrated in relation to embryonic stem cell research itself. I think focusing on what has happened in Korea and the fraud that happened there can, I think, enlighten people about this issue of embryonic stem cell research and the negative things about that. So I think we can change peoples' minds. I think we can enlighten people. And I think we can do it in a way that is respectful of human life and not destructive of human life.

So I applaud you for holding the hearing, and look forward to our shedding some light on this issue that is the truth, rather than letting something like this continue to be a fraud. We have allowed—unfortunately, people in very sad circumstances think that by the use of embryonic stem cell research, we are going to have a cure right around the corner. And we know that it has brought no cures, whereas adult stem cell research has.

So thank you for doing this, and thank you for calling attention to the issue.

Mr. SOUDER. Thank you. I ask unanimous consent that all Members have 5 legislative days to submit written statements and questions for the hearing record, and that any answers to written questions provided by the witnesses also be included in the record.

Without objection, it is so ordered.

I also ask unanimous consent that all exhibits, documents, and other materials referred to by the Members and the witnesses may be included in the hearing record, and that all Members be permitted to revise and extend their remarks.

Without objection, it is so ordered.

Before swearing in our first panel, I feel compelled to tell all of our witnesses to remember: This is an oversight committee, not a legislative committee. We only have legislative jurisdiction over narcotics. We do oversight and legislation on narcotics.

On the Department of Health and Human Services, we do not write the bills. We are here to talk about the past. What the question is in front of us is what happened there and whether in fact they are inherent to the process, or whether in fact controls can be made to regulate this.

It is a legitimate debate, but it is not about where we are headed legislatively. First, we are here to analyze the past, analyze what has happened, analyze what the different agencies are doing and what the potentials are, that then Energy & Commerce and the Health Committee and others would look at legislatively. I think there was some confusion on the panel as to the role of our hearing and what our committee does. And I think it is important to clarify that.

Now, as you know, it is the practice of this committee to swear in their witnesses. Our first panel is Dr. James Battey, Chair of the NIH Stem Cell Task Force and Director of the National Institute for Deafness and Other Communication Disorders; Mr. Bernard Schwetz, Director of the Office for Human Research Protections; and Chris Pascal, Director of the Office of Research Integrity.

Would you each stand and raise your right hand?

[Witnesses sworn.]

Mr. SOUDER. Let the record show that each of the witnesses responded in the affirmative.

We appreciate that you have joined us, and we will start with Dr. Battey.

STATEMENTS OF JAMES F. BATTEY, JR., M.D., Ph.D., CHAIR, NIH STEM CELL TASK FORCE, DIRECTOR, NATIONAL INSTITUTE ON DEAFNESS AND OTHER COMMUNICATION DISORDERS, NATIONAL INSTITUTES OF HEALTH, U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES; BERNARD SCHWETZ, D.V.M, Ph.D., DIRECTOR, OFFICE FOR HUMAN RESEARCH PROTECTIONS, U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES; AND CHRIS B. PASCAL, DIRECTOR, OFFICE OF RESEARCH INTEGRITY, U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

STATEMENT OF JAMES F. BATTEY, JR.

Dr. BATTEY. Good afternoon, Chairman Souder and distinguished members of the subcommittee. I am pleased to be joined here by my two other colleagues from the Department of Health and Human Services. And I appear before you today in my joint roles as a scientist and Chair of the NIH Stem Cell Task Force to discuss the recent events concerning stem cell research fraud that is reported to have occurred in South Korea.

As you know, a review and analysis by the Seoul National University Investigation Committee concluded that human embryonic stem cell lines were not derived from embryos created by somatic cell nuclear transfer, as claimed, that fabricated data was used in

publications, and that there had been ethical violations in the donation of human oocytes used in these experiments.

In 2004, Dr. Woo Suk Hwang and collaborators published an article in the journal Science claiming that they had derived a stable human embryonic stem cell line, which they referred to as NIGHT–1, from an embryo generated by somatic cell nuclear transfer. That is a process, as Mr. Waxman described, where the nucleus is removed from a human oocyte and replaced by the nucleus from a somatic cell.

Subsequent investigation by the Seoul National University investigation committee revealed that this claim was not supported by rigorous DNA testing. In addition, the investigation revealed that the photographs allegedly taken of the NT–1 cell line were in fact photographs of an existing stem cell line not derived from an embryo created by SCNT, but instead derived from an embryo produced by in vitro fertilization.

In 2005, Dr. Hwang and collaborators published a second article in Science, where they claimed to have made the process or deriving human embryonic stem cell lines from embryos created by SCNT much more effort than was reported in the 2004 publication, where several hundred oocytes were reported to be needed to create a single stem cell line, which we now know was not created in the way they described.

In this paper, the authors claimed to have developed an improved protocol for deriving patient-specific embryonic stem cells from embryos created through SCNT. They reported the creation of 11 human embryonic stem cell lines from 185 embryos created by SCNT, many of which involved nuclei from cells derived from individuals with debilitating diseases such as spinal cord injury, juvenile diabetes, or congenital inherited deficiencies of the immune system.

Subsequent review by Seoul National University led the investigation committee to conclude that the data presented in this 2005 paper was based on only two human embryonic stem cell lines, neither of which was derived from an embryo created by SCNT. They concluded that no disease-specific human embryonic stem cell lines derived from SCNT embryos are represented in this publication, nor is there any factual basis for believing the Koreans ever successfully created any such lines.

While the events in South Korea are deeply troubling to all of us here and everyone in the scientific community, I think it is important to point out that scientific fraud of this type is not common at all, and is certainly not restricted to the area of stem cell research. As one of your colleagues pointed out earlier, John Darcy fabricated data in hundreds of publications in the area of cardiology over a decade ago. That doesn't mean that it was inappropriate to continue doing work in the area of cardiology.

The scientific community must remain as vigilant as we can be to ensure that the risk of scientific fraud is minimized. It is also important to note that such fraud is sometimes revealed, often revealed, when other reputable scientists cannot reproduce results that are subsequently revealed to be fabricated, and the great majority of scientists around the world are deeply committed to rigorous standards of proof and verification. The Rosetta Stone of

science is reproducibility in another independent laboratory. And this is where scientific fraud is typically uncovered.

The scientific enterprise absolutely depends on such standards. And while the stem cell research fraud in South Korea is completely unacceptable, it does not reflect on the potential of human embryonic stem cell research one way or the other. The vast majority of my scientific colleagues are honest and hardworking in pursuing their research, which they deeply hope will ultimately benefit the human condition.

I thank you very much for your time, and I will do the very best I can to answer any questions that the subcommittee may have for me.

[The prepared statement of Dr. Battey follows:]

Testimony
Before the Subcommittee on Criminal Justice, Drug Policy and Human Resources
Committee on Government Reform
United States House of Representatives

Recent Events Concerning Stem Cell Research Fraud in South Korea

Statement of
James F. Battey, M.D., Ph.D.
Director, National Institute on Deafness and Other Communication Disorders, and
Chair, NIH Stem Cell Task Force
National Institutes of Health
U.S. Department of Health and Human Services

For Release on Delivery
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Tuesday, March 7, 2006

Good afternoon, Chairman Souder and Distinguished Members of the Subcommittee. I appear before you today, in my roles as scientist and Chair of the National Institutes of Health (NIH) Stem Cell Task Force, to discuss the recent events concerning stem cell research fraud that is reported to have occurred in South Korea. As you know, a review and analysis by the Seoul National University Investigation Committee concluded that human embryonic stem cell lines were not derived from embryos created by somatic cell nuclear transfer (SCNT), as claimed, that fabricated data was used, and that there had been ethical violations in the donation of human oocytes used in the experiments.

In 2004, Dr. Woo Suk Hwang and collaborators published an article in the journal Science claiming that they had derived a stable human embryonic stem cell line (NT-1) from an embryo generated by somatic cell nuclear transfer (SCNT). Subsequent investigation by the Seoul National University Investigation Committee revealed that this claim was not supported by DNA testing. In addition, the investigation revealed that the photographs allegedly taken of the NT-1 cell line were in fact photographs of an existing stem cell line derived not from an SCNT embryo, but instead derived from an embryo produced by in vitro fertilization.

In 2005, Dr. Hwang and collaborators published a second article in Science, where they claimed to have made the process of deriving human embryonic stem cell lines from embryos created by SCNT much more efficient than was reported in the 2004 publication. In this paper, the authors claimed to have developed an improved protocol for deriving patient-specific embryonic stem cells from embryos created through SCNT. They reported the creation of eleven human embryonic stem cell lines from 185 embryos created by SCNT, many of which involved nuclei from cells derived from individuals with spinal cord injury, juvenile diabetes, or congenital hypogammaglobulinemia, an inherited

immunodeficiency disorder. Subsequent review by Seoul National University led the Investigation Committee to conclude that the data presented in this 2005 paper was based on only two human embryonic stem cell lines, neither of which was derived from an embryo created by SCNT. They concluded that no disease-specific human embryonic stem cell lines derived from SCNT embryos are represented in this publication, nor is there any basis for believing the Koreans ever successfully created any such lines.

While the events in South Korea are extremely troubling, scientific fraud is not common, though it is also not restricted to this one area. There have been reports in recent years of fraudulent research in other areas of science as well. The scientific community must remain vigilant to ensure that the risk of scientific fraud is minimized. It is also important to note that such fraud is sometimes revealed when other reputable scientists cannot reproduce results that are subsequently revealed to be fabricated, and that the great majority of scientists around the world are deeply committed to rigorous standards of proof and verification. The scientific enterprise absolutely depends upon such standards. And while the stem cell research fraud in South Korea is unacceptable, it does not reflect on the potential of human embryonic stem cell research one way or the other. The vast majority of scientists are honest and hardworking in pursuing their research to benefit the human condition.

I thank you for your time. I will answer any questions that you may have.

Mr. SOUDER. Thank you.
Dr. Schwetz.

STATEMENT OF BERNARD SCHWETZ

Dr. SCHWETZ. Mr. Chairman and distinguished members of the subcommittee, I am Bernard Schwetz, the Director of the Office for Human Research Protection. Thank you for inviting me here today to discuss the Department of Health and Human Services [HHS], Protection of Human Subjects regulations, particularly as they relate to human cloning and embryonic stem cell research.

These HHS regulations are designed to protect the rights and welfare of all who participate in research studies that are conducted or supported by HHS. They are based in large part on the ethical principles for human subjects research identified in the Belmont Report that was written by the congressionally mandated National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research in 1978.

The protection of human subjects in research studies is a priority for HHS, and it is the mission of the Office for Human Research Protections [OHRP], to support, strengthen, and provide leadership to the Nation's system for protecting volunteers in research that is conducted or supported by HHS.

By signing an assurance of compliance with OHRP, an institution pledges to conduct its HHS-funded or supported research in accordance with these regulations. In addition to assurances of compliance, the HHS regulations also stipulate a number of other requirements for which the institution and its institutional review board [IRB], are responsible.

Primary among these is the need to determine if the risks to subjects are reasonable in relation to anticipated benefits, if any, to the subjects, and the importance of the knowledge that may reasonably be expected to result. Some research studies offer individual studies the prospect of direct benefit, and others do not.

When research studies offer no prospect of direct benefit to research subjects, IRBs must consider whether the potential benefits to society justify the risks to the individual subjects. For these studies, including some research involving human embryonic stem cells, the expected benefits would occur often in the future, and would only be of help to others.

Informed consent: At the heart of the human subject protection system is the requirement relating to informed consent. The investigator must seek a potential subject's informed consent according to the requirements laid out in the regulations. The investigator's method for obtaining this consent must be approved by the IRB before it can be used.

In seeking informed consent, HHS regulations require that investigators do so only under circumstances that provide the prospective subject with sufficient opportunity to consider whether or not to participate, and that minimizes the possibility of coercion or undue influence.

As part of the consent process, the prospective research subject must be given sufficient information about a research study to make an informed decision about whether or not to participate in the research. If the study does not offer the subjects the possibility

of direct benefit, this must be clearly stated in the informed consent process.

For example, if a research study that involves identifiable human cell lines is not intended to offer donors with the prospect of direct benefit, then prospective donor subjects would need to be informed of this unless the requirement for the informed consent has been waived by the IRB.

OHRP guidance on research involving stem cells: OHRP has provided guidance to help insure that investigators and IRBs understood how the HHS regulations apply to research involving human embryonic stem cells, germ cells, and the stem cell-derived test articles. A copy of this guidance is included in my written statement for your consideration.

In essence, this guidance indicates when such research does and does not generally meet the HHS definition of human subjects research. Under the HHS regulations, "human subject" means a living individual about whom an investigator conducting research obtains either data through intervention or interaction with an individual, or identifiable private information.

OHRP considers that neither of these definitions is met with research involving embryonic stem cells as long as the investigator has not obtained data about an individual through a research intervention or interaction, and cannot readily ascertain the identity of the individual from whom the human material was obtained. In such cases, the study would not be considered human subject research and the institution's IRB would not be required to review this type of research.

However, some research may use established human cell lines where the donor or donors may be readily identified by investigators, or may involve the obtaining of data through research interventions or interactions with individuals. In these cases, the research is considered to have involved human subjects, it would be governed by the HHS regulations, and IRB review and approval would be required for the research to proceed.

Finally, I would like to emphasize that the stem cell research conducted at Seoul National University by Dr. Hwang which provided the impetus for this hearing was neither conducted nor supported by HHS. Quite apart from the issues of fraud and abuse, such research could not have been conducted or supported by HHS under Federal law in the United States.

Dr. Hwang's research involved attempts to create new human embryonic stem cell lines solely for research purposes through the process of somatic cell nuclear transfer, sometimes called human cloning. HHS is specifically prohibited by law from supporting research in which a human embryo or embryos are destroyed, as well as from supporting the creation of a human embryo or embryos for research purposes. And that law defines "human embryo" to specifically include embryos created by cloning.

As it was not conducted or supported by HHS, and does not appear to have been conducted at an institution that voluntarily agreed to comply with the HHS regulations for all human subjects research conducted at the institution, Dr. Hwang's research was therefore not subject to any of the regulatory protections that I have discussed throughout this statement.

Thank you for your attention, and I would also be happy to answer any of the questions you may have.

[The prepared statement of Dr. Schwetz follows:]

Testimony
Before the Subcommittee on Criminal Justice, Drug Policy and Human Resources
Committee on Government Reform
United States House of Representatives

The Role of the HHS Office for Human Research Protections in Protecting Human Research Subjects

Statement of
Bernard A. Schwetz, D.V.M., Ph.D.
Director
Office for Human Research Protections
U.S. Department of Health and Human Services

For Release on Delivery
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Tuesday, March 7, 2006

Mr. Chairman and Distinguished Members of the Subcommittee, thank you for inviting me here today to discuss the Department of Health and Human Services' (HHS') Protection of Human Subjects Regulations, particularly as they relate to human cloning and embryonic stem cell research.

These HHS regulations are designed to protect the rights and welfare of all who participate in research studies that are conducted or supported by HHS. They are based in large part on three fundamental ethical principles for human subjects research – respect for persons, beneficence, and justice. These principles were identified in the *Belmont Report,* written by the congressionally created National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research in 1978.

In 1991, the core HHS regulations for human subjects protections – codified at subpart A of 45 CFR part 46 – were extended to14 other Federal departments and agencies, when those entities joined HHS in adopting a uniform set of regulations that are identical to HHS' subpart A. This standardization of protections is known as the Federal Policy for the Protection of Human Subjects, and generally referred to as the "Common Rule."

The protection of human subjects in research studies is a priority for HHS, and it is the mission of the Office for Human Research Protections (OHRP) to support, strengthen and provide leadership to the Nation's system for protecting volunteers in research that is conducted or supported by HHS.

HHS Regulations

The HHS regulations encompass all research involving human subjects that is conducted or supported by HHS. By signing an assurance of compliance with OHRP, an institution pledges to conduct its HHS-funded or -supported research in accordance with these regulations. An institution also may voluntarily extend these HHS protections to all its human subjects research, regardless of funding source; and many institutions choose to do so.

In addition to assurances of compliance, the HHS regulations also stipulate a number of other requirements, for which the institution and its institutional review board (IRB) are responsible. These include but are not limited to:

- IRB membership;
- Criteria for the IRB to review and approve or disapprove research;
- IRB procedures;

- Suspension or termination of IRB approval of research;
- Documentation of informed consent; and
- Use of Federal funds.

Two requirements are fundamental to compliance with the regulations:

- First, the research institution must designate one or more IRBs with responsibility for reviewing human subjects research. Among an IRB's many duties is its duty to ensure that the risks to subjects are reasonable in relation to any anticipated benefits, and in relation to the importance of the knowledge that may reasonably be expected to result. (45 CFR 46.111(a)(2))

- Second, the IRB must ensure that the research meets the provisions for informed consent of the subject. These provisions are designed to allow potential subjects to be made fully aware of both the risks as well as reasonably foreseeable benefits of involvement with the study.

Over the years, HHS has adopted additional research protections for various populations considered to be particularly vulnerable. These are in addition to the basic protections for human subjects in subpart A. The additional protections include:

- Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research (codified at Subpart B of the regulations);
- Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects (codified at Subpart C); and
- Protections for Children Involved as Subjects in Research (codified at Subpart D).

IRB Review and Approval

Much research is an inquiry based on a hypothesis whose outcome cannot be known in advance. Although some research studies offer subjects the prospect of direct benefit and others do not, an important feature of all research is that individual human subjects may or may not benefit from participation.

For example, when comparing two clinical interventions, researchers must be uncertain about which intervention will be found superior. This is known as "clinical equipoise" and is based on the ethical principles of beneficence and justice, as explicated in the *Belmont Report*, which I mentioned earlier. Some research studies offer individual subjects the prospect of direct benefit and others do not. But it is always important for subjects to know – before taking part in the study – that they may or may not experience any direct benefit from their participation.

As part of an IRB's review, the IRB must make several determinations before it can approve the research. Primary among these is need to determine if the "risks to subjects are reasonable in

relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result" (45 CFR 46.111(a)(2)).

When research studies offer no prospect of direct benefit to research subjects, IRBs must consider whether the potential benefits to society justify the risks to the individual subjects. For these studies, including some research involving human embryonic stem cells, the expected benefits would often occur in the future and would be of help to others who suffer from the same disease or condition as the subject participating in the research.

Informed Consent

At the heart of the human-subject protections system that governs HHS-funded or -conducted research is the requirement relating to informed consent. The investigator must seek a potential subject's informed consent, according to the requirements laid out in the regulations. And the investigator's method for obtaining this informed consent must be approved by the IRB before it can be applied. The only exception to this requirement for informed consent is if the IRB has determined that specified waiver criteria have been met (45 CFR 46. 116(d)).

The requirement for informed consent under the HHS regulations embodies the ethical principle of respect for persons, and further protects the rights and welfare of research subjects. In seeking informed consent, HHS regulations require that investigators do so only under circumstances that provide the prospective subject with sufficient opportunity to consider whether or not to participate, and that minimize the possibility of coercion or undue influence.

As part of the informed consent process, the prospective research subject must be given sufficient information about a research study to make an informed decision about whether to participate in the research, or not. If the research study does not offer subjects the possibility of direct benefit, this must be clearly stated in the informed consent process.

For example, if a research study that involves identifiable human cell lines is not intended to offer donors with the prospect of direct benefit, then prospective donor-subjects would need to be informed of this during the informed consent process, unless the requirement for informed consent had been waived by the IRB.

OHRP Guidance on Research Involving Stem Cells

The Office for Human Research Protections has provided guidance to help ensure that investigators and IRBs understand how the HHS regulations apply to research involving human embryonic stem cells, germ cells, and stem cell-derived test articles. A copy of this guidance is included with my written statement for the Subcommittee's consideration and is also available online at http://www.hhs.gov/ohrp/humansubjects/guidance/stemcell.pdf.

In essence, this guidance indicates when such research does and does not generally meet the HHS definition of human-subjects research. Under the HHS regulations, "human subject" means a living individual about whom an investigator conducting research obtains: (1) data through intervention or interaction with the individual; or (2) identifiable private information. OHRP

considers that neither of these definitions is met with research involving human embryonic stem cells, germ cells, and stem cell-derived test articles – as long as the investigator has not obtained data about an individual through a research intervention or interaction, and cannot readily ascertain the identity of the individual from whom the human material was obtained.

For example, if an investigator carrying out research using established human cell lines cannot readily ascertain the identity of the donor or donors of the original cell line, then the study would not be considered human subject research and would not be governed by the HHS human subject protection regulations. Because of this, the institution's IRB would not be required to review this type of research.

However, some research may use established human cell lines where the donor or donors may be readily identified by investigators, or may involve the obtaining of data through research interventions or interactions with individuals. In these cases, the research is considered to involve human subjects, it would be governed by the HHS regulations, and IRB review and approval would be required for the research to proceed.

Finally, I would like to emphasize that the stem cell research conducted at Seoul National University by Dr. Woo Suk Hwang, which provided the impetus for this hearing, was neither conducted at nor supported by HHS. Quite apart from the issues of fraud and abuse, such research could not have been conducted or supported by HHS under Federal law in the United States. Dr. Hwang's research involved attempts to create new human embryonic stem cells lines (solely for research purposes) through the process of somatic cell nuclear transfer, sometimes called human cloning. HHS is specifically prohibited by law from supporting "research in which a human embryo or embryos are destroyed," as well as from supporting "the creation of a human embryo or embryos for research purposes," and that law (most recently P.L. 109-149, Title V, Section 509) defines human embryo to specifically include embryos created by cloning. As it was not conducted at or supported by HHS, and does not appear to have been conducted at an institution that voluntarily agreed to comply with the HHS regulations for all human subjects research conducted at the institution, Dr. Hwang's research was therefore not subject to any of the regulatory protections that I have discussed throughout this statement.

Conclusion

In conclusion, through this system of IRB review and informed consent, the HHS regulations protect the rights and welfare of human subjects, while enabling investigators to conduct important, ethical research that is of benefit to society.

Thank you for you attention, and I would happy to answer any questions you may have.

Mr. SOUDER. Thank you.

Director Pascal. Did I say that correctly? Or Pascal? Thank you.

STATEMENT OF CHRIS B. PASCAL

Mr. PASCAL. Chairman Souder and distinguished members of the subcommittee, I appreciate the opportunity to talk to you today about research misconduct and the work of the Office of Research Integrity in the Department of Health and Human Services.

ORI is charged with overseeing allegations of research misconduct in biomedical and behavioral research supported by the U.S. Public Health Service. ORI has over 10 years of experience in reviewing misconduct allegations and making findings of research misconduct.

PHS-supported research institutions and ORI make findings of research misconduct when evidence demonstrates that fabrication, falsification, or plagiarism has occurred in PHS-funded research. ORI has made more than 160 findings of misconduct since 1992, and has reviewed hundreds of additional allegations of misconduct that did not result in misconduct findings.

In May 2005, HHS published a new, more comprehensive regulation governing research misconduct investigations entitled, "Public Health Service Policies on Research Misconduct," codified at 42 CFR part 93, which can be found on the ORI Web site. This new regulation replaces the previous regulation from 1989 for dealing and reporting research misconduct.

ORI is aware of the controversy regarding Dr. Hwang's human stem cell research project at Seoul National University and the findings of fraud by the Seoul National University investigation committee. However, based on current information available to ORI, ORI has no jurisdiction in this matter since the research was not supported by PHS funds, and ORI does not have jurisdiction over non-PHS-supported research.

Had the actions been under the purview of HHS, ORI has a staff of scientists and additional consultants who have developed extensive knowledge and exploits in overseeing and assessing allegations of research misconduct, primarily through evaluating investigations conducted by the PHS-funded research institution.

By law, direct investigations are usually initiated by the research institutions that receive allegations of research misconduct. These allegations are generally made by members of the grantee institution who are part of the particular laboratory or department conducting the research. And I might add that ORI considers these individuals to be heroes in coming forward with allegations of research fraud because without them, it would continue and grow. And those individuals take great risk to come forward.

One or more members of the team may suspect misconduct and then report it to the grantee institution directly. Sometimes the investigator suspecting fraud will report to ORI, and then ORI will refer the matter to the appropriate grantee institution for review. Grantee institutions are required by the HHS regulations to report allegations to ORI when they reach the formal stage of investigation of the process, and when admissions of misconduct are made by the accused scientist.

In conducting the investigation, the institution must promptly secure the research records—without access to the research records and to the original data, it is very difficult to solve these cases—and other relevant documents in order to have a sound basis to identify and evaluate any evidence of research misconduct.

When an institution has completed its investigation, it must submit a written report to ORI. ORI will then engage in a thorough oversight review of the report and, depending on the quality and thoroughness of the investigation, may accept the institutions report and find either misconduct or no misconduct based on the institution's findings.

If ORI believes further investigation is required, we may request and review the grantee institution's entire investigation record, including the research data, copies of interviews or tapes of interviews, and other relevant documents. When the analysis is completed, ORI may find no misconduct and close the case, or propose findings, PHS findings of research misconduct.

ORI findings of no misconduct, as well as open cases that are under review, are considered confidential, both by the ORI regulation and other Federal law, and ORI does not discuss these cases publicly. When HHS makes a finding of misconduct, however, it formally announces the finding, which is then published in the Federal Register, summarized on the ORI Web site and in our newsletter, and the finding is listed in the NIH Guide for Grants and Contracts. In ORI's view, it is important to make these findings public. Otherwise, scientists can move around to other institutions and commit fraud again if it is not public information.

HHS takes findings of research misconduct seriously and takes appropriate action. Findings of research misconduct typically result in remedial HHS administrative actions that may include debarment or suspension from PHS-funded research, which means they cannot come back to the Public Health Service and get new funding for a period of time. And in very serious cases, they could be precluded from doing so for life.

ORI also strives to correct the research record that may have been corrupted by fraudulent studies. As you heard earlier today, Science withdrew two articles that were published because of the fraud, and we think that is very important to making sure that the scientific record is accurate and honest for other scientists and the public to rely upon.

In those research misconduct cases that result in criminal fraud charges, which has happened a couple of times, and civil proceedings of false claims, ORI works collaboratively with the Department of Justice and other Federal law enforcement agencies, including the HHS Office of the Inspector General. Accused scientists who wish to contest findings of research misconduct are offered a due process administrative hearing to defend themselves.

In order to promote research integrity and responsible research practices, ORI has an active education program. We collaborate with the scientific community, and we provide resources to institutions to develop their own educational products.

ORI believes that its educational programs and collaborations with the research community can help prevent research mis-

conduct. It will not ever eliminate it just because of the nature of the human condition.

For example, ORI has a collaboration with the Association of American Medical Colleges to fund scientific and academic societies to hold workshops and conferences on research integrity issues, or develop guidelines or educational programs describing appropriate normative standards for conducting and reporting research.

ORI has a collaboration with the Council of Graduate Schools to fund pilot projects at 10 institutions to provide formal training to graduate students in the responsible conduct of research. ORI has published a booklet on responsible conduct of research that has been translated into Chinese and Japanese, as well as in English.

Finally, ORI has an active program of evaluation and research studies, partly in collaboration with the National Institutes of Health within HHS, to determine what scientific practices are working well and to learn what practices can be improved. It is important to study the science of science itself in order to improve how you conduct research.

Although any individual case of research misconduct can have serious consequences for biomedical research, it is ORI's experience that the great majority of scientists are dedicated to conducting research in a responsible and professional manner, and are committed to producing research results that will benefit all Americans and healthcare consumers around the world.

Thank you for the opportunity to discuss ORI's work, and I would be pleased to answer any questions you have.

[The prepared statement of Mr. Pascal follows:]

Testimony
Before the Subcommittee on Criminal Justice, Drug Policy and Human Resources
Committee on Government Reform
United States House of Representatives

The Role of the HHS Office of Research Integrity in Investigating Research Misconduct

Statement of
Chris B. Pascal, J.D.
Director
Office of Research Integrity
U.S. Department of Health and Human Services

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Chairman Souder and Distinguished Members of the Subcommittee, I appreciate the opportunity to speak to you today about research misconduct and the work of the Office of Research Integrity (ORI) in the Department of Health and Human Services (HHS).

ORI is charged with overseeing allegations of research misconduct in biomedical and behavioral research supported by U.S. Public Health Service (PHS) funds. ORI has over 10 years of experience in reviewing misconduct allegations and making findings of research misconduct. PHS-supported research institutions and ORI make findings of research misconduct when evidence demonstrates that fabrication, falsification, or plagiarism has occurred in PHS-funded research. ORI has made more than 160 findings of misconduct since 1992 and has reviewed hundreds of additional allegations that did not result in misconduct findings. In May 2005, HHS published a new, more comprehensive regulation governing research misconduct investigations entitled, "Public Health Service Policies on Research Misconduct" ("the HHS regulation"), codified at 42 CFR part 93, which may be found on the ORI website at: http://ori.dhhs.gov/documents/42_cfr_parts_50_and_93_2005.pdf. This new regulation replaces the previous regulation from 1989 (42 CFR part 50 subpart A) for dealing with and reporting research misconduct.

ORI is aware of the controversy regarding Dr. Woo Suk Hwang's human stem cell research project at Seoul National University and the findings of research fraud by the Seoul National University Investigation Committee. However, based on the information currently available to ORI, ORI has no jurisdiction in this matter, since the research was not supported by PHS funds, and ORI does not have jurisdiction over non-PHS-supported research.

Had the actions been under the purview of HHS, ORI has a staff of scientists and additional consultants who have developed extensive knowledge and expertise in overseeing and assessing allegations of research misconduct, primarily through evaluating investigations conducted by PHS-funded research institutions. By law, direct investigations are usually initiated by the research institutions that receive allegations of research misconduct. These allegations are generally made by members of the grantee institution who are part of the particular laboratory or department conducting the research. One or more members of the team may suspect misconduct and then report it to the grantee institution directly. Sometimes the investigator suspecting fraud will report to ORI, and then ORI will refer it to the appropriate grantee institution for review. Grantee institutions are required by the HHS regulation to report allegations to ORI when they reach the formal investigation stage of the process or when admissions are made by the accused scientist.

In conducting the investigation, the institution must promptly secure the research records and other relevant documents in order to have a sound basis to identify and evaluate any evidence of research misconduct. When an institution has completed its investigation, it must submit a written investigation report to ORI. ORI will then engage in a thorough oversight review of the report and, depending on the quality and thoroughness of the investigation, may accept the institution's report and find either misconduct or no misconduct based on that report.

If ORI believes further investigation is required, ORI may request and review the grantee institution's investigation record, including the research data, copies of interviews or tapes, and other relevant documents. When the analysis is completed, ORI may find no misconduct and close the case, or propose PHS findings of research misconduct. ORI findings of no misconduct, as well as open cases that are under review, are considered confidential, and ORI does not discuss these cases publicly. When HHS makes a finding of misconduct, however, it formally announces the finding which is then published in the Federal Register and summarized on the ORI website and in our newsletter, and the finding is listed in the NIH Guide for Grants and Contracts.

HHS takes findings of research misconduct seriously and takes appropriate action. Findings of research misconduct typically result in remedial HHS administrative actions that may include debarment or suspension from PHS-supported research, supervision or certification of the responsible researcher's future work, and prohibition from PHS advisory committee service. ORI also strives to correct the research record that may have been corrupted by fraudulent studies, requesting that scientific journals publish retractions or corrections of papers containing falsified or fabricated findings. In those research misconduct cases that result in criminal fraud charges and civil proceedings of false claims, ORI works collaboratively with the Department of Justice and other Federal law enforcement agencies, including the HHS Office of the Inspector General. Accused scientists who wish to contest findings of research misconduct are offered an administrative hearing by HHS.

In order to promote research integrity and responsible research practices, ORI also has an active education program, collaborates with scientific societies and institutions, and provides resources to institutions to develop their own educational products.

ORI believes that its educational programs and collaborations with the research community can help prevent research misconduct. For example, ORI has a collaboration with the Association of American Medical Colleges to fund scientific and academic societies to hold workshops and conferences on research integrity issues or to develop guidelines or educational programs describing appropriate normative standards for conducting and reporting research. ORI also has a collaboration with the Council of Graduate Schools to fund pilot projects at 10 institutions to provide formal training to graduate students in the responsible conduct of research (RCR). ORI has also published a booklet on RCR that has been translated into Chinese and Japanese. Finally, ORI has an active program of evaluation and research studies, partly in collaboration with the National Institutes of Health within HHS, to determine what scientific practices are working well and to learn what practices can be improved.

Although any individual case of research misconduct can have serious consequences for biomedical research, it is ORI's experience that the great majority of scientists are dedicated to conducting research in a responsible and professional manner and are committed to producing research results that will benefit all Americans and health care consumers around the world.

Thank you for the opportunity to discuss ORI's work with you. I would be pleased to answer any questions you may have.

Mr. SOUDER. Let me start with the questioning. And first, if we are going to have any kind of reasonable discussion, let's cut out this cardiologist stuff and so on. There is a major difference between the exceptions in fraud that we see in the scientific community in fields of research where we have had research for decades and decades, and fraud in the sole big case touted in journals and touted by all sorts of researchers in a field that has no history of such research, and the question of whether the fraud involved was endemic to the process. Don't treat us like little children and try to BS us. It is not going to work.

Now, one of the things that Mr. Waxman, Mr. Cummings, and I have had a question about baseball and steroids is whether or not you can trust an institution to patrol itself when they have a financial stake in the matter that is being investigated.

And Mr. Pascal, you went through this detail, but you said the first, basic, where you get your information whether there is fraud is whether the grantee discovers there is fraud, who clearly has a conflict of interest. Could you elaborate on this and how you would—how we find out, if the institution chooses to cover up? Because South Korea had tougher laws than we have in the United States, and they weren't followed.

Mr. PASCAL. Well, it is true that an institution can have a natural preference for not finding research misconduct. It can lead to embarrassment, it may lose—loss of funds from NIH or whoever the funding source is, or whatever.

But based on ORI's many years of experiences with institutions, we think most of them want to do a good job in finding out what actually happened, and make findings when it is appropriate. In fact, some institutions make findings of research misconduct that ORI does not pursue because we don't think the evidence is substantial enough to support a finding that we could uphold in an administrative hearing.

Also, part of this is in the structure of the regulatory process. Our new regulation has followed the policy established by the Office of Science and Technology Policy which was adopted in 2000, which states that research institutions bear primary responsibility for prevention and detection of research misconduct, and for the inquiry and investigation and adjudication of research misconduct alleged to have occurred in association with the institution.

There are also a number of checks and balances in the ORI regulation. ORI has oversight review over the institution's findings. The institution sometimes will make minimal findings or weak findings, and ORI will come in and do additional analysis and investigation with its scientists, and we make additional findings.

There is a regulatory requirement that the institution must utilize experts in the relative scientific field, and must ensure objectivity in the investigation. That is a regulatory——

Mr. SOUDER. Let me ask a followup question and we will submit your full answer for the record.

Mr. PASCAL. OK.

Mr. SOUDER. Because that is basically the procedure that Korea had.

In ORI, you have given a major grant to University of Pittsburgh researcher Gerald Schatten, who is the co-author of these studies,

who withdrew after the fraud became public, but who was co-author. And I am going to have some detailed questions that we submitted before and we are trying to get the answers to.

But given that he cited this Korean research multiple times in his grant application, are you in the process of reviewing that grant? And do you have a process—because in effect, what you were just giving me is a whole process that, if the review was weak, if you had questions about it, then you could step in. Are you reviewing this grant?

Mr. PASCAL. Due to ORI confidentiality constraints, we cannot admit nor deny any specific——

Mr. SOUDER. OK. Let me re-ask. Do you have the authority to review this grant based on the information that came out that he had been a co-author of the fraudulent study in Korea?

Mr. PASCAL. If there is a matter that involves PHS funds and alleged research misconduct, yes. ORI would have authority to review the results of the investigation by the institution.

Mr. SOUDER. And Dr. Battey, I am going to read a number of questions here. You have been—we sent these over 2 years ago. Your response to some of the questions was—not these particular questions, but you responded slowly to some of the others. But we are trying to make a policy. And I am going to read a couple of these. If you can kind of give a general feeling, and then submit back in the record regarding Pittsburgh researcher Schatten's question.

One is, how much money was spent on human embryonic stem cell research in 2005, and how much of that went to University of Pittsburgh researcher Gerald Schatten?

Also, is his research on the Bush-approved stem lines as well as on primate embryos, and could you separate that funding for us?

Also, of his $16.1 million, how does this compare to other people who have embryonic stem cell grants? If you could give us his rank in terms of grants for the research on monkeys and approved stem lines, and how many grants he has been awarded. And is he your top single grantee? Because his grant makes reference several times to this Korean research, which he was co-author of till he withdrew after the fraud became public.

And also, will you give us the 2005 figures for ESCR grant awards? How many grants, total dollar amount, smallest grant award, and largest grant award? Because quite frankly, and your agency is doing oversight, this is just basic data, and it shouldn't take 2 years to get to this oversight committee to get basic data.

Now, if you don't have it today, although we did submit these in advance.

Dr. BATTEY. Let me do the best I can to answer your questions immediately.

In fiscal year 2005, NIH supported about $40 million in research involving human embryonic stem cells. In fiscal year 2005, Dr. Schatten's NIH-supported research involving human embryonic stem cells was approximately $1.1 million.

Getting to your issue about size of grants, Dr. Schatten is not the champion in terms of garnering NIH support for human embryonic stem cell research. Larger awards have been made, and in fact, an award of a little over $4 million was made to WiCell, which is a

biotechnology firm associated with the University of Wisconsin, to form the National Stem Cell Bank, which is an effort to make the stem cell lines that are eligible for Federal funding more readily available to the research community.

In fiscal year 2005, NIH supported 154 individual research projects involving human embryonic stem cells at the total amount of about $40 million. Of these, the smallest grant was $2,000 awarded to NGRI Intramural Scientists to conduct genome instability in cancer development research. The largest human embryonic stem cell project was the $4.2 million that I mentioned earlier awarded to the WiCell Research Institute.

Mr. SOUDER. Thank you very much. That was helpful. Can you submit a full list of the grants for the record?

Dr. BATTEY. The full list of the 154 individual research projects? Yes.

Mr. SOUDER. In 2005?

Dr. BATTEY. Yes.

Mr. SOUDER. OK. Thank you very much.

Yield to Mr. Cummings.

Mr. CUMMINGS. Thank you very much.

Dr. Battey, I think it was you that said that one of the best ways to discover fraud in these instances is when you have to duplicate the research in another lab. Is that correct?

Dr. BATTEY. Yes. If I can elaborate on that for just a moment.

Mr. CUMMINGS. Please do.

Dr. BATTEY. When a major scientific breakthrough takes place, it generally has implications for research going on in a number of other independent laboratories. And one of the first things they will try to do to take the next step and build on that research is to take the protocol that was reported in the published literature to have given a specific result and reproduce that result.

Now, when multiple laboratories around the world or in the United States cannot reproduce a major scientific finding, it rapidly falls into disrepute.

Mr. CUMMINGS. Now, you stated in your testimony that while the stem cell research fraud in South Korea is unacceptable, it doesn't reflect on the potential of human embryonic stem cell research one way or the other. Is that what you said?

Dr. BATTEY. I am saying that the arguments for or against doing human embryonic stem cell research are not directly implicated by the—or directly influenced by the fraud that everybody agrees was inappropriate that took place in South Korea.

Mr. CUMMINGS. You know, the thing that has—I think you listened to the opening statements, and you heard Ms. Norton. And I think one of the major concerns here is, do you—I mean, are you a scientist?

Dr. BATTEY. I am reported to be a scientist, yes.

Mr. CUMMINGS. OK. Well, I will take your word for it.

Dr. BATTEY. My mother thinks I am a scientist.

Mr. CUMMINGS. I am sorry. Say that again?

Dr. BATTEY. My mother thinks I am a scientist.

Mr. CUMMINGS. Your mother?

Dr. BATTEY. Yeah.

Mr. CUMMINGS. OK. That is good. [Laughter.]

Dr. BATTEY. She also thinks I am a doctor.

Mr. CUMMINGS. I guess the question becomes—I think at least two of you, and I know Mr. Waxman, referred to it, and others—this whole thing of fraud and whether the fraud in an area like this should then cause us not to go into that area. And then the chairman got very upset when we talked about—you all talked about the cardiology piece.

But I guess the point is that you can have these problems. You are going to have problems as long as you have human beings doing things. The question becomes, do you stop going in the direction because of that research. Is that what you all are saying?

Dr. BATTEY. My comment was that there is an enormous potential to improve the human condition through research that involves all types of stem cells. And it is my belief, and the belief of the National Institutes of Health, that we need to move forward and explore all avenues that are reasonable and ethically sound that have the potential to alleviate human suffering.

Mr. CUMMINGS. And when you see instances like California and Maryland moving toward funding this research, how does that affect the people in you all's shops? In other words, if you see States now moving toward that and you are, I guess, kind of standing on the sideline and watching, does that create concern for you all at all?

Dr. BATTEY. My job as the Chair of the NIH Stem Cell Task Force, which is a role that I was asked to assume by the NIH Director, Dr. Zerhouni, in the summer of 2002, is to try to find areas within the President's policy where we can accelerate the pace of research using stem cells.

And I think it is fair to say that there has been very significant progress made by support provided by the National Institutes of Health. As I mentioned, in the last fiscal year we have 154 research projects. We invested $40 million. And much has been learned about the fundamental events that drive cells to become specialized adult cell types.

This is the information that will ultimately allow us to potentially generate cells for cell replacement third party in the laboratory; to potential mobilize endogenous populations of stem cells within patients to become these interesting cell types; or, ultimately, to understand the molecular mechanisms that determine this magical process of nuclear reprogramming whereby an adult nucleus in a specialized cell can turn back the clock and become a pluripotent cell nucleus, and in so doing, allow us the opportunity to generate pluripotent cells without the destruction of human embryos.

Mr. CUMMINGS. We have a tough time situation, but I have to ask you this one last question. You know, so you—based upon what you just said and your testimony, you don't see this area of research as some pie in the sky. And it has been implied that some of this research is just giving people false hope. You don't see that based upon your knowledge and expertise? Do you understand the question?

Dr. BATTEY. I understand the question very well, I believe. I will say freely that the comments that have been made about therapies using adult stem cells and the therapies using embryonic stem cells

at this time are 100 percent true. There are no therapies using human embryonic stem cell lines at the current point in time.

Adult stem cells, in particular hematopoietic stem cells, stem cells of the blood-forming organ, the bone marrow, have been part of the research landscape for nearly 3½ decades. Human embryonic stem cells first became available to the research community in 1998, when James Thompson published his landscape paper.

I think it is premature at this point in time to evaluate exactly what type of stem cell and in what way knowledge gleaned from studying that type of stem cell in 10, 20, or 30 years is going to inform the medicine of the future and empower the next generation of physicians.

Mr. CUMMINGS. And I imagine if we had taken that position in a lot of our science, we wouldn't be where we are today in various areas of science.

Dr. BATTEY. It is unfortunate, but the progress of science is usually incremental. And we make slow steps forward, and it takes many, many of those slow steps over a long period of time, before we have even done the safety and efficacy testing in animal models that poise us to do the first experiments that involve human patients.

And I am delighted to be joined here by my colleagues from Office of Human Research Protection, who see to it that we do these studies in people in a responsible fashion. You know, we are absolutely bound to do that, as human beings and as physicians.

Mr. CUMMINGS. Thank you very much.

Mr. SOUDER. I really need to hold to the 5-minute rule because we have a lot of Members, and we are trying to reach a 5 p.m. deadline, and we have six witnesses on the second panel.

Ms. Foxx.

Ms. FOXX. Thank you very much.

I want to ask Dr. Battey: Did SCNT create Dolly the sheep?

Dr. BATTEY. Dolly the sheep was created by somatic cell nuclear transfer. That was in fact the time that we learned that an adult cell nucleus could be reprogrammed. That was the first demonstration that I am aware of in a mammal that was possible, although such experiments had been done in amphibians for decades.

Ms. FOXX. Then what is the difference between somatic cell nuclear transfer and cloning?

Dr. BATTEY. Somatic cell nuclear transfer is the process whereby the nucleus is removed from an oocyte and replaced by the nucleus from a somatic cell, a body cell. That is why it is called somatic cell nuclear transfer.

When this procedure is done with the goal of creating an embryonic stem cell line that is genetically matched to an individual or has a specific genetic background, that term that is used for that is therapeutic cloning. When it is done with the intent of creating a new life through—all the way through gestation and having, in this case, a baby sheep born, in the case of Dolly, that is reproductive cloning.

And, you know, the nomenclature—you mentioned that language can be very tricky. And the whole word "cloning" is a word that is a tricky word because it is used in many different ways. In my laboratory, we talk about cloning a cell line, which means basically

taking a culture of cells and growing up a new culture from a single cell.

We talk about cloning a recombinant DNA molecule, where we take a single recombinant DNA molecule and make 10 to the 8 copies of that molecule. And then here we talk about therapeutic cloning and reproductive cloning. And while they employ similar technologies at the beginning, they have different end points.

Ms. FOXX. Well, I am curious about the phrase that you use, "ethically sound." I wonder whose definition of ethically sound it is. And I will tell you what went through my mind when you said that, and I want to be very careful how I say this.

I heard a presentation a couple of weeks ago by a physician, and he raised the issue of the Tuskegee experiments that were done. If there is anybody here who doesn't know those, those were experiments done on African American men in Alabama, I believe, or—I am not sure what State it was in, 40 years ago, 40 or 50 years ago, where they were injected with syphilis, I believe, and then studied for it.

I wonder if those people said those studies were ethically sound. And would you feel that those were ethically sound studies?

Dr. BATTEY. No. I would not feel they are ethically sound. And they led, in fact, to the creation of human subjects protection rules as we know them today.

Ms. FOXX. OK. Then how would you define ethically sound if, in the process of doing embryonic stem cell research, you are destroying human life? How do you define ethically sound?

Dr. BATTEY. That is the subject of a national debate at this time. And there are many different opinions on that subject that cut to the very heart of when people believe that life begins. That is a subject where the major religions of the world are divided. And it will be a subject that I predict will be a contentious subject that will need to be debated for the foreseeable future.

Ms. FOXX. Mr. Chairman, that is the last question I had. But I would really like to go back to some of the testimony that might have been given around the Tuskegee experiments, and I will have a feeling that a lot of the scientists who were engaged in those used the very same language that you use.

Mr. SOUDER. Mr. Waxman.

Mr. WAXMAN. The Tuskegee experiments were reprehensible. They involved human subjects who were not informed of the nature of the experiments. As I understand it, they never were reviewed by any outside agency. And you indicated, Dr. Battey, that is why the whole protections for human subjects has been created, so that an institutional review board has to approve any kind of experiment to be sure that it is ethical and meets ethical standards. Is that correct?

Dr. BATTEY. That is correct.

Mr. WAXMAN. Now, a lot of people worry that embryonic stem cell research is going to be conducted. It is going to be conducted by private companies.

If embryonic stem cell research is conducted by the Government, is there a greater chance that ethical standards will be met, that there are going to be—there will be greater scrutiny of all the procedures that go into that research?

Dr. BATTEY. I think it is fair to say that there will be the same scrutiny that we have applied to other areas of biomedical research, with doubling scrutiny because of the respect that one has to have for the sensitive area of research where there is an enormous divide in our country.

Mr. WAXMAN. Well, the American Society for Cell Biology emphasized the importance of public funding. And they at one point said that without Federal funding, the Nation's top academic researchers at universities, medical schools, and teaching hospitals cannot join in the search for cures, which means slower progress, and that the Government oversight will ensure that research complies with ethical guidelines.

Do you agree with that statement, that last point, and how does it guarantee or ensure that research complies with ethical guidelines?

Dr. BATTEY. We can insist that before Federal funds are expended, that proper oversight has taken place. And that in fact is done with all the research that involves human subjects, where the experiment must be reviewed by an institutional review board in the institution in question before such an experiment goes forward.

Mr. WAXMAN. In your view, does the Korean scandal establish or suggest that the field of embryonic stem cell research is unique in being susceptible to scientific fraud and/or patient exploitation?

Dr. BATTEY. Unfortunately, I am afraid that scientific fraud has been found in many areas of science, as I mentioned earlier. It is rare, but it happens in many different areas. And scientists need to be vigilant to try to prevent it.

But I would emphasize that it is my sincere belief in my 23 years of experience as a scientist has taught me that the overwhelming majority of individuals engaged in biomedical research are sincere, hardworking, and would like nothing better than to see what they do in their laboratories lead to better cures and better health of the Nation.

Mr. WAXMAN. Should women be allowed to donate eggs for purely research purposes under any condition? And if so, what should those conditions be? Maybe you want to——

Dr. BATTEY. I think that might be a better question for Mr. Schwetz to try to answer, if he would like to, or I will answer to the best of my ability if he would prefer.

Mr. SCHWETZ. All we can say is that if in fact there is going to be research that involved eggs from donors, and this is research that is funded by HHS and doesn't involve the cell lines—it doesn't get outside of the cell lines that are acceptable for HHS-funded research, then all we can say is that we have a network in place through the institutional review board system that determines that these protocols must be reviewed, and they need to meet the standards that are set in our regulation.

Mr. WAXMAN. Well, what if we changed the ban on this research through NIH and broadened it to further investigations using embryonic stem cells, does a—exploitation of women is a major and disturbing theme in the story of the Korean scandal. Would this be something that we could make sure is done appropriately, if a woman wishes to participate in donating an egg for research beyond stem cells that are available now?

Mr. SCHWETZ. It is hard to know what is going to come up in the future. But based on what we know today, these—we are faced—this is an enterprise that is faced with a number of risks in research, and the possibility that there would be a problem with harvesting eggs from females is one of a number of risks that would be handled by the institutional review board system on a regular basis.

So I don't think there are limitations in the regulations that would suggest we shouldn't go into this kind of research because we don't know how to handle it.

Mr. WAXMAN. We don't know how to handle it until it is reviewed? Until some proposal is reviewed?

Mr. SCHWETZ. That is correct.

Mr. WAXMAN. OK. Thank you. Thank you, Mr. Chairman.

Mr. SOUDER. I have a feeling that though Mr. Waxman and I may disagree fundamentally on where life begins and in embryonic research, if this were to go forward with congressional standards, I have a feeling that we would want more than an institutional review because that is partly what happened here. In other words, just trusting the university isn't going to cut it in something this controversial ethically. Is that——

Mr. WAXMAN. Well, I don't think an institutional review board is trusting the university, and maybe we can have the experts inform us on the subject. But I think an institutional review board is to oversee the work of the universities and their proposals when they evaluate the ethics of any experiment.

Mr. SOUDER. This is important to clarify because we had it in the testimony in response to several questions. My understanding is that unless you feel there has been abuse, the research on whether there has been fraud, and the guidelines are standard, they submit. Then they do an internal review, and unless you feel something is wrong, you don't review it. Is that correct?

Mr. WAXMAN. I think they have to review it in advance to prevent an abuse, not wait till——

Mr. SOUDER. They set the guidelines, but to make sure that the guidelines are being followed, it is self-reported unless somebody blows a whistle or you suspect something. Is that correct, Mr. Pascal?

Mr. PASCAL. Is your question to me?

Mr. SOUDER. Yes.

Mr. PASCAL. I am sorry. Yes. We normally get complaints of allegations from individual scientists. Also, the institution is required to report to us when they get to the investigation stage.

Mr. SOUDER. Thank you. Is that clarified?

Mr. WAXMAN. Well, I think it is an answer, and I appreciate the answer. Thank you.

Mr. SOUDER. OK. Ms. Schmidt.

Ms. SCHMIDT. Thank you. I have a question. But before I ask my question, Ms. Foxx said that language is important. And Dr. Battey, this goes to you as well as the question. Language is important, and I don't think we should discuss the term "religion" when we are discussing when life begins because I have a very dear friend that is an atheist, and he believes the same as I do as to

when life begins. And he doesn't believe in any God or in any religion.

But having said that, I have been concerned about the issue of appropriate stem cell research for some time. In my days when I was in the Ohio Legislature, I actually went to the University of Cincinnati to find out exactly how they were handling this. And so I know that extrapolating information is important. And when I got here, I did some research, and I found out that this committee in its past has had a difficult time getting information from you.

As you know, and as I found out, this subcommittee requested information from you in October 2002 seeking a detailed report providing comprehensive information on the medical applications of adult and embryonic stem cells, as well as cells from cloned embryos and aborted fetuses. The subcommittee received a response from you in June 2004, 20 months after its initial request, during which time the subcommittee staff continuously inquired about the status of this report, and subsequent chairmen's letters were sent seeking this material. And I have copies of them.

Your reply to this oversight request, 20 months in the making, was completely insufficient and unresponsive to the plain meaning of the committee's request. Ultimately, you acknowledged this and apologized for the inadequacy of the response.

But throughout this entire period, when Congress was seeking critical information about these very issues we are discussing today in 2006, information that would have been useful for complex policy decisions being faced by the Congress and our President, members and their staffs were unable to obtain the kind of accurate, timely, and up-to-date information from NIH necessary to do, quite frankly, the people's work.

This happened on your watch. It seems only appropriate that while we are examining the problems in this research area, that you explain to this body why such critical information was withheld from Congress for so long. And the second part of that is: Will you be forthcoming when we ask for additional information in a timely manner and a comprehensive format in the future? Because I believe the public has a right to know.

Dr. BATTEY. It is a fair question. I am very sorry that response was delayed the length of time that it was. But I must inform the committee that the NIH had developed its response within a few weeks of when the request was initially received. Once we develop a response, it is then subject to a clearance process in the Department of Health and Human Services over which I have no control.

So yes, it was done on my watch, and I take responsibility for it. But aspects of that delay were beyond my control. And what I will tell you is that I will do what I can to get information to this subcommittee or any other subcommittee, factual scientific information, in as timely and accurate a fashion as the resources I have at my disposal allow me to do.

But again, I say I am sorry you were without that information for a 2-year period.

Ms. SCHMIDT. Well, I have a followup, sir. And again, I am new to this process. But information is key——

Mr. SOUDER. Mr. Schmidt, will the gentlelady yield a second?

Ms. SCHMIDT. I would be honored, yes.

Mr. SOUDER. And I will put your time back on. And if Ms. Norton and Ms. Watson will let me make a brief comment, that I appreciate your apology. Ms. Schmidt will have a followup question.

But in the role of oversight in the U.S. Congress—and this is not directed at you—I am getting increasingly frustrated with this administration coming up with multiple excuses as to why they can't give us documents on this, on HHS, on the State Department, on the Office of Faith-Based, and other departments. We constantly hear, well, it has to be reviewed.

We represent the American people. Two-year review is not acceptable. And I am not sure who we have to call in, whether we have to do this at the full committee level. But other subcommittees are having the same problem, in that exactly what takes 2 years of review to figure out, when we ask data and the data is coming over to us, what kind of review has to happen for elected officials to see the fundamental data.

Then second, then we are told that the process of why it took 2 years is pre-decisional, as though there was some sort of a political discussion over what they were going to get us. And quite frankly, both at Department of HHS under this Secretary and at the State Department under multiple Secretaries, if it wasn't for individuals leaking us documents, we wouldn't know that when we get the documents, often, what has been taken out.

And different agencies are saying—because we will make a document request. Then we will be told that this is all the documents. Then we will show the department—this happened three times in one State Department request. This, I think, dealt with Afghanistan. And it is getting increasingly exasperating. Then you are sent up here having to defend that.

But the bottom line is: We need timely responses. The type of requests we made were basically factual requests. They shouldn't have had such a political screen. Even though we know this is a difficult subject, we are the same party. We know how difficult the subject is, but elected officials have a right to know what this data is.

And the extra-exasperating part of this is that by the time we get the data, then we don't have the trust in the data. And then we—in the example of the State Department—had to request 10,000 documents. And then they came back and said the great cost.

Well, we lost confidence in the trust of the Department. And HHS is headed this direction, too. If you can take this back. We will try to target our document requests if we get them in a timely fashion and get the documents that we requested. But if we don't get the documents requested in a timely fashion, we have to keep broadening the search because we are an oversight committee.

And quite frankly, this happened under the last administration until the last stretch, and then they started sending over like truckloads of documents and taking forever to go through. But at least they were more forthcoming. And I appreciate your willingness to cooperate, and that this administration, hopefully at higher levels than yourself, will start to respond. But the frustration is building, and it is going to boil over if we can't figure out how to do it.

So thank you for having the other data earlier. I yield to Ms. Schmidt. But sorry, I wanted to go on the record that this is far greater, even, than just his Department. We are having a tremendous problem in doing oversight right now for this very reason, getting 2 years and then not getting the—getting an incomplete amount, and not knowing what we are missing. That is because we don't know what has been taken out.

Do you have any insight as to what took 2 years to review?

Dr. BATTEY. No.

Ms. SCHMIDT. Thank you, Mr. Chairman. As a followup, since you had to put this through a review process, who are the people we have to call to stop the delay in the review? Who—give me the name, please, of the person that is accountable for the holdup in this document request because as the chairman said, it is not just Congress that has the right to know. It is the people that have the right to know.

We represent the people of the United States. And we have the right to know information in a timely fashion, sensitive information on this issue, and this is a very controversial issue. If we don't have that information, we can't make the appropriate policy decisions that the people expect us to make.

So who at your Department held this up for 2 years, so we can bring him in and ask why?

Dr. BATTEY. I don't know.

Ms. SCHMIDT. Can you find that out for us?

Dr. BATTEY. I can try to find it out for you.

Ms. SCHMIDT. Thank you, Mr. Chairman.

Mr. SOUDER. Thank you. Ms. Norton.

Ms. NORTON. Mr. Chairman, I have a couple of questions, but I want to just say a word because both gentleladies have mentioned the word—the care we must take in language. And I want to second what they said.

I want to say I appreciate that the gentlelady from North Carolina said she wanted to be careful about her language when she made analogies to the Tuskegee experiments involving living, Black men who were treated in a way that was emblematic of the way Black people were treated in the Southern States.

And I just want to say for the record, for those of you who want to use those analogies into the African American experience, you are right. You had best be careful. Because I believe I speak for African Americans when I say we do not want anybody comparing Black people to human embryos.

Mr. Chairman, I just want to say, because you have always been very remedy-oriented and I was a little surprised at what you said to the ranking member about BS'ing about analogies, we just heard some analogies that, frankly, I resented.

But I really don't think you meant that we are only interested in the past. I have never seen you approach an issue that way. And I know you don't—you are not holding the hearing for political reasons or to keep any information we get from these witnesses to ourselves.

And Mr. Chairman, if I can remind you, our own Chair, Mr. Davis, has said repeatedly that the Government Reform Committee, by the way, has the largest staff in the Congress of the United

States because its writ is to investigate anything involving the Government.

And I suppose the best indication of that, Mr. Chairman, for something that some would argue is totally outside our jurisdiction, is not only the hearings, not only the investigation, but the bill we passed on baseball. I mean, there is another committee that has primary jurisdiction over that matter, but the chairman brought forward his own bill on it.

And I think when we are talking about this matter, we would want to be remedy-oriented. And in light of my work with you on this committee and my respect for your work on this committee, I know that you would want us, if we could uncover some remedies for adult stem abuses or embryonic stem abuses, to let everybody know about it.

Let me have—let me ask a question to Mr.—Dr.—I think it is Battey. Am I pronouncing that Right?

Dr. BATTEY. Yes, ma'am.

Ms. NORTON. And your role is the chair, of course, of this important task force on stem cell research. And Mr. Pascal, who is a lawyer, who speaks from another angle.

First of all, I was relieved that both of you appear to have testified that we don't yet have this problem in this country, Dr. Battey, that the vast majority are honest, do not reflect on even the potential on the human embryonic cell research one way or another.

You refuse to draw conclusions in advance. By the way, everybody, that is how the scientific—how the scientific method works. You come in with a hypothesis and you say, prove it one way or the other. Prevent it if you can. Mr. Pascal says virtually the same thing. Serious consequences if you had any particular case of—great majority of scientists here are dedicated.

My question, and as far as you know have not been involved in anything like this kind of fraud and human rights violation. Let me ask you this. We talked about how fraud gets uncovered. Again, going back to scientists, who first uncovered this fraud?

Dr. BATTEY. The initial——

Ms. NORTON. In Korea?

Dr. BATTEY. The initial allegations of fraud involved members of the research team in Korea.

Ms. NORTON. Very important point to put on the record, that it is a primary obligation of scientists themselves, as any ethical scientist moves forward, to replicate, to investigate, and moves forward in the spirit of great skepticism and that. But very important, as we seek guidance—at least people like me seek guidance—from the Federal Government, I don't know what form it should take to indicate how most fraud is uncovered, how most matters of this kind are uncovered.

Are most of them brought forward by scientists, or was that unusual?

Dr. BATTEY. I will yield to my colleague, Mr. Pascal, who probably knows better than I do, but would comment that in my experience generally, they are brought forward by individuals familiar with the research in question.

Mr. PASCAL. I would agree with that, that it is usually somebody who is in the laboratory or the department and is familiar with the

research being done so they have enough knowledge to know that something is wrong.

Ms. NORTON. Whereas whistleblowers are uncommon in the Federal Government, that is the job of a scientist. And I am just pleased to hear that for the most part, it seems to be working in this country.

I have a question that bothers me very much, though, and this involves the testimony of Mr. Schwetz—yes, of Mr. Schwetz, who said that—in page 4 of your testimony that the guidance, the stem cell guidance, does not generally meet the—your definition, HHS definition, of human subjects research, and that is where you have offered guidance. Is that correct?

Mr. SCHWETZ. Let me clarify because there are circumstances where research involving stem cells would be human research that would have to be reviewed and approved by an institutional review board, and you would have to have——

Ms. NORTON. No. I am trying to establish—I am not trying to understand that. What I am trying to establish is that you have no guidance involving stem cell research.

Mr. SCHWETZ. Yes. We do have guidance to the IRB and investigator community on their responsibilities if they are doing research involving stem cells. We do have guidance on that.

Ms. NORTON. So the guidance you have—the guidance you have offered would keep—in your judgment, would alert the scientific community that the kind of abuses we find in South Korea are not—or violate, I guess, your regulations and U.S. law?

Mr. SCHWETZ. I am not sure I really understand your question. But there are some circumstances where fraud would represent risk to subjects. But there are other—to research subjects. There are other cases where fraud would not necessarily represent risk to subjects of research, but would have other implications for the quality of the data that are coming out of a laboratory.

Guidance that we have put out regarding research involving human subjects and stem cell research is meant to be taken in the context of our broader regulations that tell investigators and the IRB community how to ethically review the research.

Ms. NORTON. Dr. Battey, one last question. Are you aware of the research—they have been very careful in how they have described it. I have read it. I have seen some of it on television involving rats, where rats have been injected with human embryonic cells. These rats were totally paralyzed before, and you see that the rats now move, awkwardly but amazingly and astoundingly.

Without commenting on where this would lead because I don't think anybody knows where it would lead, and those who have been involved in this astounding, this startling, this amazing research are careful to say that these are rats only, but they were injected, were they not, with embryonic human stem cells?

Dr. BATTEY. I believe that is correct.

Ms. NORTON. Very important to note since we had all kinds of opinion from non-scientists on the other side that there is no progress whatsoever. And Congress, however, knows best.

Thank you very much, Mr. Chairman.

Dr. BATTEY. I am. Could I add just one comment, though? It is not clear in what way the embryonic stem cells are enabling the rats to move their hind legs again.

Ms. NORTON. That is precisely why this work is going on, Dr. Battey. And in fact, you know, I mention it only because of the implication on the other side that there is no evidence of any results from embryonic—not because——

Mr. SOUDER. He just said there was no evidence.

Ms. NORTON [continuing]. And to their credit—to their credit, I have to say not because even those who are responsible for this——

Mr. SOUDER. Ms. Norton.

Ms. NORTON [continuing]. Scientific feat have said, hey, right around the corner, guess what? Everybody who is paralyzed is going to walk. All they have said is, we have a moral obligation——

Mr. SOUDER. He said——

Ms. NORTON [continuing]. To proceed with this——

Mr. SOUDER. Ms. Norton, your time is well past.

Ms. NORTON [continuing]. With this kind of scientific research. And I agree they do.

Mr. SOUDER. There is no evidence. What he said is there is hope in that research. His opinion gives hope, among other potential research. But there is no evidence.

Ms. Watson.

Ms. WATSON. Thank you, Mr. Chairman. And thank you for this oversight hearing on the issue.

In listening to the questions my colleagues have asked, there was a mention of the challenges of when life begins and so on. And in reading through the materials that were prepared for this hearing, it comes to light that the Korean government had approved of Dr. Hwang's research.

Now, my question is: Do we have a bioethic commission similar within your Department, NIH or HHS? And do we run papers through it? When they have come up with a new piece of research, what do we do in response? Because in other countries, the ethics and morals and principles upon which they might do research can differ with the country, the culture, and tradition.

And what do we do when we receive something called research and, you know, the controversy is over the fact that he misrepresented how he got the ova. So our concern should be: How do we protect our research and not allow this to happen? So can you respond?

Dr. BATTEY. I will respond to the best of my ability. You are correct in pointing out that there are different national standards for providing Government funding or private funding for research in the area of human embryonic stem cells and human somatic cell nuclear transfer.

Right now, the Department of Health and Human Services is operating under the President's policy as well as legislative language that is on the DHHS appropriation. The legislative language prohibits the use of DHHS funds for human embryo research. This is often called the Dickey language.

The President's policy allows Federal funds to be used for human embryonic stem cell research so long as the embryo was created for reproductive purposes; was no longer needed for those purposes; in-

formed consent was obtained from the donors; and no fiduciary incentive was provided for the donation of the embryo, with the condition that the inner cell mass be removed from the 5-day-old blastocyst on or before 9 p.m. Eastern Daylight time, August 9, 2001.

So the policy under which DHHS currently operates is a policy that oversees the use of Federal funds for research. There is no national policy governing this research when the funds being used come from sources other than the Federal Government. And there is a patchwork of regulations in various States that provide different sets of guidelines for the legality or the provision of funds for this area of research.

Ms. WATSON. I think you make my point. And if we are results-oriented and remedy-oriented, and I too must agree with my colleague that our Chair seems to try to get to that point, and I appreciate that because that is the function of our committee, to have that kind of oversight.

I would hope that you and maybe HHS could come together and talk about what the standard would be for Federal funding. We cannot control what other countries do. We look at their results and we look at the 50 States, and I know I chaired a committee where we dealt with this issue.

We look at—as you say, they are a patchwork. But maybe we could develop some standards that would be guidelines. And when we read a piece of research that comes from another country, it has to go through a screening process before we make a big deal over it. You know, that is the way the Koreans dealt with this. The professor resigned. The doctor resigned, but he is going to go on with his research. So there is a cloud over whatever he produces.

But I think we ought to set some standards where anything that comes from abroad flows through. And we ought to have a bioethics unit through which they go so we can discuss, you know, all these different theories and all these different ethics, and separating church from State, and, you know, what I believe in my religion versus what you believe. You are the scientist, and all.

So I would like you to respond to that. I think I heard you mention that we needed something like that. Can you respond, please?

Dr. BATTEY. You raise a very interesting issue. My response is that the fraud that was perpetrated in South Korea is reprehensible to everybody in the scientific community, every physician that I know in this country, and in fact, every responsible citizen that I know.

It was wrong. It should never have happened. It was revealed because responsible individuals, subordinates within the laboratory, brought forward allegations. And in a very short amount of time, the problem was explored and revealed, and the fraud revealed to the entire world, and Dr. Hwang discredited.

Had this individual not come forward, when it became apparent that no one else could reproduce his results, his results would have fallen into discredit. So we have a process that sorts out the truth from fabrication. And the linchpin of that process is reproducibility in another laboratory. And it isn't science if it can't be reproduced in another laboratory.

Ms. WATSON. Did you want to mention my suggestion that we look at the bioethics and try to work that piece out so that when

you come forth with your empirical evidence that this can be duplicated, we have run it through these tests, including our discussion? Because I think there is a future for this research, and particularly here in this country. But we want to be sure that we can avoid the fraudulent practices up front.

Dr. BATTEY. I think that is an interesting suggestion that should be considered by those who are higher ranking than I am in the administration.

Ms. WATSON. Well, I throw that out for whoever is listening. Maybe it will get into the press and somebody will start considering it.

Thank you so very much, panel.

Mr. SOUDER. I want to also thank this panel. We will most likely have some written questions. Hopefully we can get a timely response. We will leave the record open longer than 3 days. But if we can't, my inclination will be to write that we could not get clearance of the Secretary of HHS, OMB, and the White House for the answers because we will try to keep the questions narrow enough. When this hearing book comes out, it should include a fair amount of data with that.

I also want to clarify two things that Ms. Norton said. She is correct that we do—in this committee, what I said is we look back on the past. We look in the past, at Katrina, at steroids, at whatever the issue is, to try to then develop and highlight what can be solutions that would then move to legislative committees. And so we have a future orientation by looking back on the past, and I didn't mean to imply we didn't have a future orientation.

The second thing, but I do think the record needs to reflect this: This committee does have jurisdiction over both the oversight on baseball, but also the legislation. There was a difference of opinion, which we have worked out, that if the steroid was overseen by the Office of National Drug Control Policy, it would be our legislative as well as oversight. If it is DEA, it is Judiciary. If it is FDA, it is Energy and Commerce.

The only question of where jurisdiction fell was on oversight, and that is really what we are battling over because we did have—in narcotics, we do have legislative as well as oversight. So I wanted the record to show that.

I once again thank this panel. Thank you for your time, and I look forward to continuing to work with you.

If the second panel could come forward.

Dr. BATTEY. Thank you, Mr. Chairman.

Mr. SOUDER. Thank you.

Our second panel is Dr. Richard Chole, Lindberg professor and chairman of the Department of Otolaryngology—the subcommittee stands in brief recess.

[Recess.]

Mr. SOUDER. The subcommittee will come to order.

Our second panel is Dr. Richard Chole, Lindberg professor and chairman, Department of Otolaryngology, Washington University School of Medicine, St. Louis; Judy Norsigian, executive director, Our Bodies Ourselves, co-author of "Our Bodies, Ourselves"; Dr. Diane Beeson, professor emerita, Department of Sociology and Social Services, California State University, East Bay; Mr. Richard

Doerflinger, deputy director of secretariat for pro-life activities, the U.S. Conference of Catholic Bishops; Dr. Debra J.H. Mathews, assistant director for science programs, the Phoebe R. Berman Bioethics Institute; and Joe Barden—Brown, excuse me, Parkinson's Action Network State coordinator of Texas.

If you will each stand—well, why don't I swear the four of you in, and then I will catch the other two, maybe, by the time we do the third one.

[Witnesses sworn.]

Mr. SOUDER. Let the record show that Dr. Chole, Judy Norsigian, Richard Doerflinger, and Joe Brown all responded in the affirmative. We will swear in the other two witnesses before their testimony.

We will start Dr. Chole. Thank you for coming.

STATEMENTS OF RICHARD A. CHOLE, M.D., Ph.D., LINDBERG PROFESSOR AND CHAIRMAN, DEPARTMENT OF OTOLARYNGOLOGY, WASHINGTON UNIVERSITY SCHOOL OF MEDICINE, ST. LOUIS; JUDY NORSIGIAN, EXECUTIVE DIRECTOR, OUR BODIES OURSELVES, CO-AUTHOR OF "OUR BODIES, OURSELVES"; JOE BROWN, PARKINSON'S ACTION NETWORK STATE COORDINATOR, TEXAS; DIANE BEESON, M.A., Ph.D., PROFESSOR EMERITA, DEPARTMENT OF SOCIOLOGY AND SOCIAL SERVICES, CALIFORNIA STATE UNIVERSITY, EAST BAY; RICHARD DOERFLINGER, DEPUTY DIRECTOR, SECRETARIAT FOR PRO-LIFE ACTIVITIES, U.S. CONFERENCE OF CATHOLIC BISHOPS; AND DEBRA J.H. MATHEWS, M.A., Ph.D., ASSISTANT DIRECTOR FOR SCIENCE PROGRAMS, THE PHOEBE R. BERMAN BIOETHICS INSTITUTE, JOHNS HOPKINS UNIVERSITY

STATEMENT OF RICHARD A. CHOLE

Dr. CHOLE. Thank you, Mr. Chairman. I am Richard Chole. I am a professor at Washington University, but I am not representing Washington University but rather myself as a private citizen.

I am a physician and a scientist. I have been funded for about 25 years by the institute, actually, that Dr. Battey directs. I am going to restrict my comments because of a lot of territory that has been covered already.

Biomedical sciences are on a brink of a real revolution in the development of our science. This is the era of regenerative medicine. This is an exciting area. It is not necessarily a new area, but it is the result of incremental change over several decades. These incremental changes continue to occur. This might in the future allow us to not only ameliorate and manage disease, but actually cure some diseases. Organ transplants are an example of the beginning part of that.

While the potential to help mankind is great, this new era poses some ethical and moral issues that we have never really encountered before that must be addressed not only by the scientists and physicians doing the research, but the public, probably more importantly by the public.

The source of these regenerative cells for regenerative medicine will come from a variety of sources, and I would like to briefly discuss a couple—make a couple of comments about these sources.

They might be embryonic, at the very earliest part of development. They might be fetal, at later parts of development. Or they may be adult, so-called adult, from the time of birth on. All of these sources of regenerative cells are called stem cells in that they can differentiate into any particular type of tissue. Some are more restricted than others.

Embryonic stem cells, as we have been referring to them, come from the very earliest human embryos, those from the stage of fertilization, the zygote, through the blastocyst, about 5 to 9 days. In order to get the embryonic stem cells from these early embryos, the early human embryo must be destroyed. And this is a human being at the earliest stage of developmental life.

Those inner cells, that inner cell mass, are the stem cells. They then are the ones that have been studied to lead to differentiation into different types of tissues. And indeed, scientists have been able to coax these cells to develop into a variety of types of tissues with potential uses for medical therapeutics.

Research into these cells has been incremental, and unlike the hype in the popular press, these have not been major breakthroughs but incremental, very small breakthroughs, showing some difference between experimental and control animals. The pitfalls of this type of research are that by definition, it requires the destruction of a living human being at the embryonic stage.

There are others as well. An embryonic stem cell is a different person. If you take the cells from that person and then put them into a different individual, there is a rejection process that goes on. That rejection would lead to the destruction of those cells unless the person was immunosuppressed by very powerful drugs.

These cells by nature are vigorous growers. They don't know when to stop growing in many cases, and most of this research has resulted in implantation of these cells where they will grow rather uncontrollably into tumors called teratomas. This particular question has not been answered.

These cells, once transplanted into an individual, may not—although they may function like a particular type of cell, may not be controllable. And in that environment, they may make too much of a hormone or not enough of the hormone. And there is no reason to—no evidence that these can really be controlled.

So those are some potential problems with embryonic stem cells. One of those problems, that they may be rejected, may be surmounted, scientists say, by cloning them. Cloning, as we have heard, is the placement of a nucleus from the body into an empty egg from an egg donor. This develops into a zygote and then a blastocyst.

If it were done in a human being, and it has never been done in a human being, this would recreate a living human being at the embryonic stage. The same ethical issues are faced by destroying this human being, albeit a cloned human being, if that were indeed possible. The advantage of this, theoretically, would be there would be no problem with cell compatibility. And I think that is why the excitement about this.

The difficulties are many. These cloned embryos are not normal embryos. Dolly was not a normal sheep. It took 250-plus times to get a cloned embryo from a sheep to become Dolly the lamb. These

cells have many, many different problems. They are defective embryos, and they are defective cells.

These stem cells in cloned embryos are defective stem cells. So they are not normal at all. They are defective. And the idea of using a defective embryonic stem cell that really can't be controlled for medical therapeutics is pretty conjectural thinking and far, far off from current scientific knowledge.

On the other hand, adult stem cells have their advantages and disadvantages as well. Adult stem cells, which are cells in our body—the most notable ones are in bone marrow, bone generation cells—have been shown to have more and more potential in development into specific tissue types. We have found recently that these cells can be caused to de-differentiate and become more like elementary stem cells, and can then be guided to develop into other types of tissue.

This line of research has great promise because it is taken from—the cells are taken from the individual, and there are no compatibility or rejection problems when the cells are given back. It also has great potential because of the variety of diseases that can be treated with it, and in fact, we treat many diseases with it in common clinical practice, and clinical trials in humans for lupus and heart problems and other problems have showed very promising results.

So the opportunities for adult stem cells are tremendous. There are disadvantages of adult stem cells, of course, in that they don't have all of the potential of an embryonic cell. But the problems can be overcome by further research into how these are developed.

I would like to just make a comment about this question of when life begins. It is my contention that life begins at the fertilization of the egg and the development of the zygote. Every, single person in this room was once a zygote, a unique zygote. From the time of the fertilization of the egg until this moment, it has been a process of your development. The genes were set. You are a human being at that point.

Medical science really has had little question about that, and I will read to you from a couple of textbooks that I took off the shelf at Washington University.

The first one: "The development of a human being begins with fertilization, a process by which the spermatozoon from the male and the oocyte from the female unite."

Another textbook: "Union of these gametes"—that is, the sperm and the egg—"during fertilization produce the zygote or fertilized ovum, which is the beginning of a new human being."

Another one: "Although life is a continuous process, fertilization is the critical landmark because under ordinary circumstances, a new, genetically distinct human organism is formed."

So, really, there has never been any question in the teaching in embryology and the textbooks, maybe until the current era—these may be changed—that life begins at that point.

Finally, I would like to make a comment about scientific hype and hype in the press about this.

Mr. SOUDER. You need to summarize. We let you go over 2 minutes.

Dr. CHOLE. OK. In the popular press, one might get the impression that paralyzed rats can walk again. This is incorrect. The studies have shown that when the experimental animals are compared to the control animals, both recover quite well in the experiments that she was citing, but the embryonic stem cell animals recover a little bit better. It is not the contrast that has been depicted in the popular press.

This drama to this field has led some scientists to assume the position of celebrity. Scientists are not prepared to be celebrities. The scientist's role is to use cold, dispassionate analysis for his or her data, and then present it in an honest way. This element of celebrity has led to some distortion, maybe the distortion that led to the big scandal in Seoul.

Thank you very much.

[The prepared statement of Dr. Chole follows:]

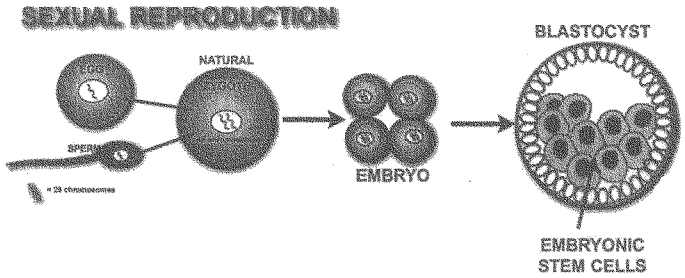
Human Cloning and Stem Cell Research

Richard A. Chole, MD, PhD
St. Louis, MO

Biomedical sciences are beginning a new era, that of regenerative medicine. This is not a new trend but rather incremental changes which will allow us to treat and possibly cure patients with diseases and injuries that have previously been managed or ameliorated. Organ transplantation is now performed throughout the country. The transplantation of regenerative stem cells is only beginning. While the potential to help mankind is great, this new era poses some new ethical and moral issues that must be addressed, not only by the scientists and physicians who develop these techniques, but by the citizens of our country. In order to understand the issues we face, decision-makers must have an understanding of the biology of stem cells and the beginning of human life.

Human Embryonic Stem Cells

Human embryonic stem cells are obtained from living human beings at the pre-implantation embryonic stage usually 5-9 days after fertilization. The tiny embryos (blastocysts) contain an "inner cell mass" which is destined to continue development. When these cells are removed from the embryo, the embryo is destroyed. These cells (embryonic stem cells – ES cells) are "totipotent" in that they can develop into all tissue types in the body.



Scientists have been able to coax animal and human embryonic stem cells to become numerous types of tissues in the laboratory. Since these stem cells are "programmed" by their very nature and/or definition to grow, they grow vigorously, even when separated in culture dishes in the laboratory. Because of their propensity to grow vigorously and to differentiate into various cell types, scientists have performed studies in animals designed to replace or regenerate missing tissues.

The Potential

- The hope in these studies is that the ES could be caused to differentiate and replace damaged or missing tissues in diseases such as diabetes, Parkinson's disease, Alzheimer's disease, spinal cord injuries, heart disease, etc.

The Pitfalls

- In order to obtain human ES cells, a human being at the embryonic stage must be destroyed.

- The ES cells are vigorous growers and when implanted into animals, their growth is often uncontrollable and results in the formation of tumors called teratomas. Techniques to suppress this tumor growth are under investigation, but a complete understanding of the early growth and development of the embryo is lacking at this time.

- Since a human blastocyst is a unique human being at the embryonic stage, its tissue type never matches another person perfectly. Just as in organ transplantation, transplantation of human ES cells into an individual would stimulate an immune response that would have to be suppressed using powerful anti-rejection drugs. To circumvent the rejection problem, scientists have suggested using cloned embryos which have a more perfect tissue match with the subject. (See cloning section.)

- Once transplanted into an animal (or someday into a human) transformed ES cells, although they may assume a new tissue type, may not function as they are intended. The control of the action of these implanted cells and their exact location will pose research challenges in the future.

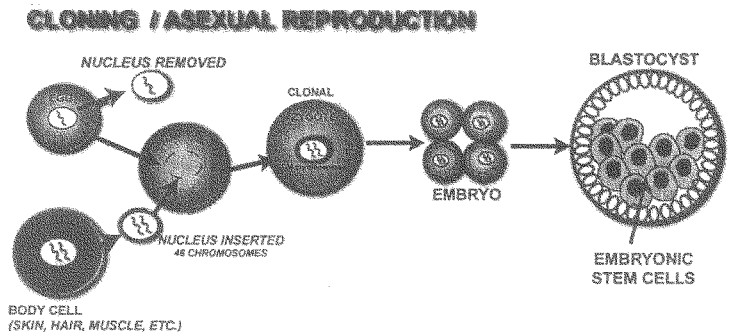
- There have been no successful human ES transplants.

Cloning to make Embryonic Stem Cells

In order to circumvent the inevitable problems of immune rejection of transplanted human embryonic stem cells, scientists have proposed to clone embryos so that their genetic makeup is identical with the subject being treated. Since a cloned human embryo would be genetically identical to the donor, immune rejection would not occur and transplanted cells would be free from rejection.

Cloned embryonic stem cells would be obtained from cloned human beings at the pre-implantation embryonic stage. These cloned embryos would be the source of cloned ES cells. The cloned embryo would be destroyed in order to obtain the ES cells from its inner cell mass. This is hypothetical; no one has been able to clone a human embryo.

The cloning process, as it is currently performed, is the process of somatic cell nuclear transfer (SCNT). This is the process that Ian Wilmut used to clone Dolly the sheep in 1997.[1] In this process, an animal (or young woman) is caused to hyperovulate by hormonal manipulation. Oocytes are surgically removed from her ovary and taken to the laboratory. In the laboratory, the nucleus from the oocyte is removed and replaced by a nucleus from a body cell (somatic cell) from the donor. The oocyte then functions like a fertilized egg (zygote) and begins the process of embryonic development. At the blastocyst stage, scientists can remove the inner cell mass to obtain cloned ES cells to use for research and potentially transplantation. Removing the cell mass kills the cloned embryo.



The Potential

- The hope in these studies is that the cloned ES could be caused to differentiate and replace damaged or missing tissues in diseases such as diabetes, Parkinson's disease, Alzheimer's disease, spinal cord injuries, heart disease, etc. without eliciting an immune response and rejection since the cloned cells are genetically identical (nearly identical[2]) to the donor cell.

The Pitfalls

- In order to obtain cloned human ES cells, a cloned human being at the embryonic stage must be created and destroyed.
- No one has ever cloned a human embryo, although there has been some success with cloning primate embryos.[3]
- Cloned embryos are defective.[4]

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[1] Schneike AE, et al Science. 1997 Dec 19;278(5346):2130-3

[2] In the process of SCNT some of the cell contents (cytoplasm) of the donor cell are mixed with that of the oocyte. Since cytoplasm contains some genetic material (mitochondrial DNA), the resultant cloned embryo contains cytoplasmic DNA from two individuals. This does not occur in nature. This adherent does not occur naturally.

[3] Simmerly C, et al Dev Biol. 2004 Dec 15;276(2):237-52.

- The pitfalls associated with the use of "natural" ES cells obtained from sexual reproduction apply to cloned ES cells also. (with exception of their tendency to be rejected)

When does human life begin?

One of the central questions that our society must answer in the stem cell debate is the question of when life begins. Biologically, there has never been a question as to when human life begins. A unique human being begins at the point where the chromosomes from the egg and sperm unite to form the earliest stage of human life, the zygote. One only has to look in a textbook of human embryology to understand this fact:

> "The *development of a human being begins with fertilization*, a process by which the spermatozoon from the male and the oocyte from the female unite to give rise to a new organism, the zygote."[5]
>
> "...Union of these gametes during fertilization produces a zygote or fertilized ovum which is the primordium or *beginning of a new human being*. (emphasis in original text) This highly specialized, totipotent cell marked the beginning of each of us as *a unique individual.*"[6]
>
> "Although life is a continuous process, fertilization is a critical landmark because, under ordinary circumstances, a new, genetically distinct human organism is formed when the chromosomes of the male and female pronuclei blend in the oocyte." [7]

Human Adult Stem Cells

By definition embryonic stem cells are "totipotent" being able to develop into any type of tissue in the body. Stem cells have been identified in many locations in the human body which were at first thought to develop into only one or two cell types. However, it is now established that some adult stem cells have "multipotency" that they can develop into many types of cells. The scientific literature is now replete with examples of pluripotency of adult stem cells.[8,9,10,11]

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[4] "NT embryos appear inferior to fertilized ones due to spindle defects resulting from centrosome and motor deficiencies that produce aneuploid preimplantation embryos, among other anomalies including genomic imprinting, mitochondrial and cytoplasmic heterogeneities, cell cycle asynchronies, and improper nuclear reprogramming." Simmerly C, et al Dev Biol. 2004 Dec 15;276(2):237-52.

[5] Langman J., Medical Embryology, 4th edition. Baltimore: Williams & Wilkins 1981, p.
[6] Keith L. Moore & T.V.N. Persaud. The Developing Human: Clinically Oriented Embryology, 6th Edition, 1998
[7] Ronan O'Rahilly & Fabiola Muller, 2001 Human Embryology & Teratology, 3rd. Ed

[8] Krause DS, et al. Cell 105:369-377
[9] Jiang Y et al Nature 418:41-49 2002
[10] D'Ilppolito G, et al. J Cell Sci 117:2971-81 2003
[11] Zhao Y, et al PNAS 100:2426-32 2003

Unlike human embryonic stem cells, adult stem cells are in routine clinical use in the successful treatment of some malignancies.

Animal studies have demonstrated the regenerative potential of adult stem cells in retinal degeneration,[12] diabetes,[13] Lupus,[14] and many others. Positive clinical trials in human subjects using adult stem cells, including umbilical cord stem cells, have been observed in Lupus,[15] Crohn's disease,[16] myocardial infarction,[17] and many others.

The Potential

- The hope in these studies is that the adult multipotent stem cells can be removed from a patient, modified in the laboratory, and used to regenerate missing or damaged tissues.
- The potential for developing tumors is low.
- Implanted cells will not be rejected because, in most cases, they are the patient's own cells.
- Adult stem cells cannot become embryos; therefore, there are no ethical concerns about destroying human life.
- Primitive adult stem cells may have the potential of being "de-differentiated" to become truly pluripotent stem cells.

The Pitfalls

- Adult stem cells are not pluripotent and may not have the growth potential of embryonic stem cells
- Certain adult stem cell populations may not be accessible for clinical use (e.g. neural stem cells).

Scientific Hype vs. Reality.

Although there has been slow, incremental advancement of the sciences underlying stem cell research, unverifiable claims of successes by some investigators and gross exaggerations in the lay press have given people false impressions about the current state of the science of stem cell research and regenerative medicine.

The well publicized scientific fraud by Korean investigators is, of course, the principal example. Media exaggeration and mis-representation of solid, reputable scientific advances have also misled the public. Exaggeration of research findings in this field have led many people to false assumption that legitimate "cures" are available in other countries and would be available here if only restrictions were lifted.

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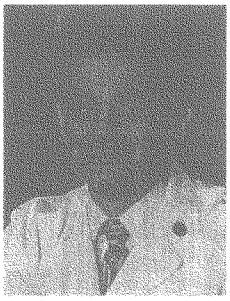
[12] Otani A, et al. J Clin Invest 114:765-74
[13] Sapir T, et al PNAS 102:7964-9 2005
[14] Burt RK, et al JAMA 295:527-535 2006
[15] Burt RK, et al JAMA 295:527-535 2006
[16] Kreisel W, et al Bone Mar Trans 32.337-40 2001
[17] Wollert KC, et al. Lancet 364:141-8 2004

Because of media hype about the significance of some findings, investigators may assume celebrity status which they are ill-equipped to handle. This celebrity status may impair a scientist ability to deal with research results in the cold, critical and dispassionate manner that is expected of all investigators.



Richard A. Chole, MD, PhD

Representing St. Louis Center for Bioethics and Culture
and Missourians Against Human Cloning

Lindburg Professor and Chairman
Department of Otolaryngology
School of Medicine
Washington University in St. Louis

Residence: St. Louis, Missouri

MD – University of Southern California
PhD – University of Minnesota

Research: Inflammatory bone disease. Continuously funded by NIH for 25 years
Medical Practice: Otologic and Neurotologic Surgery

Director of the American Board of Otolaryngology
Board of Scientific Counselors – NIDCD
Member National Advisory Council – NIDCD 2000-2004

Past President of the Association for Research in Otolaryngology
Past President of the American Otological Society

Board Member/Secretary – Missourians Against Human Cloning
Board Member – St. Louis Center for Bioethics and Culture

Mr. SOUDER. Thank you very much.

Our next witness is Judy Norsigian.

STATEMENT OF JUDY NORSIGIAN

Ms. NORSIGIAN. Thank you, Chairman Souder, Mr. Cummings, and members of the committee for the opportunity to speak. Judy Norsigian, executive director of Our Bodies Ourselves, a women's health education and advocacy organization, best known for our landmark book about women's health and sexuality, "Our Bodies, Ourselves."

At the outset, let me make clear, as I did at similar hearings 4 and 5 years ago, that my organization supports most embryonic stem cell research. We fully support ESC research that utilizes otherwise discarded embryos from IVF clinics. Thus, we do not agree with President Bush, for example.

At the same time, we have serious concerns about a small subset of ESC research known as somatic cell nuclear transfer, more commonly referred to as research cloning, therapeutic cloning, or embryo cloning, as we have discussed today. My organization believes that our country should follow the prudent example already adopted by Canada and place a moratorium on all SCNT research until better safety data are available for some of the drugs used during multiple egg extraction procedures.

There are several reasons for this position, but I will focus my remarks primarily upon our concerns regarding the risks of multiple egg extraction. And although women who undergo these procedures experience similar risks whether doing this for reproductive purposes, as is the case in an IVF clinic, or for research purposes, there is a critical difference.

In the former instance, there is a 10 to 40 percent chance that someone, either the woman herself or another woman who is seeking to become pregnant at an IVF clinic, will be able to have a baby. That is a clear benefit. In the latter instance, when a woman undergoes these procedures solely for research purposes, the benefits to her or someone else are far more dubious at this time.

Although some stem cell researchers have discussed this matter and even share our concerns, few have been willing to write about these issues. It may be that one positive outcome of the scandal in South Korea will be greater recognition of just how risky multiple egg extraction can be, as well as how easily frenetic competition and unjustified hype can lead to a more ready dismissal of these risks.

In a recent issue of the American Journal of Bioethics, Stanford faculty David Magnus and Mildred Cho write the following: "In a previous paper, we argued that there were risks associated with being an oocyte donor that were not given adequate attention in the informed consent process. This claim was based upon the informed consent documents by the South Korean researchers, an accompanying written description of the consent process, and their responses to questions posed."

"We argued that it would be easy to give short shrift to the small but serious risks that typically arise in a clinical setting precisely because these risks are not associated with the research aspects of oocyte donation."

They go on to say that: "The language used to describe scientific experiments also makes a great deal of difference in how accurately we convey the nature of stem cell research."

Finally, they say, "There is an important distinction between oocyte donation for research and live organ donation for transplantation. Live organ donation has a clearly established clinical value. Stem cell research does not. If that should change, we would agree that allowing women to donate oocytes for stem cell-based treatments would be permissible, if conducted properly. But allowing research donation to take place under these circumstances is an invitation for a new kind of therapeutic misconception, and should be avoided at this early stage of scientific development."

The risks of multiple egg extraction are not well-enough studied, especially the risks associated with the drugs most often used to suppress a woman's ovaries. Lupron, generally referred to as leuprolide acetate, the generic term, is the drug I would like to focus on now.

I have listed many of the adverse reactions in my testimony. These include: pituitary and liver function abnormalities; chronic joint, muscle, and bone pain; headaches and migraines; dizziness and blackouts; and serious memory disturbances and brain fog that persist well after the drug is discontinued.

And we have had this from numerous reports. The FDA has received numerous adverse drug reports, and one of the things we are hoping we will see in the near future is a data mining analysis by scientists at the FDA to give us better direction on what kind of research we need to conduct.

Lupron's use in the IVF setting is off-label use, and as former Chief Medical Officer Suzanne Parisian pointed out in her memorandum of February 2005, there are serious safety concerns yet to be resolved. Only well-designed research will answer critical questions that would then allow true informed consent for women undergoing multiple egg extraction procedures for any purpose.

The drugs used to hyperstimulate the ovaries after ovarian suppression also have negative effects, most notably Ovarian Hyperstimulation Syndrome, a condition in which the ovaries continue to enlarge even after the eggs have been collected. Serious cases of this syndrome involve the development of many cysts and massive fluid buildup in the body. Rarely, death has resulted. The most recent one documented was in England in December.

And it is not only the women undergoing the procedures who may be at risk from ovarian hyperstimulation. A very important article published in the past month by a Dutch team including medical and basic scientists suggests that infants may also suffer adverse consequences.

This group has shown that female mice subjected to ovarian hyperstimulation had offspring with reduced birth weight as well as a high incident of congenital anomalies, including delayed formation of bones and an eightfold increase over background levels of cervical ribs, a condition which, when present in human infants, is associated with stillbirth and cancer.

Should SCNT research go forward despite the concerns mentioned here, it will be left to women's health advocated to emphasize the inadvisability of women undergoing these procedures, espe-

cially younger women, whose risk of Ovarian Hyperstimulation Syndrome is actually greater than that for older women.

Also, if such research does go forward, certain regulations and oversight of the research with respect to egg procurement are essential. I have listed seven here: that eggs should be obtained without any hormonal stimulation, since there is still insufficient information to get true informed consent. No relatives or coworkers of those doing research on eggs should be allowed to provide eggs for research.

All medical expenses resulting from egg extraction for research should be covered; in cases where would be hormonally manipulated, longer-term healthcare coverage may be necessary to provide medical care for certain delayed health problems.

Those performing egg extraction for research purposes should function totally separate from IVF services. And no research should be allowed on eggs or stem cell lines developed from eggs procured by means other than those just mentioned. This would avoid use of stem cell lines created in other countries or regions where safeguards to women's health might not be in place.

We also believe that no patents should be allowed for products that might result from research on these eggs. Without such a policy, many therapies will likely never be accessible to the wider public. I can give you other such examples already. In addition, it would be extraordinarily difficult to avoid a problematic commercial market in women's eggs.

And, of course, no payment to egg providers beyond direct expenses. We think both the researchers and the women who provide eggs in this case may be going to be making a sacrifice.

So in conclusion, many scientists now acknowledge that individualized disease third parties will not research from embryo cloning research anyway, in part because of the need for massive numbers of eggs. The main benefit of embryo cloning would be the ab light to develop research models for studying particular diseases and conditions, but some of this type of work can be done already with otherwise discarded embryos that result from PGD, pre-implantation genetic diagnosis, testing.

At this point in time, given both the known and unknown risks involved in multiple egg extraction procedures, these procedures should not be done solely for SCNT research. At the same time, we do support most embryo stem cell research.

Thank you.

[The prepared statement of Ms. Norsigian follows:]

Statement of Judy Norsigian
Executive Director, Our Bodies Ourselves

Subcommittee on Criminal Justice, Drug Policy and Human Resources
Government Reform Committee
U.S. House of Representatives

Hearing on Human Cloning and Embryonic Stem Cell Research after Seoul: Examining Exploitation, Fraud, and Ethical Problems in the Research
March 7, 2006

I am Judy Norsigian, the Executive Director of Our Bodies Ourselves, a women's health education and advocacy organization now in its 37th year. We are best know for our landmark book about women's health and sexuality - ***Our Bodies, Ourselves*** - which appeared in its 8th edition as a major revision last May. Thank you for this opportunity to speak.

At the outset, let me make clear, as I did at similar hearings four and five years ago, that my organization supports most embryonic stem cell (ESC) research. We fully support ESC research that utilizes otherwise-discarded embryos from IVF clinics. At the same time, we have serious concerns about a small subset of ESC research known as somatic cell nuclear transfer (SCNT) and more commonly referred to as "research cloning," "therapeutic cloning," or "embryo cloning." We believe that our country should follow the prudent example already adopted by Canada and place a moratorium on all SCNT research until better safety data are available for some of the drugs used during multiple egg extraction procedures.

There are several reasons for this position, but I will focus my remarks primarily upon our concerns regarding the risks of multiple egg extraction required for research cloning. Although women who undergo multiple egg extraction procedures experience similar risks whether doing this for reproductive purposes (as is the case in an IVF clinic) or for research purposes, there is a critical difference. In the former instance, there is a 10-40% chance that someone – either the woman herself or another woman who is seeking to become pregnant at an IVF clinic – will be able to have a baby. That is a clear benefit. In the latter instance, where a woman undergoes these procedures solely for research purposes, the benefits to her or someone else are far more dubious at this time.

Although some stem cell researchers have discussed this matter and even share our concerns, few have been willing to write about these issues. It may be that one positive outcome of the scandal in South Korea will be greater recognition of just how risky multiple egg extraction can be, as well as how easily frenetic competition and unjustified hype can lead to a more ready dismissal of these risks. In a recent issue of the *American Journal of Bioethics*[1], Stanford researchers David Magnus and Mildred Cho write the following:

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[1] **A Commentary on Oocyte Donation for Stem Cell Research in South Korea**
by David Magnus, Mildred K. Cho. 2006. *The American Journal of Bioethics* 6(1):W23

> "In a previous paper ('Issues in oocyte donation for stem cell research.' Science, v.308: 1747-1748, 2005), we argued that there were risks associated with being an oocyte donor that were not given adequate attention in the informed consent process. This claim was based upon the informed consent documents by the South Korean researchers, an accompanying written description of the consent process, and their responses to questions posed. We argued that it would be easy to give short shrift to the small, but serious, risks that typically arise in a clinical setting precisely because these risks are not associated with the research aspects of oocyte donation. We therefore recommended recognition of a new category of research participants—research donors."

They go on to say:

> "The language used to describe scientific experiments also makes a great deal of difference in how accurately we convey the nature of stem cell research. We argued, for example, that referring to the process of deriving stem cells by somatic cell nuclear transfer as "therapeutic cloning" reinforces the mistaken impression that experiments are therapeutic in nature. In fact, there is no therapy currently associated with SCNT."

Furthermore, they take a cautious position regarding egg procurement procedures for research cloning:

> "....there is an important distinction between oocyte donation for research and live organ donation for transplantation. Live organ donation has a clearly established clinical value — stem cell research does not. If that should change, we would agree that allowing women to donate oocytes for stem cell-based treatments would be permissible, if conducted properly. But allowing research donation to take place under these circumstances is an invitation for a new kind of therapeutic misconception, and should be avoided at this early stage of scientific development."

The risks of multiple egg extraction are still not well-enough studied, especially the risks associated with the drugs that first suppress the ovaries. (Afterwards, different drugs are used to create controlled ovarian hyperstimulation.) The drug most often used to suppress a woman's ovaries is Lupron™ (leuprolide acetate), a GnRH agonist. Adverse reactions to this and similar drugs include the following: anemia; high blood pressure; formation of blood clots that could potentially cause damage to vital organs; fluid accumulation in the limbs; thyroid enlargement; liver function abnormality; joint, muscle and bone pain; chest pain; difficulty in swallowing; intestinal bleeding; headaches and migraines; dizziness and blackouts; memory disturbances; depression; anxiety; numbness; swelling of hands; constipation; nausea; vomiting; diarrhea; and vision abnormalities. Many people assume that this drug has been approved by the FDA for this particular indication, but that is not the case. All use of Lupron in the IVF setting is "off-label" use, and as former Chief Medical Officer Dr. Suzanne Parisian points out in the attached memorandum, there are serious safety concerns yet to be resolved. Only well-designed research will answer critical questions that would then allow true informed consent for women undergoing multiple egg extraction procedures for any purpose.

The drugs used to "hyperstimulate" the ovaries after ovarian suppression also have negative effects, most notably Ovarian Hyperstimulation Syndrome (OHSS), a condition in which the ovaries continue to enlarge even after the eggs have been collected. Serious cases of this syndrome involve the development of many cysts and enlargement of the ovaries, along with

massive fluid build-up in the body. As noted in an article about OHSS, "the reported prevalence of the severe form of OHSS is small, ranging from .5 to 5%. Nevertheless, as this is an iatrogenic complication of a non-vital treatment with a potentially fatal outcome, the syndrome remains a serious problem for specialists dealing with infertility."[2] In her memo, Dr. Parisian also notes that ovarian stimulation in rare cases can lead to stroke and "arterial occlusion with loss of a limb and death."

These risks were also noted in the informed consent document developed at the Bedford Stem Cell Institute several years ago (see "Consent to Participate in a Study Involving Egg Donation for Stem Cell Research"). Following is an excerpt from this document: "Complications associated with being an egg donor include unpredictable response to the hormones provided to you, surgical complications during the egg collection, and unknown long-term side effects from the hormones. If any of these complications arise the reproductive biologists involved in this research may choose, at their discretion, to terminate your continued participation in this research." What is unclear, however, is whether or not the costs of medical treatments for problems resulting from these procedures would be covered.

And it is not only the women undergoing the procedure who may be at risk from ovarian hyperstimulation. An article published in the past month by a Dutch team including medical and basic scientists suggests that their infants may also suffer adverse consequences.[3] This group has shown that female mice subjected to ovarian hyperstimulation had offspring with reduced birth weight as well as a high incidence of congenital anomalies, including delayed formation of bones and an eight-fold increase over background levels of cervical ribs, a condition which, when present in human infants, is associated with stillbirth and cancer.

Should SCNT research go forward despite the concerns mentioned here, it will be left to women's health advocates to emphasize the inadvisability of women undergoing these procedures (especially younger women, whose risk of Ovarian Hyperstimulation Syndrome is greater than that for older women).

Also, if such research goes forward, certain regulations and oversight of the research with respect to egg procurement are essential. The following policies should be adopted:

1. Eggs should be obtained without any hormonal stimulation, since there is still insufficient information to get true informed consent from would-be egg providers. Although Antagon, a GhRH antagonist, IS approved for such use, there are no long term safety data for this drug. Thus, only single cycling or extraction at the time of a sterilization or ovariectomy should be allowed for extracting eggs for SCNT research.

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[2] Delvigne, Annick and Rozenberg, Serge. "Epidemiology and prevention of ovarian hyperstimulation syndrome (OHSS): a review" *Human Reproduction Update*, vol. 8, no. 6, 2002, pp 559-577.

[3] Steigenga, Marc J., Helmerhorst, Hans M., De Koning, Jurien, Tijseen, Ans M.I., Ruinard, Sebastiaan, A.T. and Galis, Frietson. Evolutionary conserved structures as indicators of medical risks: increased incidence of cervical ribs after ovarian hyperstimulation in mice *Animal Biology*, vol. 56, no. 1, 2006, pp. 63-68.

2. No relatives or co-workers of those doing research on eggs should be allowed to provide eggs for research.

3. All medical expenses resulting from egg extraction for research should be covered. In cases where cycles would be hormonally manipulated, longer-term health care coverage may be necessary to provide medical care for certain delayed health problems.

4. Those performing egg extraction for research purposes should function totally separate from IVF services (an effective firewall is needed to avoid both financial and professional conflicts of interest).

5. No research should be allowed on eggs or stem cell lines developed from eggs procured by means other than those described in #1-4. This would avoid the use of stem cell lines created in other countries or regions, where safeguards to women's health might not be in place.

6. No patents should be allowed for products that might result from research on these eggs. Without such a policy, many therapies will likely never be accessible to the wider public. In addition, it would be extraordinarily difficult to avoid a problematic commercial market in women's eggs.

7. No payments to egg providers beyond direct expenses (eg, no payment for lost wages) should be allowed.

Many scientists now acknowledge that "individualized" disease therapies will not result from embryo cloning research anyway (see "Cloning: Mining the secrets of the egg," by Carina Dennis, *Nature,* February 9, 2006) The main benefit of embryo cloning would be the ability to develop research models for studying particular diseases and conditions, but some of this type of work can be done already with otherwise-discarded embryos that result from PGD (Preimplantation Genetic Diagnosis) testing. At this point in time, given both the known and unknown risks involved in multiple egg extraction procedures, these procedures should not be done solely for SCNT (embryo cloning) research.

Some researchers are already investigating alternatives such as nurturing immature eggs, growing artificial eggs in the lab, and using animal egg substitutes. Although each of these approaches has its own technical and ethical challenges, this trend does recognize how strikingly inefficient embryo cloning is, and that it will likely require – at least for a long time to come – that hundreds of eggs be extracted to obtain even one viable clonal embryo. Dr. Arnold Kriegstein, Director of the Institute of Stem Cell and Tissue Biology at the University of California, San Francisco, takes the approach that "We'll have to wait and see how difficult human eggs are to acquire" (see *Nature* article cited above), but I would hope researchers would follow the more cautious approach suggested by Drs. Magnus and Cho.

Mr. SOUDER. Thank you.

I am going to move to Mr. Brown next because he has an airplane to catch.

STATEMENT OF JOE BROWN

Mr. BROWN. Thank you, sir. Thank you, Mr. Chairman and members of the subcommittee, for inviting me today. My name is Joe Brown. I am a State coordinator for the Parkinson's Action Network, a founding member and vice president of Texans for Advancement of Medical Research, and a founding member of the Alliance for Medical Research. I have been an advocate for 20 years.

As someone living with chronic disease, as a patient and an active caregiver, I was dismayed when I read the memorandum published by the committee that appeared to reach pertinent conclusions before this hearing was convened. It mistakenly concluded that somatic cell nuclear transfer [SCNT], is not supported by current science, and those who support this research have created an unjustified hype that plays on the hopes of suffering patients.

I am not going to talk about theory and intellectual concepts. I am going to talk about life—my life, my wife's life, and the lives of you and your families.

Having watched a genetic form of Parkinson's slowly steal the quality of life from my beautiful wife, I am concerned for my children and grandchildren. I have lived 70 years with a genetic heart condition that has sudden death as its most significant side effect. I have been fortunate enough to survive three heart attacks, bypass surgery, cardiac arrest, and cancer.

I have reason to hope, especially since I have benefited from research that was thought to be wrong and unethical. I was the ninth person in the United States to receive a procedure that took me from being unable to walk from one room to another and days filled with countless hours of angina, to being able to carry my grandchild up a flight of stairs.

This procedure, which actually gives the patient a heart attack to reduce obstructive heart muscle, was originated by a Swiss cardiologist. Switzerland didn't believe that giving heart attacks was ethical and wouldn't allow the procedure. The quality of my life was improved because Dr. Sigwart was forced to leave his country, just as American scientists are doing today in order to pursue stem cell research.

So yes, as a patient, I do have hope that SCNT will succeed. But it is not unjustified hope. The breakthroughs have been exciting and amazing, but I recognize that sound research takes time. It took 52 years for the polio vaccine to get to market. I don't expect the scientific community to have these treatments or cures available in my lifetime, but if we don't start now and start solving the problems that we have with communication with each other, the cures won't be there for our children and grandchildren.

When I visited the University of Texas Medical Branch in Galveston, scientists working with adult stem cells told me the most significant advances in adult stem cell research have occurred since embryonic stem cells were first isolated in 1998. The reason these scientists gave me is the embryonic stem cells are teaching them

how to work with adult stem cells. To promote one form of stem cell research to the exclusion of another is counterproductive.

I am astounded that there are those who don't recognize, while there may be fraudulent researchers, by definition, it is impossible for research in and of itself to be fraudulent. We don't stop basketball games when a player is called on a foul, nor do we stop having congressional sessions due to a Representative's misconduct.

In the future, as the past, scientific fraud will be detected when peers are unable to replicate the results. And unfortunately, this self-policing mechanism has been disengaged in our country because the Federal Government isn't supporting the research.

The fact that one scientist apparently procured egg donations without appropriate attention to the welfare of the patients doesn't mean that everyone else will do the same. Women have a right to donate eggs for the benefit of others when properly informed and with informed consent.

It is incumbent on the United States, where both the quality of science and dignity of life are of uppermost concern in all of our minds, to take the lead in creating an appropriate framework for stem cell research while promoting and protecting its progress.

On behalf of my family and the more than 1 million Americans with Parkinson's disease who would benefit from this research moving forward, I appreciate the opportunity to provide testimony to the subcommittee today.

[The prepared statement of Mr. Brown follows:]

Joe Brown
Parkinson's Action Network State Coordinator, Texas
March 7, 2006

Thank you, Mr. Chairman and members of the subcommittee for inviting me today. My name is Joe Brown. I am a state coordinator for the Parkinson's Action Network, a founding member and vice-president of Texans for the Advancement of Medical Research and a founding member of The Alliance for Medical Research. I have been an advocate for twenty years.

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I have lived 70 years with a genetic heart condition that has sudden death as its most significant side effect. Having been fortunate enough to survive 3 heart attacks, bypass surgery, cardiac arrest and cancer, I have reason to "hope"– especially since I have benefited from research that was thought to be wrong and unethical. I was the ninth person in the United States to have a procedure that took me from being unable to walk from one room to another and with days filled with countless hours of angina, to being able to carry my grandchild up a flight of stairs.

This procedure, which actually gives the patient a heart attack to reduce obstructive heart muscle, was originated by a Swiss cardiologist. Switzerland didn't believe that giving heart attacks was ethical and wouldn't allow the procedure. The quality of my life was improved because Dr. Sigwart was forced to leave his country, just as American scientists are doing today in order to pursue stem cell research.

So, yes, as a patient, I do have hope that SCNT will succeed. But it is not "unjustified" hope. The breakthroughs have been exciting and amazing, but I recognize that sound research takes time. It took 52 years for the polio vaccine to get to market. I don't expect the scientific community to have these treatments or cures available in my lifetime, but if we don't start now the cures won't be there for our children and grandchildren.

When I visited the University of Texas Medical Branch in Galveston, scientists working with adult stem cells told me that the most significant advances in adult stem cell research have occurred since embryonic stem cells were first isolated in 1998. The reason the

scientists gave me is that the embryonic stem cells are teaching them how to work with adult stem cells. To promote one form of stem cell research to the exclusion of another is counterproductive.

I am astounded that there are those who don't recognize, that while there may be fraudulent researchers, by definition, it is impossible for research in and of itself, to be fraudulent.

We don't stop basketball games when a player is called on a foul, nor do we stop having congressional sessions due to a Representative's misconduct. In the future, as in the past, scientific fraud will be detected when peers are unable to replicate the results. Unfortunately this self-policing mechanism has been disengaged in our country because the federal government isn't supporting the research.

The fact that one scientist apparently procured egg donations without appropriate attention to the welfare of the patients doesn't mean that everyone else will do the same. Women have a right to donate eggs for the benefit of others.

It is incumbent upon the United States, where both quality of science and dignity of life are of uppermost concern, to take the lead in creating an appropriate framework for stem cell research, while promoting and protecting its progress.

On behalf of my family and the more than one million of Americans with Parkinson's disease who would benefit from this research moving forward, I appreciate the opportunity to provide testimony to the Subcommittee today.

Mr. SOUDER. Thank you, and whenever you feel you need to head to the airport——

Mr. BROWN. It is going to be a little while.

Mr. SOUDER. Now, I did the full introductions. But Dr. Beeson and Dr. Mathews, I need to swear you in yet. So if you will both stand and raise your right hands.

[Witnesses sworn.]

Mr. SOUDER. Let the record show that both Dr. Beeson and Dr. Mathews responded in the affirmative. And I will go to Dr. Beeson.

STATEMENT OF DIANE BEESON

Ms. BEESON. Thank you, Chairman Souder, Representative Cummings, and committee members. I appreciate being invited to testify today.

My name is Diane Beeson. I am medical sociologist and professor at California State University, East Bay. For over 30 years, I have conducted research on social issues related to genetics and new reproductive technologies. I am a lifelong supporter of women's abortion rights, and I support embryonic stem cell research using embryos left over from IVR treatments.

Like many social scientists, I have broad concerns related to the wisdom of developing cloning technologies. However, today I will focus on the most immediate social and ethical problems created by the demand for human eggs needed in experimental cloning, or SCNT, and that is the threat to women's health.

Dr. Hwang and his colleagues used over 2,000 eggs without producing even one clonal embryo. This means we still do not know how many thousands or tens of thousands of eggs this research may require before achieving even preliminary success. Furthermore, it has become clear that payment, coercion, and lying were used to acquire the eggs that the media reported many women were eager to donate.

Because egg extraction has come into expanded use since the birth of the Nation's first test tube baby in 1981, it is often assumed to be safe. Unfortunately, this is not the case. The fact is that egg extraction as currently practiced poses inadequately understood but clearly significant risks to the health of women.

As you have heard from Ms. Norsigian, extraction of eggs involves introducing powerful hormones into a woman's body to manipulate it into producing many eggs at a time rather than the normal one or two. It often uses drugs not approved for this process, off-label, or drugs for which no long-term safety data are available.

The FDA currently has on file over 6,000 complaints regarding Lupron alone, including 25 reported deaths. These complaints must be investigated and analyzed before more women are exposed to such potential dangers.

We know that a coalition of Korean women's organizations is suing their Government for damage to the health of Korean egg providers. Scientific replication will not help these women.

We should understand that the problems related to egg extraction are not unique to Korea. I have included with my testimony a letter from the mother of a young woman who died an agonizing death from Ovarian Hyperstimulation Syndrome in Dublin in 2003.

Last April in London, another young woman dropped dead from a massive heart attack at a bus stop, linked directly to OHSS.

While such events appear to be rare, it is possible that many deaths and other longer-term side effects have simply not been linked officially to the egg extraction procedures that preceded them. And if we look at the history of the use of hormones in this country, with DES particularly, we find that it often takes 30 years and hundreds of thousands of women being hurt by these things before they are taken off the market.

A former Chief Medical Officer of the FDA, in a letter I have attached to my written testimony, reminds us that, "Studies to date have not ruled out a possible link between stimulation drugs and increased risk of ovarian cancer."

Another destructive consequence of ovarian hyperstimulation for women may be serious abnormalities in their children. Just this month, a new study reports that ovarian hyperstimulation treatment in mice results in several significant abnormalities in their later offspring. One in particular is associated, in humans, with an increased incidence of deformities and cancer.

These concerns must be investigated before involving thousands of women in egg extraction purely for research purposes. Informed consent to participate in egg extraction is not possible without first following up on these serious warnings, particularly in the context of research.

Informed consent is also made difficult by the fact that scientists and other proponents of SCNT have been reluctant to confront forthrightly the dangers related to egg extraction. Certainly in California this has been the case.

This reluctance is a function of conflicts of interest resulting from recent legal changes affirming the right to patent genetically engineered life forms, and also allowing universities and their researchers to patent even those research products funded by the Federal Government. As a result, the field of embryonic stem cell research has become a virtual biotech gold rush.

Under these conditions, it is highly unlikely that any regulation can adequately manage the ethical quagmire created by moving forward with SCNT. As a society, we are at a turning point in our relationship to science. We are being asked to make women the servants of biotechnology rather than insisting on a biotechnology that promotes the well-being of all people.

For these reasons, until we understand more fully its human costs, I strongly urge your support for a moratorium on somatic cell nuclear transfer in both publicly and privately funded contexts. Thank you.

[The prepared statement of Ms. Beeson follows:]

Subcommittee on Criminal Justice, Drug Policy and Human Resources
Statement by Diane Beeson, PhD
March 7, 2006

Chairman Souder, Representative Waxman, and Members of the Committee, thank you for inviting me to testify today on exploitation, fraud, and ethical problems related to human embryo cloning and embryonic stem cell research.

My name is Diane Beeson. I am a medical sociologist and Professor Emerita of Sociology at California State University, East Bay. I received my PhD at the University of California, San Francisco (UCSF) and was a Pew Postdoctoral Research Fellow at UCSF's Institute for Health Policy Studies. I have a long-standing professional interest in reproductive genetics and have worked at UC Berkeley's Center for the Study of Social Change on several federally funded studies on the social implications of genetic technologies. I have also been a Visiting Fellow at Stanford University's Center for Bioethics and have served on many review committees for the Human Genome Research Institute's Ethical, Legal and Social Implications Research Program. I am currently an affiliated scholar with the Institute on Biotechnology and the Human Future at the Illinois Institute of Technology and the Chicago-Kent College of Law.

First, I would like to emphasize that I am a life-long supporter of women's abortion rights and I support embryonic stem cell research using embryos left over from IVF treatments. However, in 2004 when the California Stem Cell Initiative was placed on the ballot asking voters to authorize $3 billion in state bonds for research that prioritized the development of human cloning technologies, I decided to speak publicly about my concerns and became a founder of the Pro-Choice Alliance Against Proposition 71.

Like many social scientists I have broad concerns related to the wisdom of developing cloning technologies. However, my comments today will focus on social and ethical problems created by the demand for human eggs needed in experimental cloning, a process also known as somatic cell nuclear transfer, or SCNT. Specifically, the concerns I will raise today are related to the exploitation of women necessary for the development of SCNT. These are the same problems that have been uncovered in the scandal surrounding Dr. Hwang's research and that we can expect to persist wherever SCNT is pursued.

Dr. Hwang Woo-suk's original claim to have successfully used SCNT to create a human embryo from which stem cells were extracted was first announced in February 2004. California was then in the early stages of a $35 million political campaign and media blitz to assure voters that if they supported massive public funding of this research miracle cures would soon be available for an unlimited list of lethal disorders.

Initial reports indicated Hwang's team used 242 human eggs to create one embryo in 2004. Then in 2005 he claimed to have generated "11 patient-specific stem-cell lines with a success rate of 1 line for approximately every 20 oocytes."[1] This created the illusion that significant progress had been made in bringing down the number of eggs SCNT would require. It has now been revealed that Dr. Hwang used over 2000 eggs in his discredited research.[2] His failure to produce even one cloned embryo reminds us that we still do not know how many thousands, or possibly even millions of eggs it may require to perfect SCNT. Furthermore, it has become clear that payment, coercion, and lying were used to acquire the eggs that we were told many women were eager to donate.

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[1] Snyder, E.Y. and J.F. Loring. Beyond Fraud—Stem-Cell Research Continues. *New England Journal of Medicine* 2006; Vol. 354, No. 4, pp. 321-324.
[2] Steinbrook, R. Egg Donation and Human Embryonic Stem Cell Research. *New England Journal of Medicine* 2006; Vol. 354, No. 4, pp. 324-326.

Californians, influenced by irresponsibly inflated claims of imminent cures, reinforced by excitement over Hwang's fraudulent research successes, have already cast their votes to massively fund SCNT; but the public has yet to be adequately informed about the human costs of such research. Today I would like to make three points in that regard:

1. Egg extraction as currently practiced poses inadequately understood, yet clearly significant, risks to the health of women.

2. Under current conditions informed consent to participate in egg extraction for research purposes is not possible.

3. The same social conditions that drive the demand for women's eggs set the stage for other violations of the public trust.

In light of this situation, I support the call for a moratorium on SCNT. This is a position supported by the feminist pro-choice women's health organization, Our Bodies, Ourselves, the California Nurses Association,[3] and many other pro-choice progressives.

To explain my position, let me begin with a brief background on egg extraction. Because such practices have come into expanded use since the birth of the nation's first test tube baby in December 1981, it is widely assumed that they have been proven to be safe. Unfortunately, this is not the case.

Extraction of multiple eggs involves both ovarian suppression and what is known as "ovarian hyperstimulation" using powerful hormones into a woman's body to manipulate it into producing many—often a dozen or more—eggs at a time rather than the normal one or two. The mature eggs are then collected for use in infertility treatments, in vitro fertilization, or research.

Contrary to common assumptions, these procedures have not been adequately studied. For example, one drug commonly used in egg extraction, Lupron, has not been approved for this purpose, but rather is used off label. Another such drug, Antigon, has been approved for such use, but no data are available on its long-term safety.[4]

As Suzanne Parisian, former Chief Medical Officer of the Food and Drug Administration, explains, "Pharmaceutical firms have not been required by either the government or physicians to collect safety data for IVF drugs regarding risk of cancer or other serious health conditions despite the drugs having been available in the United States for several decades." [5]

The FDA currently has on file over 6000 complaints regarding Lupron, including 25 reported deaths.[6] These complaints must be investigated and analyzed.

In the absence of long-term follow-up it is impossible to assess accurately the seriousness of the risks to women's health from the expanding use of egg extraction. One study reports that up to 14 percent of patients undergoing ovarian hyperstimulation experience some form of ovarian hyperstimulation syndrome, or OHSS.[7] This is a condition whose pathophysiology remains unclear. Common symptoms of

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[3] See Appendix A. California Nurses Association Position Statement on Embryonic Stem Cell Research.
[4] See Appendix B. Letter from Dr. Suzanne Parisian, Former Chief Medical Officer, FDA. Also on-line at http://www.genetics-and-society.org/resources/items/200502_letter_parisian.html.
[5] See Appendix B.
[6] Lazar, Kay. Wonder Drug for Men Alleged to Cause Harm in Women. *Boston Herald*, August 22, 1999.
[7] Hugues, in Vayena, E. *et al.* (eds). *Current Practices and Controversies in Assisted Reproduction.* World Health

mild OHSS include abdominal discomfort, ovarian enlargement, nausea and vomiting. Those who develop severe OHSS may experience a wide range of serious conditions including loss of future fertility, kidney or multiple organ failure, and death. The frequency of severe OHSS is estimated to be as high as 10 per cent of women who undergo the procedure.[8]

We don't yet know the full extent of the damage to the health of the Korean women who provided the eggs used by Dr. Hwang. But we do know that a coalition of 35 women's groups is suing the South Korean government on behalf of women who have been harmed in the process of egg extraction. Reports are that about 20 percent of the donors have experienced side-effects.[9] We also know that serious problems with egg extraction are not unique to the Korean experience.

Jacqueline Rushton, who died as a direct result of OHSS in Dublin, Ireland, in 2003, suffered a gradual deterioration of her organs, virtually all of which were slowly destroyed.[10] Temilola Akinbolagbe, a young woman who died last April in London, suffered a more sudden death from a massive heart attack linked directly to OHSS.[11]

While such events seem to be rare, it is possible that many deaths and other longer-term side effects of ovarian hyperstimulation have simply not been linked officially to the egg extraction procedures that preceded them. For example, Dr. Parisian reminds us that "studies to date have not ruled out a possible link between stimulation drugs and increased risk of ovarian cancer." She concludes that it is very likely that "those promoting SCNT research may be unknowingly tackling a far more costly and serious health burden by allowing the expanded use of current IVF stimulation drugs for SCNT." [12]

One of most destructive consequences of ovarian hyperstimulation for women may be serious abnormalities in their children. Just this month a new study reports that ovarian hyperstimulation treatment in mice results in several significant abnormalities in their later offspring. These effects include growth retardation, a delay in ossification (bone development) and an eight-fold increase in a significant rib deformity. This particular deformity in humans is associated with an increased incidence of abnormalities and cancer. Because of these associations, the authors conclude that it is possible that their findings may have implications for the use of ovarian hyperstimulation treatments in women. This question must be answered before involving thousands of women in ovarian hyperstimulation purely for research purposes.[13]

Scientists and other proponents of SCNT have been reluctant to confront forthrightly the dangers related to egg extraction. This reluctance has been demonstrated repeatedly in recent California politics. For example, during the campaign to pass Proposition 71 its proponents took legal action in an effort to

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Organization, Geneva, Switzerland, pp 102-125 (2002).

[8] Magnus, D. and M.K. Cho. Issues in Oocyte Donation for Stem Cell Research. *Sciencexpress/www.sciencexpress.org* May 19, 2005, p.1.

[9] Hwa-young, Ova Donors Demand Compensation from Government. *AsiaNews.it.* 2-7-2006. www.asianews.it/view_p.php?1=en&art=5322

[10] See Appendix C. Letter from Rushton's mother. Mrs. Angela Hickey.

[11] Woman died after starting IVF treatment. Richmond & Twickenham Times. 20 April 2005. http://www.richmondandtwickenhamtimes.co.uk/mayor/other/display.var.589076.0.0.php

[12] See Appendix B

[13] Steigenga, MJ, et al. Evolutionary Conserved Structures as Indicators of Medical Risk: Increased Incidence of Cervical Ribs After Ovarian Hyperstimulation in Mice. *Animal Biology*, vol 56, No. 1, pp. 63-68 (2006). See Appendix D for full text.

prevent opponents from explaining in the state Voters' Guide that the measure involved human embryo cloning, requiring thousands of women's eggs.[14]

Although efforts to keep this information out of the Voters' Guide failed, the heavily funded campaign nevertheless successfully undermined broader public dialogue on this issue. It did so by incorrectly characterizing all opposition to the measure as motivated primarily by concern with the moral status of the embryo. To the very limited extent that the term "cloning" entered the discussion, it was invariably inaccurately termed "therapeutic cloning," in spite of the fact that no therapies have yet been associated with SCNT. It was not until the election was over that the press began to raise many of the ethical problems implicit in the initiative.

A series of recent legal developments have fueled scientists' reluctance to confront ethical difficulties with SCNT. In 1980, the U.S. Supreme Court, in *Chakrabarty v. Diamond,* affirmed a right to patent genetically engineered life forms.[15] In the same year, Congress passed the Bayh-Dole Act, which allowed universities and their researchers to patent even those research products funded by the federal government.[16] As a result, the field of embryonic stem cell research has become the focus of a virtual biotech gold rush, inevitably creating gross conflicts of interest.

These conflicts of interest have been built into the structure of the newly established California Institute of Regenerative Medicine (CIRM). For example, at least half of its inaccurately named governing board (Independent Citizen's Oversight Committee [ICOC]) represent institutions likely to conduct stem cell research. In addition, at least seven of the 29 ICOC members have significant business relationships, including substantial equity investments and board memberships, with companies involved in stem cell research.[17]

California's Stem Cell Initiative campaign illustrates how the need to secure massive amounts of funding has led advocates to obscure major scientific and technical obstacles to the research. These include difficulties in restricting the potential of embryonic stem cells to desired differentiated types, as well as their tendency to form tumors in adult hosts.[18]

Disclosures to women who are being asked to take significant risks to their health and fertility by making altruistic donations of eggs should not be limited to acknowledging potential negative consequences to the donor's health. They should also reveal the researchers' intent to develop patents using these donated eggs and the potential of these patents to harm the public health and to impede other research. These problems with patenting have been described in detail by Andrews.[19]

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[14] Memorandum of Points and Authorities in Support of Petition for Writ of Mandate and Alternative Writ of Mandate/Order to Show Cause. (7-28-04, Case No. 04C501015) Paul Berg, Robert Klein, and Larry Goldstein, Petitioners vs. Kevin Shelly, Secretary of State of California, Respondent, Geoff Brandt, State Printer; Bill Lockyer. Attorney General of California ; Tom McClintock; H. Rex Green; John M. W. Moorlach; Judy Norsigian; Francine Coeytaux; Tina Stevens; Does I through X, inclusive, Real Parties In Interest. See also Declaration of Dr. Stuart A. Newman, PhD. In Opposition to Petition for Writ of Mandate and alternative Writ of Mandate/Order to Show Cause.

[15] 447 U.S. 303(1980).

[16] For the Bayh-Dole legislation see, Government Patent Policy Act of 1980, Pub. L. No. 96-517, 94 Stat. 3019.

[17] Reynolds and Darnovsky, Reynolds, J. and M. Darnovsky, et al. *The California Stem Cell Program at One Year: A Progress Report.* Center For Genetics and Society. January 2006, p 26. http://www.genetics-and-society.org

[18] Newman, S. A. (2003). Averting the Clone Age: Prospects and Perils of Human Developmental Gene Manipulation. *J. Cont. Health Law and Policy* 19, 431-463.

[19] See Appendix E. Andrews, L.B. "Genes and Patent Policy: Rethinking Intellectual Property Rights." Nature Reviews/Genetics, Vol. 3, October 2002.

Until financial conflicts of interest are brought under control we can expect the pursuit of profit to trump humanitarian concerns in determining the directions science takes. We also can expect continuing challenges to established ethical norms. The conflicts of interest and pressures that existed for Dr. Hwang and his colleagues, two of whom were American, are not unique to Korea. They operate very strongly within the borders of the United States as well.

Some liberal and progressive supporters of stem cell research who are concerned with preventing these abuses have argued that what is needed is "public sector bodies with the power to establish and enforce comprehensive regulations that apply to both publicly and privately funded research."[20] They call for prohibitions on payments to egg providers except for out-of-pocket expenses to prevent the emergence of a market in eggs, a requirement that egg extraction be carried out by those not involved in stem cell research, and follow-up medical care to treat adverse reactions that women who provide eggs suffer.

However, due to rampant conflicts of interest among those involved in the field, I have serious doubts that any regulatory structure could avoid implicitly condoning SCNT, and therefore it would be ineffective in protecting women's health. Proposed regulations are particularly silent on the long-term threats to the health of egg providers, for which researchers must be held responsible.

As a society we are at a turning point in our relationship to science. We are being asked to make women the servants of biotechnology, rather than insisting on a biotechnology that promotes the well-being of all people. For these reasons, until we understand more fully its human costs, I strongly urge your support for a moratorium on SCNT.

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[20] Reynolds, J. and M. Darnovsky, et al. The California Stem Cell Program at One Year: A Progress Report. Center For Genetics and Society. January 2006, p 17. www.genetics-and-society.org

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Evolutionary conserved structures as indicators of medical risks: increased incidence of cervical ribs after ovarian hyperstimulation in mice

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Abstract—The presence of a rib on the seventh cervical vertebra (a cervical rib) represents one of the most common intraspecific variations of the number of cervical vertebrae in mammals. Cervical ribs are highly associated with stillbirths, congenital abnormalities and embryonal tumours. These associations indicate strong stabilising selection against such a change to the highly conserved number of cervical vertebrae in humans. We propose, therefore, that the presence of variation for this highly conserved trait can be used as an indicator of medical risks. We have tested for prolonged effects of controlled ovarian hyperstimulation treatments (OHS) in mice by analysing the frequency of cervical ribs in the offspring of females that had received OHS treatment. We found that OHS treatment in mice had several significant effects on the offspring after adjusting for multiple pregnancy: these included an increase in cervical rib incidence, gestational period and nest size, and a decrease in birth weight and ossification, indicating growth retardation.

The high incidence of cervical ribs in the OHS group compared to the control group (39.5% vs. 4.7%) indicates that the OHS treatment affects embryogenesis during a period that is highly sensitive to disturbance, the early organogenesis stage (phylotypic stage). This implies that in mice OHS treatment of the mother has a prolonged effect and continues during early pregnancy.

Keywords: cervical ribs; evolutionary conservation; homeotic transformation, IVF; organogenesis; ovarian hyperstimulation; Barker hypothesis.

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INTRODUCTION

The number of cervical vertebrae is remarkably constant in mammalian species and is nearly always seven. Nonetheless, variations frequently occur within species and there is, therefore, extremely low interspecific variation, as well as high intraspecific variation (Galis, 1999). We have earlier hypothesised that conservation of the number of cervical vertebrae is due to strong selection against changes of this number due to association with negative pleiotropic effects (Galis, 1999; Galis and Metz, 2003). The presence of cervical ribs (a transformation of the seventh cervical vertebra into a thoracic one, hence a decrease in the number of cervical vertebrae) is one of the most common anomalies in human stillbirths and occurs in up to 50% of stillborn foetuses (Noback and Robertson, 1951; Meyer, 1978; Galis et al., subm.). This implies strong selection against variation in the number of cervical vertebrae. In addition, cervical ribs in humans are associated with an increased incidence of abnormalities and cancer (Gladstone and Wakeley, 1931-1932; Narod et al., 1997; Schumacher et al., 1992; Galis and Metz, 2003). In mice, cervical ribs can be induced at embryonic days 7-8 (Abdulrazzaq et al., 1997), at the beginning of the sensitive early organogenesis stage (Galis and Metz, 2001). Cervical ribs, therefore, appear to be a good indicator of disturbances of early organogenesis that presumably lead to medical risks.

Controlled ovarian hyperstimulation (OHS) in humans is frequently used in ovarian stimulation and ovulation induction to enhance the chance of becoming spontaneously pregnant, but also as part of assisted reproductive technologies. Assisted reproductive technologies are frequently associated with an increased frequency of spontaneous abortions, congenital anomalies, low birth weight, preterm birth and perinatal mortality, albeit with a low prevalence (Helmerhorst et al., 2004; Jackson et al., 2004; Bonduelle et al., 2005; Hansen et al., 2005). Similar abnormalities have been found for OHS treatment alone (Olivennes et al., 1993; Brinton et al., 2004). A low birth weight, often reflecting a disturbance early in life, is associated with cardiovascular diseases later in life (Holt, 2002; Phillips, 2002), an association first hypothesised by Barker (Barker, 1992). In addition, early embryogenesis is, in general, the most sensitive period for disturbances (Galis and Metz, 2001). Ovarian hyperstimulation and other assisted reproductive techniques, therefore, may disturb early embryogenesis, including the very sensitive phase of early organogenesis. To investigate possible effects of OHS treatments on early embryogenesis, the frequency of cervical ribs in the offspring of female mice with and without OHS treatment was measured, and used as an indication of disturbance of early embryogenesis.

MATERIALS AND METHODS

Virgin adult female CD1 mice (8-10 weeks, Charles River, Germany) were randomly assigned to the different experimental groups and mated with randomly assigned CD1 males. Each male mated only once. Females were used irrespective of

the day of the cycle and 142 were intraperitoneally injected with Metrodin (purified urinary hFSH; 5 units in 0.1 ml saline; Serono, Coinsins, Switzerland) at 12:00 and 48 h later with Pregnyl (urinary hCG; 5 units in 0.1 ml saline; Organon, Oss, The Netherlands). Control females (n = 115) received saline injections. Females were examined every morning for vaginal plugs indicating fertilisation (day of detection was considered as embryonic day (E.D. 0)). After birth the mother and newborn mice were weighed. For the control group 115 females were exposed to males, and for the OHS group 142, resulting in 38 (33.04%) and 53 (37.32%) conceptions, respectively. For the experiments, nests of five females were used for each group. Directly after birth, newborn mice were euthanised (peritoneal Nembutal injection), fixed in 4% formaldehyde and stained in a 0.2% silver nitrate solution for 2 weeks. X-ray photographs were taken (15 A, 20 kV, 20 s) and analysed for the number of cervical and thoracic vertebrae. X-ray photographs with insufficient staining were excluded from analysis. All animal experiments were in accordance with governmental guidelines for care and use of laboratory animals and approved by the Animal Care Committee of the University of Leiden.

RESULTS

The OHS group had a more than eight-fold increased incidence of cervical ribs compared to the control group (39.5% of OHS-treated mice showed cervical ribs vs. 4.7% in the control group, $\chi^2 = 19.14$, df = 2, $P < 0.01$, table 1). Part of the increased incidence of cervical ribs was due to the larger litter size in the OHS group, as there was a significant positive correlation between the incidence of cervical vertebrae and the weighted average of litter size between nests from the OHS group ($R^2 = 0.12$, df = 1, $F = 48.52$, $P < 0.01$). The OHS treatment was responsible for at least part of the increased incidence of cervical ribs, because there was also a significant increase in the smaller nests of the OHS group (within the size range of the control group) compared to those of the control group (Log Linear Model, $G^2 = 9.32$, df = 1, $P < 0.01$, litters <20 individuals).

The duration of pregnancy was longer (10.32%) in the OHS group than in the control group (ANOVA, df = 1, $F = 177.99$, $P < 0.001$, table 1) but, despite the longer pregnancy length, there were no significant differences in weight of the offspring (Pearson = 0.032, $P > 0.05$) and growth was thus slower in the treatment groups. Females from the OHS group had a significantly, although only moderately, larger average litter size (32.46%) compared with the control group (control litter size = 15.25, OHS litter size = 20.20, ANOVA, df = 1, $F = 22.88$, $P < 0.01$). In the OHS group the average weight of an individual at birth was negatively correlated with the litter size, but not in the control group (OHS group: $R^2 = 0.74$, df = 1, $F = 134.28$, $P < 0.01$, control group: $R^2 = 0.024$, df = 1, $F = 1.45$, $P > 0.1$). The absence of a litter size effect in the control group may have been due to the smaller size of the nests, i.e., there may be a threshold before litter size negatively affects weight.

Table 1.
Effects of OHS treatment on mice.

	OHS (N)	Control (N)	df	F	P
Incidence of cervical ribs in the total number of offspring per group (OHS and Control)	39.53% (n = 62)	4.65% (n = 61)	2	$\chi^2 = 19.14$	<0.01
Average duration of pregnancy, days (mean value ± standard error, SE)	20.96 ± 1.46 (n = 5)	19.0 ± 0 (n = 5)	1	177.99	<0.001
Average litter size (mean value ± SE)	20.20 ± 7.10 (n = 5)	15.25 ± 3.23 (n = 5)	1	22.88	<0.01
Average weight of siblings, grams (mean value ± SE)	1.39 ± 0.31 (n = 111)	1.43 ± 0.15 (n = 79)	1	6.97	<0.01
Average weight of mothers, grams (mean value ± SE)	38.78 ± 0.18 (n = 6)	35.57 ± 0.43 (n = 5)			
% new-born mice not analysed (rejection X-ray photographs, delayed ossification)	44.14% (n = 111)	22.78% (n = 79)	2	$\chi^2 = 21.77$	<0.01

The OHS treatment had an effect on individual weight. When comparing the weighted average individual nestling weight, corrected for the influence of litter number on litter weight, the weight at birth of individuals was significantly lower (2.80%) in the OHS group than in the controls (General Linear Model, df = 1, $F = 117.098$, $P < 0.01$).

Significantly more individuals from the OHS group could not be analysed compared to the control group (93.42%) due to insufficient staining of the X-ray photographs, indicating a delay in ossification at birth in the OHS treatment group (44.1%, $N = 111$ vs. 22.8 %, $N = 79$, $\chi^2 = 21.77$, df = 2, $P < 0.01$, table 1). The delay in ossification appears to be due to a direct effect of the treatment itself, because in the OHS group there was no significant difference in rejection rate of photographs between larger litters (larger than the average litter size for the control group, >15) and smaller ones (ANOVA, df = 1, $F = 2.96$, $P > 0.05$). Furthermore, in the smaller litters of the OHS group the rejection rate was also higher than in the control group (49.1% vs. 22.8%, respectively). However, this difference was not significant, presumably due to the low number of small litters in the OHS group (ANOVA, df = 1, $F = 3.26$, $P > 0.1$).

DISCUSSION

OHS treatment with urinary gonadotrophins in mice resulted in a significant increase in the frequency of cervical ribs in the offspring. In addition, we observed a prolonged gestational period, an increased litter size and a low birth weight, in agreement with earlier results on the effect of OHS treatment in mice (Ertzeid and

Storeng, 2001; Van der Auwera and D'Hooghe, 2001; Sibug et al., 2002, 2004). The prolonged gestational period and low birth weight in the treatment group indicate growth retardation. Ossification was also delayed by the OHS treatment, as apparent from the diminished response to silver nitrate.

In mice, cervical ribs are induced at E.D. 7 and 8, during the early organogenesis stage (Abdulrazzaq et al., 1997). The high frequency of cervical ribs, therefore, indicates that the OHS treatment affects early embryogenesis, a period that is highly sensitive to teratogenesis (Galis and Metz, 2001). This implies that, at least in our experiments with mice, the OHS treatment of the mother has a prolonged effect and continues during the early vulnerable stages of pregnancy. Although the response of mice to the OHS treatment may be different from those of humans undergoing OHS treatment, it is possible that similar processes take place in humans. The high incidence of cervical ribs in our experiments and the many associations of cervical ribs with serious abnormalities in humans suggest that these data may have implications for the use of OHS treatments in humans.

We propose that more general variations of highly conserved traits such as the number of cervical vertebrae and the number of digits (see Galis et al., 2002) may be useful as indicators of medical risks.

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To whom it may concern:

I am a former Chief Medical Officer of the Food and Drug Administration (FDA), as well as physician, Board Certified Pathologist, past researcher in genetics and developmental biology, author of *FDA Inside and Out*, and President of Medical Device Assistance, Inc., a regulatory and clinical consulting firm. I personally have been involved in drug, biotechnology and device human clinical trials and am familiar with United States requirements for ethical biomedical conduct. I write this memo for scientists, physicians, legislators, press, and public health advocates who have an interest in SCNT research. I strongly urge that sound ethical and medical practices are adopted regarding the manner in which eggs will be extracted from healthy women donors. Important facts for you to consider:

1. Although it is common practice in IVF facilities to extract eggs as part of infertility treatment, many of the drugs used during these procedures have not been adequately studied for long term safety, nor do some of these drugs have FDA approval for these specific indications. This is not widely understood and has led to significant misunderstanding about the risks involved for women who donate eggs, whether for reproductive purposes or for SCNT research.

Pharmaceutical firms have not been required by either the government or physicians to collect safety data for IVF drugs regarding risk of cancer or other serious health conditions despite the drugs having been available in the United States for several decades. Lack of FDA approval and/or review of these drugs as part of egg extraction procedures should be a major concern of anyone considering SCNT research.

2. The long term health risks for a woman receiving IVF drugs for egg retrieval are unknown.

A woman undergoing IVF stimulation today to conceive a child has accepted that there are "unknown" long term health risks to her body from the stimulation drugs but accepts the risks in terms of a potential benefit to conceive a child. The risk versus benefit calculation for a healthy woman providing her eggs for stem cell research is not the same.

The FDA has approved some of the stimulation drugs specifically for IVF stimulation. IVF stimulation approval was based on bioavailability studies in small numbers of healthy female volunteers, and studies of single cycle exposure in small populations of infertile women. There was no requirement for long-term follow up.

Regarding potential acute short-term risks which have been seen in stimulation trials submitted to FDA, severe Ovarian Hyper-Stimulation Syndrome (OHSS) occurs rarely - in about 3-8% of patients. This condition that results from over-stimulation of the ovary can progress rapidly to a serious life-threatening condition days after completion of egg collection. Based on symptoms, it is classified as mild (7%) or moderate to severe (1%). OHSS has been associated with death and has been reported in women with polycystic ovaries, in younger women, and in women with high estrogen hormone levels and after a woman receives either GnRH agonist or hCG. OHSS carries an increased risk of clotting disorders, kidney damage, and ovarian twisting. Ovarian stimulation in general has been associated with serious life threatening pulmonary conditions in FDA trials including thromboembolic events, pulmonary embolism, pulmonary infarction, cerebral vascular accident (stroke) and arterial occlusion with loss of a limb and death.

Risks of the egg retrieval procedure, although rare, include death, respiratory or cardiac arrest, brain damage, paraplegia, paralysis, loss of function of a limb or organ, hemorrhage, allergic reaction, and infection Bleeding or other injuries which occur during retrieval may require an invasive surgical procedure to correct and could affect future fertility.

Regarding the unknown long term risks, studies to date have not ruled out a possible link between stimulation drugs and an increased risk of ovarian cancer. All stimulation drugs are Pregnancy X - which means they are contraindicated for use in women that are pregnant due to a lack of information regarding the safety of these drugs during pregnancy.

As a scientist, physician, former FDA official, and clinical trial consultant, I understand why some have expressed enthusiasm for SCNT. However, as a physician, I cannot condone SCNT at the expense of a woman's health without giving her an opportunity for adequate informed consent and establishing a mechanism to ensure her safety. Women, scientists, policy makers, physicians, and funding organizations should require that pharmaceutical firms first disclose the actual FDA approved indications for drugs as well as all available safety data before multiple egg extraction from healthy female donors is pursued. All drug data should be reviewed by a neutral, knowledgeable, and independent oversight body whose sole purpose is to protect the safety and rights of healthy women wishing to participate in egg donation. Once such basic drug safety data have been gathered and reviewed, and a regulatory framework and monitoring system are in place, the risks and benefits of SCNT for healthy women can be better assessed.

In the meantime, extraction at the time of an ovariectomy or a tubal ligation offers a far safer and more ethical approach to begin collecting eggs for SCNT research. Even single egg extraction with natural cycling (no hormonal manipulations of the ovary) would be safer than conventional egg extraction procedures.

Additionally and importantly, any woman willing to provide eggs for research should have her own physician - someone not involved in any way with the research or the research institution and whose only job is to look out for the well-being of the woman.

Finally, there needs to be a mechanism in place for long-term follow-up regarding the health of women egg donors. This follow-up must be mandatory, and also under the aegis of the independent monitoring body. Such follow-up of the health of IVF donors has NOT yet been conducted by pharmaceutical firms or IVF physicians despite the long availability of these drugs and technology in the United States.

In conclusion, there is an unfortunate and false assumption of the public, legislators, press and physicians that all current IVF stimulation drugs have been scientifically recognized as "safe" by the FDA and suitable for use in healthy women for multiple egg extraction. That simply and sadly is not correct.

From a purely practical perspective, those promoting SCNT research may be unknowingly tackling a far more costly and serious health burden by allowing the expanded use of current IVF stimulation drugs for SCNT. It is wiser to first require pharmaceutical firms supplying the IVF drugs to provide adequate long term safety data.
It is in the best interests of everyone - including patients, researchers and potential egg donors - for all women contemplating donating their eggs to be treated according to the highest ethical and medical standards, and for their rights and safety to be protected.

Thank you,

Suzanne Parisian, MD

OPINION

Genes and patent policy: rethinking intellectual property rights

Lori B. Andrews

Concerns about human gene patents go beyond moral disquiet about creating a commodity from a part of the human body and also beyond legal questions about whether genes are unpatentable products of nature. New concerns are being raised about harm to public health and to research. In response to these concerns, various policy options, such as litigation, legislation, patent pools and compulsory licensing, are being explored to ensure that gene patents do not impede the practice of medicine and scientific progress.

Although gene patents have been granted worldwide for several years, the wisdom of this action is now being questioned. Lawsuits, proposed legislation, international protests and even patent-office proposals have recently been initiated to eliminate, undermine or otherwise challenge the scope of patents on human genes. The challenges come from various interested parties — people from whom patented genes have been isolated, researchers who wish to undertake genetic epidemiological studies or to develop gene therapies, clinicians and health-care providers who cannot afford expensive licensing fees for genetic tests and policy-makers who want to ensure that the patent system actually meets its goal by encouraging invention. Evidence is mounting that gene patents are inhibiting important biomedical research, interfering with patient care and provoking criticisms from international trading partners.

So far, the US Patent and Trademark Office (USPTO) and the European Patent Office (EPO) have treated isolated and purified nucleotide sequences as if they were the same as man-made chemicals[1] (BOX 1). Although many believe that human genes should not be viewed with such a cavalier attitude[2,3], recent challenges to gene patents have moved beyond the initial moral concerns about making a commodity out of a part of ourselves. Now, the concerns are being expressed in terms of harm to public health and research. These concerns have generated debate and the exploration of policy options to ensure that gene patents do not impede the practice of medicine and the progress of science.

In my view, the decision to allow patents on human genes was inappropriate, both legally and as a matter of sound policy. The useful properties of a gene's sequence (such as its ability to encode a particular protein or its ability to bind to a complementary strand of DNA for diagnostic purposes) are not ones that scientists have invented, but instead, are natural, inherent properties of the genes themselves. Moreover, in my opinion, gene patents do not meet the criteria of non-obviousness, because, through *in silico* analysis, the function of human genes can now be predicted on the basis of their homology to other genes. In addition, as a matter of policy, human nucleotide sequences should not be patentable, even if their function is known, because such scientific information should be available to all.

The foundation of patent law

Industrialized nations worldwide share a belief in the importance of a strong patent system. Such a system was put in place in the United States two centuries ago in the US Constitution to create incentives for technological innovation. Article I of the US Constitution gives Congress the power "to promote the Progress of Science and useful Arts, by securing for limited Times to Authors and Inventors the exclusive Right to their respective Writings and Discoveries". Because the constitutional provision is vague, the US Congress determines the types of incentive that are necessary to encourage invention and ensure that the public receives a sufficient benefit from the temporary monopoly granted to the inventor.

Under US federal patent law, an inventor has the right to exclude others from making, using or selling his or her invention for 20 years from the date of the application. For a gene to be patented, the patent applicant must show that his or her invention is useful, non-obvious and novel. The usefulness of the inventions must be specific, substantive and "credible". The patent application must also be adequately "enabling". That is, it must describe the invention fully, in a way that would allow another person who is skilled in that field to reproduce the invention. This requirement is particularly important because one of the purposes of patent law is to ensure that the public gets information in exchange for the monopoly granted to the patent holder. When a patent is granted, the information in it becomes public. Other inventors can then use that information to further their own research. Other inventors, however, cannot make or use the patented invention itself without the permission of the patent holder. In the United States — unlike in Europe — the inventor has no duty to actually "work" (use or develop) the invention.

The US patent laws are designed to ensure that the public benefits from a new invention in exchange for the monopoly. The laws do

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Box 1 | **The legal basis for gene patents**

Although products of nature are not patentable, various courts have upheld patents on isolated and purified natural substances. The 1912 case of Parke-Davis versus H. K. Mulford[18] upheld a patent on adrenaline, a natural hormone that was found in animal glands. The patent applicant identified, isolated and purified the active ingredient — adrenaline. This created a product that did not exist in nature in that precise form and that could be used for medical treatment.

The US patent office holds that a human gene as it occurs in nature cannot be patented. However, if a DNA sequence is purified and isolated in the form of a cDNA or is part of a recombinant molecule or vector, then this 'invention' is patentable under the precedent of the adrenaline case[1].

not allow patents on products of nature because the public would not be gaining anything new. Also, patents are not allowed on scientific formulas. As the US Supreme Court has pointed out, "The laws of nature, physical phenomena, and abstract ideas have been held not patentable. Thus, a new mineral discovered in the earth or a new plant found in the wild is not patentable subject matter. Likewise, Einstein could not patent his celebrated law that $E = mc^2$; nor could Newton have patented the law of gravity. Such discoveries are 'manifestations of ... nature, free to all men and reserved exclusively to none'"[4].

Genes straddle the boundary between patentable and unpatentable substances. As Rebecca Eisenberg, Professor of Law at the University of Michigan, USA, notes, "DNA sequences are not simply molecules, they are also information. Patent claims to information — even useful information — represent a fundamental departure from the traditional patent bargain"[5]. That bargain originally allowed a patent on an invention in exchange for the disclosure of useful information in the application to spur on other inventors.

Effects on diagnosis and treatment

Gene patents have attracted capital investment to the biotechnology industry. That makes business sense, but not, in my view, policy sense. The very exclusivity of a patent — the monopoly power of its holder — has created problems in medical and scientific fields. For 20 years from the date that a gene patent was filed, gene-patent holders can control any use of 'their' gene; they can prevent a doctor from testing a patient's blood for a specific genetic mutation and can stop anyone from doing research to improve a genetic test or to develop a gene therapy based on that gene.

For example, Athena Neurosciences, Inc., which holds the patent on a gene that is associated with Alzheimer disease — the apolipoprotein E (*APOE*) gene (US Patent No. 5,508,167) — will not allow any laboratory except its own to screen for mutations in that gene[6]. Doctors and laboratories across the country face a lawsuit if they try to determine whether one of their patients carries this genetic predisposition to Alzheimer disease, even though testing can easily be done by anyone who knows the sequence of the gene, without using any product or device made by the patent holder.

In 2001 the US company Myriad Genetics was granted a European patent related to the *BRCA1* breast-cancer-associated gene. The patent (EP699754) covers all methods for diagnosing breast cancer by comparing a patient's *BRCA1* gene with the *BRCA1* gene sequence that Myriad describes in its patent[7]. Myriad is now asserting that no French doctor or scientist should be allowed to test for *BRCA1* gene mutations; instead, the company requires that all samples be sent to Myriad's laboratory[8]. However, French physicians are concerned that such a mandate compromises patient care. They allege that Myriad's test only assesses 10–20% of potential *BRCA1* mutations[9]. Indeed, a French physician has recently identified a mutation in an American family that the Myriad test had missed[9]. Moreover, geneticists in France can offer genetic tests for breast cancer for less than the US $2,680 fee per test that is charged by Myriad. It is both the breadth of Myriad's *BRCA1* patent and the company's refusal to grant licenses for *BRCA1*-mutation detection that has led to concerted and international opposition.

Exclusivity in diagnosis can also impede research. Various mutations in the same gene can cause a particular disease. But companies that do not let anyone else screen a gene sequence that they have patented for other mutations lessen the chance of other disease-associated mutations being found, as often occurs when many laboratories screen the same gene. In countries where the *APOE* gene that is associated with Alzheimer disease and the *HFE* gene that is associated with haemochromatosis have not been patented, researchers have found previously unknown mutations[10,11], which can be used to diagnose people who would not otherwise be diagnosed.

Companies now also sequence and patent the genes of disease-causing bacteria and viruses. This gives them the power to prevent others from introducing inexpensive public health genetic testing for a common infectious disease, for example, or from undertaking genetic research on the disease. The possibility of patenting human genes and the genomes of disease-causing bacteria and viruses has led Tufts University policy professor Sheldon Krimsky to comment that "the intense privatization of biomedical knowledge that has evolved since the 1980s threatens the entire edifice of public health medicine"[12].

Gene patents also hamper pharmacogenomic research. Many drugs work on only a percentage of patients who use them. Genetic testing can help to distinguish those patients for whom a drug will work from those for whom it will not. But such tests will also reduce the market for certain drugs. For example, a pharmaceutical company, GlaxoSmithKline, Plc, has filed for a patent on a genetic test to determine the effectiveness of one of its drugs, but will not develop the test, or let anyone else develop it, possibly because such a test would cause the company to lose customers[13].

Research to find additional genes that are responsible for diseases is also impeded by gene patents. In one reported example, the search for a gene that is related to autism was impeded because researchers from several prominent American universities would not share DNA samples from affected children and their families; each university wanted to capitalize on being the one to discover and patent the gene that is associated with the disease[14]. In response, families of patients with autism founded Cure Autism Now (CAN), which, through its fundraising efforts, has raised US $5 million to create a DNA bank, called the Autism Genetic Resource Exchange, that is available to all scientists who are willing to work on finding the gene or a cure for autism.

Gene patents also undermine the scientific method. Researchers who discover and patent genes have financial incentives to promote the use of those genes for diagnostics as rapidly as possible, sometimes before sufficient data are available to assess how well a test predicts future disease. The patent examiner has to take what the applicant says as correct, and there is no Food and Drug Administration review in the United States when a company offers a genetic test as a service. If a patent holder states that one in three people in the population have the gene

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mutation that is covered by its patent, the patent holder can actually prevent others from duplicating the patent holder's research and evaluating it. In one survey, 14 out of 27 gene-patent holders said that they would require a license for researchers to study the prevalence of mutations in the patented gene in the population[15]. Even if the patent holder allows research by other scientists, the licensing costs might prevent other researchers from doing the necessary epidemiological studies to determine, for example, the proportion of people in the general population who carry a gene mutation and who will actually develop the disease. Some entities that offer patented genetic tests have already apparently exaggerated the prevalence of certain diseases, possibly to scare people into being tested[16].

Economic effects on research

Patenting genes can impede invention and health care in other ways too. Gene patent holders have prevented some researchers from searching for cures for genetic diseases. A researcher who wants to find a cure for breast cancer would have to negotiate with not only the patent holder for the full wild-type *BRCA1* and *BRCA2* genes, but with all of the other patent holders who have discovered and patented any of the hundreds of other mutations in these genes.

The granting of patents on parts of genes or different alleles creates a tangle of rights that can impede innovation. It is the policy of the USPTO that the discoverer of a gene should not be able to undertake mutation testing or the development of a product that is based on that gene without the permission of the holders of any patents on expressed sequence tags (ESTs) created from that gene[1]. The EST patent holder could withhold consent entirely or charge a fee. According to John Doll, Director of Biotechnology Examination at the USPTO, "The USPTO views this situation as analogous to having a patent on a picture tube. The picture-tube patent does not preclude someone else from obtaining a patent on a television set. However, the holder of the picture tube patent could sue the television set makers for patent infringement if they use the patented picture tube without obtaining a license"[1]. But I find this analogy troubling. Other inventors can create alternatives to the picture tube, and a consumer can do without a television. There are no alternatives to the patented human genes in genetic diagnosis and gene therapy — and these inventions might mean the difference between life and death to the consumer.

> "'Patent claims to information — even useful information — represent a fundamental departure from the traditional patent bargain' ... [that] allowed a patent on an invention in exchange for the disclosure of useful information in the application to spur on other inventors."

Michigan law professors Michael Heller and Rebecca Eisenberg have discussed how patents can deter innovation in biomedical research by stifling research innovations early on in the product development process[17]. Economist Carl Shapiro elaborates on the problems created by a 'patent thicket'. Using traditional economic analysis, he has shown how, when several monopolists exist that each control a different raw material needed for development of a product, the price of the resulting product is higher than if a single firm controlled trade in all of the raw materials or made the product itself[18]. However, the combined profits of the producers are lower in the presence of complementary monopolies. So, if there are several patent holders whose permission is needed to create a gene therapy (and any one of them could block the production of the gene therapy), inefficiencies in the market are created, potentially harming both the patent holder and the patent users.

Gene patents do not seem to be necessary to encourage technology transfer in the move from gene discovery to the availability of a genetic diagnostic test. As soon as information about the discovery of the haemochromatosis gene was published, laboratories began testing for mutations in the gene. After a patent on the gene was granted 17 months later, 30% of the 119 US laboratories that were surveyed reported discontinuing or not developing a genetic test for the disease[19]. The patent holder was asking for an up-front fee of US $25,000 from academic laboratories and as much as US $250,000 from commercial laboratories, plus a fee of US $20 per test[19]. The patent interfered with clinical use of the test and potentially compromised the quality of testing by limiting the development of higher quality or lower cost testing methods[19].

Professional organizations, such as the American College of Medical Genetics[20] and the College of American Pathologists, oppose gene patents as threatening medical advancement and patient care[21]. The World Medical Association considers human genes to be part of "mankind's common heritage" and urges medical organizations around the world to lobby against gene patenting[22]. This mounting concern about gene patents has lead to policy initiatives through litigation, legislation and administrative action.

Litigation

In the United States, the patent system is a three-way relationship among the USPTO, the courts and the Congress. All three have roles to ensure that the goals of the patent system are met and that the monopoly granted is not too broad. Most often, this means that the courts and the Congress reduce the breadth and scope of patents granted by the USPTO. For example, when Samuel Morse convinced the USPTO to grant him a patent on all uses of electromagnetic waves, the Supreme Court ruled that he could not patent every conceivable use of electromagnetic waves[23]. He could only patent his invention — the telegraph.

In addition, the Director of the USPTO has the authority to order patents to be re-examined. In the 1970s, the USPTO denied patents on software. When, in 1981, the US Supreme Court ruled that software was patentable subject matter[24], the USPTO lacked examiners with expertise in this area to evaluate these types of patent and, as a result, issued many patents that were criticized as being over-broad[25]. In response, the USPTO undertook more than 40 re-examinations of software patent claims that it had issued. These re-examinations resulted in the rescission of existing claims and the establishment of rules to narrow markedly the scope and breadth of these types of patent claim in the future.

There has yet to be a definitive legal case to address directly whether human genes are an appropriate subject matter for a patent in the first place. Rather than challenging the patenting of genes *per se*, the court cases on gene patents are generally battles between two entities (such as a university and a biotech company) about who has rights to a particular patent. There is no incentive for either side to challenge whether a gene patent is an inappropriate patent on a product of nature because each side wants to reap the financial rewards of a gene patent. The member of the public who could end up paying a high fee to learn genetic information about himself or herself — or be denied

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that information altogether — rarely has legal standing in the United States to bring a lawsuit to challenge the patentability of human genes. Although a physician, researcher or laboratory could challenge the patentability of human genes, various financial and institutional constraints have generally acted against this. Legal challenges against patents are financially expensive. A physician challenging a patent can expect to pay upwards of US $500,000 in attorneys' fees alone[26]. For a laboratory, it might be cheaper to pay for a license to use a gene — and pass that cost on to the patients who are tested — than to initiate a legal challenge.

Consequently, it is quite remarkable that any court challenges to gene patents are taking place. However, recently, legal assaults on gene patents were launched on two fronts. The first type of case was brought by patients against researchers and their institutions in cases in which the defendants did not specifically disclose their intentions to patent a gene that they isolated from their patients. The patients rely on precedents that require physicians/researchers to disclose potential financial conflicts of interest to the patient/research subjects in advance of undertaking the research[27]. One such suit, concerning the aspartoacylase gene, which is mutated in Canavan disease — a rare, genetic, neurodegenerative disorder that occurs most frequently in Ashkenazi Jewish families — is now pending in the federal court in Chicago. (I am a public interest (pro bono) attorney for the plaintiffs in this case.)

The second type of legal challenge, typified by that mounted by the French, contests aspects of the patentability of genes and raises policy concerns about the effects of gene patents. In October 2001, the Institut Curie in France challenged Myriad Genetics' European patent (EP 699754) on the *BRCA1* gene on the grounds of alleged lack of novelty (because predisposition tests for breast cancer on the basis of indirect methods were available before the Myriad patent); lack of inventiveness (as the gene sequence that was patented by Myriad was based, in part, on information from public genome databases); and inadequate description (because there were errors in the original sequence published by Myriad)[3] (see online link to the Institut Curie). On 22 February 2002, the Institut Curie initiated a challenge to another Myriad patent, EP 705903, on *BRCA2*. The governments of Belgium and the Netherlands intend to challenge that same patent as well (see online link to the Institut Curie). Geneticists in those countries issued a joint statement that, if gene patents were not narrowed or eliminated, "the monopolies on genes and genetic testing will wreck the reimbursement system and negatively influence health care."

Other challenges to gene patents might also try to narrow the claims that are made in patent applications. In some cases, the patent applicant has been granted rights not only to the mutations in a gene that he/she discovered, but also to any other mutations discovered later by other researchers. In other instances, the patent gives the applicant rights to all possible functions of the encoded proteins. In still other cases, patents have been granted on all methods of comparing the sequence of a high-risk individual with a known normal sequence, even though the patent has only described one method. The breadth of such patents could be challenged on the grounds that the patent has not sufficiently described all of the mutations, functions or methods that the patent holder has claimed rights to.

Legislation

Because the US Constitutional provision encouraging inventors is quite general, the actual provisions of patent law are enacted by Congress and can be modified by that body. It is not uncommon for the US Congress to limit patent rights in the public interest[28]. For example, a statute gives the federal government 'march-in' rights[29]. When a federally funded patentee has not made the invention available to the public within a reasonable time or when "action is necessary to alleviate the health or safety needs which are not reasonably satisfied" by the patentee, the government can license the patent to third parties. In addition, under the Clean Air Act, courts can, when necessary, order compulsory licensing of patents on equipment or technology used in air pollution control on reasonable terms to ensure competition[30].

The US Congress is considering a proposed law (BOX 2), introduced by Members of Congress Lynn Rivers and Dave Weldon (a physician), which would amend the federal patent statute to exempt health-care providers that are involved in genetic testing from patent infringement liability, so that their ability to diagnose patients is not compromised by gene patents. Also, because there is no statutory research exemption to patent infringement in the United States (and because rare exemptions that have been recognized by the courts have been extremely narrow), the bill, if passed, would allow non-commercial researchers to be exempt from liability for the use of patented genes. It is quite common internationally to have exceptions to patent laws. For example, the European Patent Convention Article 53(a) prohibits patents for "inventions the exploitation of which would be contrary to 'ordre public' or morality." Other inventions that the European Union's Biotechnology Directive consider to be unpatentable include processes for cloning human beings, processes for modifying the germ line of human beings; and uses of human embryos for industrial or commercial purposes[31].

Box 2 | **US legislative initiatives to reform patents on genes**

On 14 March 2002, members of the US Congress Lynn Rivers and David Weldon proposed a new law that would exempt health-care providers who carry out genetic testing from being sued by holders of patents on genes. This proposed bill, the Genome Research and Diagnostic Accessibility Act of 2002 (REF 39), aims to exempt two groups from patent infringement: first, medical practitioners and related health-care entities that provide genetic diagnostic, prognostic or predictive tests, and second, scientists that undertake non-commercial genetic research. The bill also requires that patent applications involving a genetic sequence discovered with federal funds are made public within 30 days of a patent application being filed[39].

Rivers and Weldon also introduced a companion bill — the Genomic Science and Technology Innovation Act of 2002. This proposed bill directs the Office of Science and Technology Policy (OSTP) to initiate a study of the effect of federal policies on the discovery and development of genomic technologies. This proposed bill is based on the presumption that federal intellectual-property laws and technology-transfer laws can stimulate the development of innovative genetic technologies by attracting commercial investment, but might also inhibit basic research and information sharing, thereby slowing innovation. Rivers' primary concern in drafting this bill was to assess whether gene patents are granted without an adequate understanding of their impact on innovation. The aims of this study are: to assess the impact of federal policies, including intellectual-property policies, on the innovation process for genomic technologies; to identify and quantify the actual and expected effects of patenting policy on genomic science and technology innovation; and to consider various alternatives for protecting intellectual property rights over genomic materials and their likely impact on genomic innovation.

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Exceptions in patent law to protect patients' access to health care and to protect doctors' liability have a historical basis in the United States. Originally, US patent law forbade patents on health-care inventions. Throughout the first 150 years of US history, the USPTO did not issue patents for methods used to diagnose and treat patients[26]. Such methods were not considered to be patentable subject matter by the medical profession, by the courts or by the USPTO because patents were granted for tangible inventions. Medical or surgical methods were not considered to fall in the scope of the statutory requirements until 1954, when the Board of Patent Appeals opened the door to patents on medical methods[32]. In the 1990s, such patents began to interfere with patient care. In 1996, the US Congress created an exception in the patent law so that health-care providers are not subject to patent infringement suits when they use a patented medical or surgical technique[33]. Eighty other countries already had such an exemption[34]. Until recently, many other countries did not even provide intellectual property protection to medicines and other pharmaceutical products[35]. Some developing countries had short periods of protection for such products (such as three years of patent protection in Thailand) to allow health needs to be met by the rapid introduction of generic drugs[35].

The Trade-Related Intellectual Property Rights (TRIPS) agreement of the World Trade Organization, promulgated in 1995, requires all of its international signatories to agree to provide a 20-year intellectual property protection for inventions (including those that are related to health care). But even TRIPS highlights how public health should be given greater weight than the commercial concerns of patentees. Article 27 of TRIPS specifically allows governments to exclude diagnostic, therapeutic or surgical methods from patentability. It also allows them to deny patentability of a particular invention to protect human life or health. Article 8 of TRIPS allows governments to take public health concerns into consideration in their national intellectual property laws, and Article 31 allows governments to ignore health-care patents in certain situations and to grant compulsory licenses (see next section) to third parties to produce a generic version of a health-care product. Under TRIPS, patents can be ignored in a public health emergency.

Patent pools and compulsory licensing

Policy options based on traditional patent law are also being explored, such as creating a patent pool — an agreement between two or more patent owners to license one or more of their patents to one another or to third parties. Patent pools are voluntary agreements among patent holders in which they gather all the necessary tools to practice a certain technology in one place, rather than obtaining licenses from each patent owner individually. One model to base this on is the pool created by the American Society of Composers, Authors and Publishers (ASCAP), which handles the licensing of music under copyright laws. Instead of having to negotiate with each holder of a copyright for thousands of songs, a radio station or bar can buy a blanket license from ASCAP and play any song from the pool at any time. In a similar way, a gene patent pool could extend non-exclusive licenses to all for set fees.

> "...court cases on gene patents are generally battles between two entities (such as a university and a biotech company) about who has rights... [t]here is no incentive ... to challenge whether a gene patent is an inappropriate patent on a product of nature because each side wants to reap the financial rewards..."

Patent pools are particularly appropriate when patent exclusivity is being used contrary to the public's interest. During the First World War, the Assistant Secretary of the US Navy, Franklin D. Roosevelt, pressured the aircraft industry to form a patent pool to facilitate the production of aeroplanes[18]. Previously, the Wright–Martin Aircraft Company and the Curtiss Airplane and Motor Company were able to block such production owing to their control of key patents.

Compulsory licensing is also being explored as a way to counter some of the problems of gene patents. This system has been advocated by the French Minister of Research, Roger-Gérard Schwartzenberg (see online link to Institut Curie). Compulsory licensing is the granting of a license by a government to use a patent without the patent holder's permission. This approach, which might be necessary if gene patent holders did not voluntarily create patent pools, would require gene patent holders to allow physicians, researchers and others to use the patented gene sequence for a reasonable fee. Laboratories would be able to undertake genetic diagnostic testing using their own, as well as patented, tests, which could lead to the discovery of new mutations. Furthermore, pharmaceutical companies would not be able to prevent pharmacogenomic testing related to their products. Also, researchers could not be prevented by gene patent holders from undertaking research on gene therapies (or discouraged from undertaking such research through high licensing fees).

Compulsory licensing is clearly permissible under TRIPS, and the mere threat of it sometimes serves to drive down the costs of pharmaceuticals. When the South African government passed the Medicines and Related Substances Control Act in December 1997 to authorize the compulsory licensing of drugs, 40 drug companies initiated a lawsuit to overturn the act[36]. Subsequently, the companies agreed that the law could be enforced, dropped the legal challenge and negotiated to sell their products at a lower cost[37].

Conclusion

Whatever policies society develops for gene patents, policymakers will be influenced by the fact that the 'bio' in biotechnology — the genes in the gene patents — comes from people. Researchers need the trust of those whom they study to get access to their tissue for research into diagnostics and cures. Using the biological resources of the public (and a substantial amount of public funding), genes have been discovered and patented. Now, policy makers are being asked to ensure that the public receives the benefits.

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Online links

DATABASES
LocusLink: http://www.ncbi.nlm.nih.gov/LocusLink
APOE | aspartoacylase | *BRCA1* | *BRCA2* | *HFE*
OMIM: http://www.ncbi.nlm.nih.gov/Omim
Alzheimer disease | Canavan disease | haemochromatosis

FURTHER INFORMATION
American College of Medical Genetics: http://www.acmg.net
College of American Pathologists: http://www.cap.org
Cure Autism Now: http://www.canfoundation.org
European Patent Office: http://www.european-patent-office.org
Food and Drug Administration: http://www.fda.gov
Institut Curie: http://www.curie.fr
Trade-Related Intellectual Property Rights: http://www.wto.org/english/tratop_e/trips_e/trips_e.htm
US Patent and Trademark Office: http://www.uspto.gov
World Medical Association: http://www.wma.net
World Trade Organization: http://www.wto.org
Access to this interactive links box is free online.

SCIENCE AND SOCIETY

Human genetic technologies, European governance and the politics of bioethics

Brian Salter and Mavis Jones

With human genetic technologies now an important area of European research and development, bioethics is becoming increasingly important in its regulation and future. As regulatory decisions are also statements about who should get what, bioethics cannot avoid political controversy. Can bioethics sustain its claimed role as authoritative adviser to decision makers, or will its attempts to reach a consensus on human genetic technologies be perceived as the actions of an ambitious interest group? What, in short, is its political future in Europe and elsewhere?

In a 2002 report that outlines a strategy for the life sciences and biotechnology in Europe, the European Commission recognizes a fundamental tension at the heart of its policy. On the one hand, Europe has the scientific and industrial potential to be a global leader in new biotechnologies, including human genetic technologies. On the other hand, it acknowledges that "public support is essential, and ethical and societal implications and concerns must be addressed" if Europe is to benefit from these technologies[1]. Given the European public's reaction to genetically modified food and crops, there is no guarantee that the problems that beset one area of biotechnology will not affect another. When it comes to human genetic technologies, such as pharmacogenetics, gene therapy, predictive diagnostics and therapeutic cloning, will the necessary public support be there? It remains to be seen whether the health applications of genetic knowledge will be perceived by the public as being an issue that is distinct from GM food and crops[2].

Traditionally, public support for new technologies has been assured through governmental regulatory arrangements that have relied heavily on scientific advice about the risks that are associated with a particular technology. However, the public response to the bovine spongiform encephalopathy (BSE) crisis in the United Kingdom (when conflicting scientific advice was withheld from the public until it was too late to quell the epidemic, resulting in a subsequent wide-scale inquiry) and to GM crops in Europe and Asia (where public protests about GM foods, including the occasional destruction of seeds and crops, have achieved results such as mandatory product labelling) is testament to the general decline in the public's trust in scientific authority[3–6]. Ethical and cultural concerns have been thrown to the fore and new forms of public opposition[7–9] have emerged to challenge the efficacy of what is sometimes called "the technocratic approach" to regulation. Given the uncertainties that therefore beset this science-based approach, 'red' biotechnology, as the health genetic technologies are sometimes known, could prove to be as contentious as the 'green' biotechnologies of food and crops.

With the European Union's plan to expand its investment in genomics and

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Ladies and Gentlemen

I am the mother of Jacqueline Rushton who died as a direct result of in vitro fertilisation treatment in the Rotunda Hospital, Dublin,Ireland, on the 14th January 2003. I have never spoken in public before and hope you will appreciate how this is a very daunting task for me. I feel I owe this to my beloved daughter Jacqui whose only wish was to have a baby.

She put herself into the hands of experts and she lost her own life in her attempt to give life. These words were spoken at her funeral by the priest. At that time we knew something had gone terribly wrong, but had not got the knowledge we now have. She wanted her story told.

Jacqueline was a beautiful girl in every way. She was a healthy fit thirty-two year old who was longing for a baby. Her dream was to have a big family and stay at home at home and look after them.

In 2002 she went to her local G.P. to discuss fertility problems. It was discovered that Jacqui was not ovulating properly, that was her problem. She was referred to the Fertility Unit at the Rotunda Hospital in Dublin.

She and her husband paid 3,000 euro to the clinic and in November 2002 Jacqui commenced I.V.F. treatment. This meant inhaling a drug to put her into a false menopause. She forgot to take it one day while out shopping with her sister and laughingly said as she inhaled at the bus stop, 'Oh! I hope people won't think I'm a drug addict '.

She was excited about the prospect that she might find out that she was pregnant on Christmas Day, God love her!

She had to inject herself daily with Puregon, the ovarian stimulating drug. On day eight, 3rd Dec, her levels of estradial were three times higher than the highest level in the range.

There were two possible treatment options available:

To cancel or to cut down the drug and coast.

At no time were they told to cancel. Only coasting was advised which they did. By cutting down the estradial it was hoped to bring down the levels to a safe one for the administration of HcG, the drug which releases the egg, and which is the point of no return. They were never shown any figures of safe levels of Estradial or safe numbers of eggs.

I went to hospital with Jacqui on the 3rd Dec. The drug was cut to 100 units puregon. She was feeling very bloated and could hardly walk.

She spent her time in bed the week of the treatment and I brought all her meals up to her. She felt so sore and swollen. Jacqui was saying 'I never thought it would so hard to have a baby.'

On Day ten, but she received no injection, she was so overstimulated. When she went for her scan it showed multiple follicles and the promise of a large amount of eggs. Jacqui thought this was good news, as I did, demonstrating how little we knew about safety levels. I got talking to another girl while waiting. She was also in great distress,but not as bad as Jacqui.

She could not believe how awful a procedure it was turning out to be.

When the nurse came out with Jacqui she said laughingly, 'Oh! Here are the overstimulated ones'. They both had difficulty walking . Poor Jacqui! She was always so good humoured and tried to smile through all her pain.

That evening she even made us bring down the Christmas Tree from the attic. This was always her job and she didn't trust anyone else to get it just right. She had great taste and was very artistic. She sat on the couch and gave all her instructions but eventually she struggled even to kneel down. Her tummy was so tight and it hurt so much.

Jacqui and her husband went to the clinic on day eleven. At 10 o'clock that night Jacqui received the HcG Injection. Only a nurse was present. Her Estradial level was 22,500 pmols, more than twice the safety level. The Authorisation Form was signed by Professor Robert Harrison.

According to the Royal College Guidelines, Jacqui by then had an 80% chance of developing severe ovarian hyperstimulation syndrome, which is life threatening.

On Sunday 8th Dec Jacqui went in for the egg retrieval procedure. 33 eggs were retrieved. When she was brought from the theatre, the other girl who was waiting to go in next told me Jacqui was screaming in pain. It is heartbreaking to hear about your child's suffering.

Most patients go home after egg retrieval and fertilised eggs are implanted two days later in the womb. This couldn't happen for Jacqui. Hers had to be frozen, she was so hyperstimulated.

Everyday till Wednesday we just heard 'Jacqui is not coming home, she has mild hyperstimulation'. One of my daughters phoned me on the Wednesday and said 'Mam, there is something really wrong with Jacqui, she can hardly talk'. I panicked after that phone call and rang the sister in charge and finally got permission to see my daughter.

When I saw Jacqui propped up in the bed, she looked so frail, sick and terrified. She had an oxygen mask clamped to her face. She had a catheter, elastic stockings, a monitor and a drip. I got such a shock I ran over to her and put my arms around her as best I could and said Oh! Jacqui I love you so much. What has happened ? She tried to laugh at me, she hated to worry us. I went home that night and cried and cried. The family wouldn't believe she was that bad. I knew Jacqui was very seriously ill. I felt this awful feeling in my heart she was going to die.

We were being constantly told by Doctors and Nurses, 'She'll be alright. She will pass all this fluid out through her kidneys and she'll be grand. We can only monitor and support the symptoms.'

She just got worse every day. I went in on the Thursday. The other girl had also been admitted by ambulance to the hospital. She too was very ill and breathless but she recovered, thank God.

There have, by the way, been 97 cases of OHSS in the Rotunda between 1999 and 2003.

Jacqui was so ill. No one seemed to care, there was no sense of urgency, and nothing was done. She was filling up with fluid from her ovaries. Her lungs were inundated and her breathing was becoming nearly impossible. She was on a huge amount of oxygen. She couldn't eat, drink, sleep, and was constantly nauseous and breathless. Jacqui told me that every breath she took required every ounce of her energy. Her suffering was horrific.

I went in on Friday 13th Dec in the evening . Her husband and I were still the only visitors allowed. I was demented as her swelling was increasing alarmingly. Nurses bleeped doctors but none came. Finally at 11o'clock a drip was put up.

The next day Jacqui told me she was praying to her Guardian Angel when a passing Doctor noted her condition. She was blue from lack of oxygen and he had her admitted to the High Dependency Unit

On Monday I arrived to find Jacqui being prepared to be sent to the Mater General Hospital. I'll never forget that journey; oxygen mask clamped to her little face, terror in her eyes, she was so cold . The nurse and a young doctor tried to reassure me she'd be alright. None of them seemed to realise what severe O.H.S.S. meant.

In the General Hospital no draining of fluid was done initially. Her catheter was found to have been kinked and that seemed to relieve her slightly. She also got a feeding tube. She felt safer there and thought she would get better.

Her sisters and brothers could now visit. Jacqui's deterioration shocked them to the core. Jacqui said between gulps of oxygen, 'Oh Mam I feel awful, it's not getting any better'. Her husband arrived then and we had to go. She looked at me and said 'Mam don't go'. She just looked at us going out the door with her beautiful brown eyes. That was the last time we spoke to Jacqui.

Later that night we got a summons from the hospital. Her husband Danny, her Dad and I rushed in. Only her husband was allowed in. She was being put into a drug induced coma and being placed on a ventilator.

On Christmas Eve we all visited. She looked peaceful and rested on the ventilator. But on the 25th Dec her Dad and I were distraught when we saw her. She looked like a little waxen doll. I cried and said to the doctor and nurse who didn't seem to understand us, 'My daughter is going to die in this hospital'.

We were all sent for at 7o'clock the next morning. They had tried to move her in the bed and the fluid had moved over her heart. She had crashed. They revived her with adrenalin. That day over two litres of fluid were drained from her lungs, 23 days after admission. She had put on over two stone with the fluid.

We spent every minute at her side. Her brother Daniel stayed there nearly constantly praying holding her hand and willing her to live. Jacqui was very religious and had all her little tattered prayer leaflets with her.

But all Jacqui's organs were slowly destroyed. She had five holes in her lungs, five chest drains draining into five horrible buckets around her bed. Her kidneys started to fail, she couldn't take any nutrition, she was on industrial doses of antibiotics. Next we were told her eyes were fixed indicating brain damage They couldn't close her eyes with the swelling from the fluid, so her eyes had to be taped shut. Eventually her strong heart gave out and all the machines were switched off.

She died at 12 o'clock noon a slow agonising death from O,H.S.S. She had 33 eggs recovered, even though the safe level is well under 20. Five embryos survived; five little potential babies. They were baptised and were buried with Jacqui.

This is the nightmare that happened to my daughter who only wanted to have a baby. This is what we had and have to endure for the rest of our lives. Our carefree family life is gone, Jacqui is missing, destroyed by by unsafe I.V.F. treatment.

We as parents didn't know anything about I.V.F. or its dangers and felt it was the couple's own business what they did, and that we couldn't interfere. Our only worry was that they'd be disappointed if it didn't work.

I want to thank my family for all their research and help since Jacqui's death. They didn't want me to do this as it is so hard. My gut feeling was this is what Jacqui would have wanted, she was a fighter like me and I want justice, she deserves it.

After three nerve wracking inquests, we got a verdict of Medical Misadventure. The professional conduct of the consultant, Professor Robert Harrison, is now being investigated by the Fitness to Practice Committee of the Irish Medical Council.

At her enormous funeral some of the nurses attended. One of those wonderful human beings hugged me close and said its going to be very hard. I knew she meant the grief, and the quest for justice in Ireland, where you have to be a multi-millionaire to get it.

A girl who goes for I.V.F. treatment for infertility, is no different in effect from a girl choosing to donate her eggs for altruistic or financial reasons. They both have to go through the same invasive horrific drug-based treatment.

Why is natural fertility treatment not offered to patients? It should be available as a choice. It is much safer with no drugs. This is the truth. There is indeed an alternative to these harmful drugs, and couples could have their longed for babies, without the pain and risks which cost Jacqui her life.

Mr. SOUDER. Thank you very much for your testimony.

We will now go to Mr. Doerflinger. Thank you very much for joining us.

STATEMENT OF RICHARD DOERFLINGER

Mr. DOERFLINGER. Thank you, Mr. Chairman.

As we know, Korean researchers led by Dr. Woo Suk Hwang are now seen as having perpetrated a massive fraud, details of which have been ably described here by others. I think there are scientific, political, and moral lessons to be learned from this. Each point here is documented in my longer written statement I have submitted for the record.

First, the scientific lesson: Cloning researchers must go back to the drawing board. After 8 years of effort to clone human embryos, no one has achieved even the first step in using this procedure for human treatment, so-called therapeutic cloning.

Usually, fraud by one researcher does not discredit an entire field, but Dr. Hwang's studies were the field of allegedly successful human cloning for research purposes. If his research is a fraud, there is at present nothing left of that field. As the New York Times says, "Cloning researchers are back to square one."

This is, by the way, the third time in 8 years we have heard announcements of success in cloning human embryos for their stem cells, only to find the claim had little basis in fact. The other false starts, in 1999 and 2001, were by Americans. South Korea has no monopoly on misleading hype in this field.

And let me just say, the word "fraud" is used, and it is perfectly appropriate. But Dr. Hwang did not start as a fraud. He started as someone trying to make this work. And after years of attempt, endangering the health of 100 women, thousands of eggs, creating hundreds of embryos in the lab, with those tens of millions of dollars and the full Government support of South Korea, just like everyone else, he failed.

And that is why he was tempted, in his desperation, to commit fraud. He is the biggest fraud in this field, but the key word that is common to all the cloning researchers, is failure, failure, failure. And I heard some subcommittee members say, therefore, this is the very sort of thing the Federal Government has to get into funding.

Attempts at therapeutic cloning in animals have also been discouraging. In several studies, researchers achieved any therapeutic goal only by implanting the cloned embryos in an animal's uterus and growing it to the fetal stage, then killing it for more developed fetal stem cells.

Such fetus farming is now seen by some researchers as what they call the new paradigm for therapeutic cloning, and some State laws on cloning have even been crafted to allow such grotesque practices in humans. This would compound cloning's exploitation of women as egg factories by exploiting them as incubators for cloned humans as well.

What are the implications of embryonic stem cell research in general? There is a distinction. It depends on whether cloning is essential for progress in embryonic stem cells. Cloning supporters used to say it is essential. Now that judgment is being reversed.

Evan Snyder, in the New England Journal of Medicine, said cloning plays only a minor role. One recent overview called it a boutique science, at the fringe of stem cell biology. But if it is at the fringe, why not ban cloning now and have debates about the other issues in embryonic stem cells later?

It remains possible that someone will solve these programs someday. But the prospect of making the cloning procedure efficient, separating it from the exploitation of women, and deriving cost-effective therapies from it in your lifetime seems remote.

Second, the political lesson is that while there has been some misrepresentation in the scientific field, that has been magnified 10 times in the political field, in which in order to get public support in Government funding, supporters have acted more like snake oil salesmen than scientists at times, marketing the dream of miracle cures around the corner.

Researchers are now issuing disclaimers to reduce people's unrealistic expectations about cures and looking for other people to blame. Some have even blamed the Bush administration for the failure and fraud in South Korea, as though by opposing cloning, you are some how making somebody else elsewhere do it wrongly. But no one has ever done it rightly. To blame unethical cloning in Korea on those who warned against doing it at all takes blame-shifting to new depths.

The political lesson is that we need to be aware of the human cost of this agenda here and now, not only its alleged promise down the road. And we need to demand evidence for these grandiose claims.

Third, and most importantly, a moral lesson: Utilitarianism is not useful. The ethic of the end justifies the means, and particularly the creation and destruction of life in the laboratory in order to achieve the miracle cures, has unfortunately become almost the official ethic of those seeking to justify this research.

Government advisory panels have been forced to concede the early embryo is a developing form of human life, but used a cost/benefit analysis to argue that cures for born persons is worth more. As the chief ethicist at the NIH Human Embryo Research Panel said in 1994, "If the end doesn't justify the means, what does?"

The problem is that the utilitarian ethic relativizes truth just as quickly as it relativizes lives. If human embryos are lives in a biological sense but lack the value of persons, could be sacrificed to help born patients who really matter, then the merely factual truth can sometimes be sacrificed by the same ethic for the higher truth of progress. Dr. Hwang did not violate the new ethic of his allies. He took it to its logical and inevitable conclusion.

By demeaning life, we learn to demean truth, rendering science itself meaningless. If some researchers have not learned that important lesson, a sound ethical response must come from society and its policymakers. That response should begin with a complete ban on human cloning, and with legislation to prevent the mistreatment of women as egg factories for research, or as surrogate incubators for unborn children grown for their body parts.

Only by respecting fellow human beings of every age and condition, and by refusing to treat them as mere instruments for achiev-

ing our research goals, will we promote a human progress worthy of the name. Thank you.

[The prepared statement of Mr. Doerflinger follows:]

Testimony of Richard M. Doerflinger
on behalf of the
U.S. Conference of Catholic Bishops
before the
Subcommittee on Criminal Justice, Drug Policy and Human Resources
House Committee on Government Reform
March 7, 2006

"Human Cloning and Embryonic Stem Cell Research after Seoul: Examining Exploitation, Fraud, and Ethical Problems in the Research"

I am Richard M. Doerflinger, Deputy Director of the Secretariat for Pro-Life Activities at the U.S. Conference of Catholic Bishops. I also serve as Adjunct Fellow in Bioethics and Public Policy at the National Catholic Bioethics Center in Philadelphia. On behalf of the bishops' conference I want to thank this subcommittee for asking us to present our views on cloning and embryonic stem cell (ESC) research in light of the human cloning scandal in South Korea.

Korean researchers led by Dr. Woo-Suk Hwang, the only scientists in the world to convince the scientific community that they had cloned human embryos and derived ESCs from them, are now seen as having perpetrated a massive fraud. An investigative report by Seoul National University and other reports say that, contrary to past disclaimers, the team solicited over a hundred women (often with cash incentives) and even pressured female researchers to provide human eggs for cloning experiments, at serious risk to the women's health; that from over two thousand eggs the researchers failed to produce even one stem cell line despite hundreds of cloning attempts; and that they covered up their failure by falsifying two major articles in a prestigious U.S. science journal.[1]

In the United States, reactions to this scandal span a wide spectrum. Some cloning advocates have tried to imply that this event has no implications beyond the malfeasance of a few Korean researchers.[2] By contrast, a report from Seoul National University says the scandal has "damaged the foundation of science."[3] In our view the truth lies somewhere between these extremes. The scandal implicates far more than a few Korean scientists; it does not undermine science in general, unless one foolishly equates human cloning with all of science.

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[1] Seoul National University Investigation Committee, "Summary of the Final Report on Hwang's Research Allegation," SNU News, January 10, 2006, http://www.useoul.edu/sc_sne_b/news/1196178_3497.html. See also K. Tae-gyu, "Hwang Forced Researcher to Donate Eggs," *Korea Times*, January 3, 2006, http://times.hankooki.com/lpage/tech/200601/kt2006010316440911780.htm.

[2] "Despite this apparent setback, the field of embryonic stem cell research and therapeutic cloning remains incredibly promising as demonstrated by some of our nation's leading scientists." Coalition for the Advancement of Medical Research, "Statement of Daniel Perry, President, on Hwang/Schatten Cloning Paper Published in *Science* Magazine, June 2005" (December 15, 2005), www.stemcellfunding.org/camr_news.aspx?rid=121505A. In fact, no scientist has demonstrated that so-called therapeutic cloning is possible in humans, let alone has promise. The word "incredible" may be appropriate here in a way the author did not intend.

[3] Quoted in "S. Korea Cloning Research Was Fake," *BBC News*, December 23, 2005, http://news.bbc.co.uk/1/hi/world/asia-pacific/4554422.stm.

There are scientific, political, and moral lessons to be learned from this debacle.

1. Scientific Lesson: Back to the Drawing Board

The first obvious conclusion to be drawn from the scandal, as noted by the *Washington Post*, is that "the highly touted field of embryonic stem cell research is years behind where scientists thought it was."[4] After eight years of effort around the world to clone human embryos, no one has achieved even the first step in using this procedure for human treatments (so-called therapeutic cloning). Supporters' earlier predictions that such cloning would soon provide a ready source of genetically matched tissues for human clinical use were, to say the least, premature.

It is generally true that a discovery of fraud in one researcher's claims does not discredit an entire field. But in this case, Dr. Hwang's studies *were* the field of allegedly successful human cloning for research purposes. If his research is a fraud, there is (at present) nothing left of that field. As the *New York Times* has observed, "The technique for cloning human cells, which seemed to have been achieved since March 2004, now turns out not to exist at all, forcing cloning researchers back to square one."[5]

This is at least the *third* time in eight years that we have heard announcements of success in cloning human embryos for their stem cells, only to find that the claim has little basis in fact. The two previous false starts were announced by an *American* company, Advanced Cell Technology.[6] Americans should not look down on South Korean researchers, as though they have a monopoly on misleading hype in this field.

Most Americans, and most legislators, probably assume that there are at least established

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[4] A. Faiola and R. Weiss, "South Korean Panel Debunks Scientist's Stem Cell Claims," *Washington Post*, January 10, 2006, A9.

[5] N. Wade and C. Sang-Hun, "Human Cloning Was All Faked, Koreans Report," *New York Times*, January 10, 2006, A12.

[6] See J. Cibelli et al., "Somatic Cell Nuclear Transfer in Humans: Pronuclear and Early Embryonic Development," in *e-biomed: The Journal of Regenerative Medicine* 2.5 (November, 2001): 25–31, http://earthops.net/human-clones1.pdf. Although ACT's researchers only managed to bring one cloned embryo to the six-cell stage and obtained no stem cells, the company announced this as "the first proof that reprogrammed human cells can supply tissue for transplantation." ACT news release, November 25, 2001, www.sciencedaily.com/releases/2001/11/011126000857.htm. Some news reports were breathless: "Scientists have finally cloned a human embryo. The breakthrough promises cures for terrible diseases." J. Fischer, "The First Clone," *U.S. News and World Report*, December 3, 2001, 50. But outside experts judged it a "failure." G. Kolata, "Company Says It Produced Embryo Clones," *New York Times*, November 26, 2001, A14. In 1998, ACT said it had created "hybrid" clones by fusing human nuclei with enucleated cows' eggs, but could not produce plausible evidence of this. "Company 'cloned human cells,'" *BBC News*, November 13, 1998, http://newsrss.bbc.co.uk/1/low/sci/tech/213663.stm. An early report of human embryo cloning from South Korea, in December 1998, also could not be verified. "Did South Korean Doctors Clone Human Embryos?" *Global Situation Report*, February 10, 1999, www.gsreport.com/articles/art000012.html.

models for use of ESCs from "therapeutic cloning" in animals. But this is not the case. Some studies published by Advanced Cell Technology and others have been touted as showing benefits from stem cells harvested from cloned *animal* embryos—but in each case, the study had to achieve its therapeutic goal by implanting the embryo in an animal's uterus and growing it to the fetal stage, then killing the fetus for more developed *fetal* stem cells. Such "fetus farming" is now apparently seen by some researchers as the new paradigm for human "therapeutic cloning," and some state laws on cloning are crafted to allow just such grotesque practices in humans.[7]

In short, it may be that "therapeutic cloning" cannot be made to work without conducting the "reproductive cloning" that almost everyone condemns—placing embryos in women's wombs, in this case in order to abort them later for their more developed tissues. This would, of course, also compound cloning's exploitation of women as egg factories, by exploiting them as incubators for cloned fetal humans as well.

Other claimed advances for ESCs from cloning have turned out to be a "bait and switch" ploy—that is, the advance was falsely reported to have come from cloned embryos, but turned out not to involve cloning at all.[8] This ploy has even been used in what are generally seen as serious medical journals. Last summer, for example, the *New England Journal of Medicine* reported that "human nuclear-transfer embryonic stem cells" had been shown to produce new neural tissue in an animal model of brain damage.[9] The articles the author cited for this claim, however, clearly report using existing ESC lines from fertilized embryos—cell lines eligible for federal funds under the current Bush administration policy. The studies even received NIH funding under that policy.[10]

What are the broader implications for human ESC research in general? That depends on whether cloning is essential for future use of ESCs in therapies. The Biotechnology Industry Organization testified to Congress in 2001 that cloning *is* essential, and on that basis opposed

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[7] See USCCB Secretariat for Pro-Life Activities, "Research Cloning and 'Fetus Farming': The Slippery Slope in Action," March 18, 2005, www.usccb.org/prolife/issues/bioethic/cloning/farmfact31805.htm.

[8] When Rep. Dave Weldon (R-FL) said accurately in 2003 that there were no published animal studies showing the benefits of ESCs from "therapeutic cloning," his remarks were attacked as "asinine" by three pro-cloning scientists. But the studies they cited to rebut him all turned out not to involve cloning, or not to involve ESCs. See "Reality Check: Proof of 'Therapeutic' Cloning?" Do No Harm press release, March 10, 2003, www.stemcellresearch.org/pr/pr_2003-03-10.htm.

[9] A. Perry, "Progress in Human Somatic-Cell Nuclear Transfer," *New England Journal of Medicine* 353.1 (July 7, 2005): 88. The article also hailed Dr. Hwang's research as showing that use of ESCs from human cloning is a "viable clinical proposition" (87). It concluded, "While the United States remains rooted in atavism, Hwang and coworkers have shown that Asia is moving forward." *NEJM* ceased to be a credible journal in this field in July 2003, when it announced a new politically motivated editorial policy of specially "seeking out" manuscripts touting ESCs. "We want to be sure that legislative myopia does not blur scientific insight," wrote the editor, myopically. J. Drazen, "Legislative Myopia on Stem Cells," *New England Journal of Medicine* 349.3(July 17, 2003): 300.

[10] A. Perrier et al., "Derivation of midbrain dopamine neurons from human embryonic stem cells," 101.34 *Proceedings of the National Academy of Sciences* (August 24, 2004): 12543-8; V. Tabar et al., "Migration and Differentiation of Neural Precursors Derived from Human Embryonic Stem Cells in the Rat Brain," *Nature Biotechnology* 23.5 (May 2005): 601–6.

any complete ban on human cloning.[11] If BIO was right in 2001—and apparently it still thinks so, since the organization and its state affiliates continue to oppose complete human cloning bans and even to fight for public funding for so-called therapeutic cloning—then ESCs have been discredited as a route to therapies, at least for the time being. If BIO was wrong, and cloning is (in the words of one recent overview) "a boutique science, one at the fringe of the rapidly expanding world of stem cell biology,"[12] why not ban the egregious abuse of human cloning now and debate the other issues relating to ESC research separately?[13]

In this context we should note that many stem cell experts had been expressing grave doubts about the feasibility of large-scale "therapeutic cloning" even before the Hwang research was exposed as a fraud.[14] The latest news only confirms these doubts.

To be sure, other avenues for obtaining genetically compatible tissues for human therapies from ESCs also pose formidable practical as well as ethical problems. Certainly no scientist seriously believes that the current supply of "spare" embryos frozen in fertility clinics is adequate for any clinical use.[15]

Some propose creating genetically diverse "banks" of embryos produced by fertilization, in an attempt to provide a close genetic match to most patients. Two prominent researchers say that merely determining the "best options for research" (to say nothing of treatments) would require "perhaps 1,000" stem cell lines—about four times as many as are now available nationwide.[16] Others say that to reflect the genetic and ethnic diversity of the American

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[11] "Somatic cell nuclear transfer research is essential if we are to achieve our goals in regenerative medicine.... However, this is precisely the research that would be banned by the Weldon bill." Testimony of Thomas Okarma on behalf of the Biotechnology Industry Organization against H.R. 1644, "Human Cloning Prohibition Act of 2001," House Energy and Commerce Subcommittee on Health, June 20, 2001, http://energycommerce.house.gov/107/hearings/06202001Hearing291/Okarma450.htm.

[12] R. Monastersky, "A Second Life for Cloning," *Chronicle of Higher Education*, February 3, 2006, A16.

[13] A recent *New England Journal of Medicine* commentary, for example, fights against "the impression that stem cell biology has been discredited" by the Hwang scandal, arguing that cloning by somatic cell nuclear transfer "plays only a minor role in the wider discipline of stem cell biology." E. Snyder and J. Loring, "Beyond Fraud—Stem-Cell Research Continues," *New England Journal of Medicine* 354.4 (January 26, 2006):322–323. The journal's editor had said exactly the opposite in 2003, claiming that by approving a ban on human cloning the House of Representatives had voted to "ban research on, and the use of, medical treatments derived from embryonic stem cells." Drazen, "Legislative Myopia," 300.

[14] Many of these experts' quotes are compiled in USCCB Secretariat for Pro-Life Activities, "Practical Obstacles to 'Therapeutic' Cloning," November 4, 2004, with more recent updates, www.usccb.org/prolife/issues/bioethic/cloning/clonprob11404.htm.

[15] One widely cited study estimates that there were as many as 400,000 frozen embryos in fertility clinics as of April 2002. However, that study also found that 2.8 percent (or about 11,000) of those embryos were designated for possible use in research. Destroying all those embryos solely to obtain stem cells (deemed by the authors a "highly unlikely" scenario) might produce a total of 275 cell lines. D. Hoffman et al., "Cryopreserved Embryos in the United States and Their Availability for Research," in *Fertility and Sterility* 79.5 (May 2003): 1068.

[16] S. Hall, "Bush's Political Science," *New York Times*, June 12, 2003, A33.

population, an ESC bank geared toward treating any major disease must include cell lines from many embryos *created solely in order to be destroyed for those cells*—including a disproportionate number of specially created embryos from African-American couples and other racial minorities, who are underrepresented among fertility clinic clients.[17] Yet other stem cell researchers say "millions" of embryos from fertility clinics may be needed to create cell lines of sufficient genetic diversity.[18] Is anyone in Congress seriously committed to creating and destroying human embryos on such a massive scale?

In short, supporters of expanded federal funding for human ESC research may have an agenda without an exit strategy. If mass production of ESCs from human cloning poses enormous practical and ethical problems, and the same may be true of efforts to make ESCs "therapeutic" without cloning, no one should assume that ESCs are the Holy Grail of regenerative medicine. As to human cloning research itself, it of course remains possible that someone will solve the seemingly intractable technical problems and manage to make the procedure work; but the prospect of making it "efficient," separating it from the exploitation of women, and deriving cost-effective therapies from it in our lifetimes seems remote.

2. Political Lesson: No More Free Ride for the Cloning Bandwagon

While many researchers are beginning to appreciate that human cloning for medical research may be a failure, the world of politics is another matter. The political agenda for cloning has long been divorced from the facts, and this problem is, if anything, getting worse. It was *after* the last two years' "progress" in human cloning research was found to be illusory that a leading Senate advocate declared, "This is probably the most promising medical-health-care scientific research, as far as I'm concerned, in the history of the world."[19]

To win public support and government funding, advocates for human cloning and ESC research have long made hyped claims and exaggerated promises to legislators and the general public. In short, some scientists and science organizations have acted more like snake oil salesmen than scientists, marketing the dream of "miracle cures" around the corner—and people (other than politicians) are beginning to notice.

In 2004, the state of California witnessed an especially cynical and shameless campaign by researchers and venture capitalists to put the state over $6 billion into debt to fund this research. Only now are voters beginning to realize the truth:

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[17] R. Faden et al., "Public Stem Cell Banks: Considerations of Justice in Stem Cell Research and Therapy," 33.6 *Hastings Center Report* (November-December 2003): 13–27.

[18] R. Lanza and N. Rosenthal, "The Stem Cell Challenge," *Scientific American* (June 2004): 94. Another recent study, while noting that other solutions to the immune rejection problem might be found, agrees that the creation of a sufficiently diverse bank of ESC lines is "almost impossible." M. Drukker and N. Benvenisty, "The Immunogenicity of Human Embryonic Stem-Derived Cells," *Trends in Biotechnology* 22.3 (March 2004): 138.

[19] Sen. Orrin Hatch, quoted in Monastersky, "Second Life for Cloning," A16.

> Much of the California electorate was sold last year on the idea that human embryonic stem cells might be turned into amazing cures for incurable diseases, propelling Proposition 71 to easy victory in the Nov. 2004 election. Now, it's increasingly clear that stem cell transplants for diabetes or Parkinson's or Alzheimer's are nowhere close, maybe decades away.[20]

Leading supporters, afraid of political backlash, have been issuing disclaimers to reduce people's unrealistic expectations about this research's producing cures any time soon. In some cases they are also shifting the blame for those expectations onto others.

British stem cell expert Lord Winston has warned his colleagues that the political hype in support of ESCs and cloning needs to be reined in:

> One of the problems is that in order to persuade the public that we must do this work, we often go rather too far in promising what we might achieve. This is a real issue for the scientists. I am not entirely convinced that embryonic stem cells will, in my lifetime, and possibly anybody's lifetime for that matter, be holding quite the promise that we desperately hope they will.[21]

Interestingly, one of Lord Winston's scientific colleagues protested in response that this was not scientists' fault: "It is true that Alzheimer's is not a promising candidate for stem cell therapies, but it was not scientists who suggested it was—that was all politics in the U.S. driven by Nancy Reagan."[22]

But of course, in the United States Mrs. Reagan was backed by scientific groups who want public funding of ESC research. These groups must have known about the scientific consensus against an ESC therapy for Alzheimer's but chose to ignore it. One expert explained the discrepancy between political message and scientific fact by commenting, "To start with, people need a fairy tale."[23]

As the blame game continues, some cloning supporters have even made the hypocritical argument that the Bush administration is to blame for the Korean hoax. Because our government is not "paying for and regulating" ESC research of this kind, they say, the landmark research was done in another country with no safeguards.[24]

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[20] C. T. Hall, "Stem Cell Leaders to Talk Strategy at Conference," *San Francisco Chronicle*, September 30, 2005, B4.

[21] Professor Lord Winston, "Should We Trust the Scientists?" Gresham College Lecture, June 20, 2005, www.gresham.ac.uk/event.asp?PageId=39&EventId=347.

[22] Prof. Stephen Minger, quoted in M. Henderson, "Benefits of Stem Cell Research Oversold, Says Expert," *The Times* (London), September 5, 2005, www.timesonline.co.uk/article/0,,2-1764771,00.html.

[23] Dr. Ronald McKay, quoted in R. Weiss, "Stem Cells An Unlikely Therapy for Alzheimer's," *Washington Post*, June 10, 2004, A3, www.washingtonpost.com/wp-dyn/articles/A29561-2004Jun9.html.

[24] Arthur Caplan and Glenn McGee, "U.S. Must Support, Regulate Stem Cell Research," *Albany Times Union*, November 20, 2005, E1.

But every part of this argument is demonstrably false. Not only President Bush, but President Clinton and a seemingly unanimous consensus in Congress over the past decade have opposed funding the special creation of human embryos for research purposes.[25] Moreover, South Korea did in fact have laws and regulations in place to prevent the most egregious abuses—tighter regulations, allowing more independent oversight, than cloning supporters have built into their Proposition 71 in California—but these were simply ignored by researchers obsessed with reaching their goal.[26] In fact, although ethical concerns about Hwang's practices were raised by sympathetic critics in Korea and the United States when he published his 2005 study, U.S. researchers continued to enthuse about collaborating with him right up to the most recent reports of complete fraud.[27] To blame "unethical" cloning in Korea on those who warned against doing it at all takes blame-shifting to new depths.

The political lesson from the Korean scandal, and from scandalous behavior here in the United States, is that political leaders, patient advocacy groups, and all of us must stop hearing only what we want to hear about "miracle cures." We need to be aware of the human costs of this agenda here and now, not only its alleged "promise" down the road. And we need to ask cloning supporters to provide real evidence for their grandiose claims.

3. Moral Lesson: Utilitarianism Is Not Useful

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[25] President Clinton rejected such funding in an executive directive of December 2, 1994. Every year since then, Congress has annually approved a ban on funding any harmful human embryo research; and the only serious effort to weaken that ban, in 1996, would have left in place the funding ban on research involving cloning or other creation of embryos for research. Even the major bills seeking to overturn President Bush's policy on ESC research deal only with "spare" embryos produced by in vitro fertilization, and some of them explicitly state that "the research involved shall not result in the creation of human embryos" (e.g.,"Stem Cell Research Act of 2001," H.R. 2059 / S. 723, 107th Congress, 1st session). So this charge against President Bush only underscores how out-of-step the cloning movement is with virtually *all* federal policymakers.

[26] For example, an American bioethics journal published a paper detailing the Korean team's ostensibly careful protocol for ensuring the informed and uncoerced consent of women donating eggs for the research. Unbeknownst to the journal's editors and even the article's authors, however, that protocol was not followed in practice. The journal has now retracted the article. See G. McGee, "Editorial Retraction," *The American Journal of Bioethics* 6.1 (January-February 2006): W33, http://bioethics.net/journal/j_articles.php?aid=913.

[27] The issue of *Science* carrying Hwang's 2005 study also published an ethical analysis raising concerns about informed consent, the risks to egg donors who cannot benefit directly from the research, and even the use of the term "therapeutic cloning" to describe research that may be decades away from providing therapies. D. Magnus and M. Cho, "Issues in Oocyte Donation for Stem Cell Research," *Science* 308.5729 (June 17, 2005): 1747–1748, www.sciencemag.org/cgi/content/full/308/5729/1747. Korean ethicist Koo Young-mo raised similar concerns: "Let me raise a worst-case scenario. If some of the donors suffer from ovarian hyperstimulation syndrome and they bring Hwang to court with the dubious consent form, Hwang may be in trouble." Quoted in K. Tae-gyu, "Hwang Clones Patient-Specific Stem Cells," *Korea Times*, May 20, 2005, http://times.hankooki.com/lpage/200505/kt2005052009202652820.htm. Yet when Hwang offered to collaborate with U.S. researchers and provide them with ESCs from cloning, researchers like Dr. George Daley of Harvard responded enthusiastically: "Given the access that [the Koreans] apparently have to a very willing set of egg donors, they may be much more efficient at generating these cells than anybody else," he said. Quoted in S. Okie, "An Offshore Haven for Embryonic Stem-Cell Research?" *New England Journal of Medicine* 353.16 (October 20, 2005): 1647.

The third and most important lesson is moral.

Researchers, devoted to increasing human knowledge and bettering the human condition, have long been tempted to "cut corners" on ethics, including the ethics of protecting human research subjects, to achieve their admittedly important goals. A founder of modern scientific medicine, Dr. Claude Bernard, cautioned in 1865:

> The principle of medical and surgical morality … consists in never performing on man an experiment that might be harmful to him to any extent, even though the result might be highly advantageous to science, i.e., to the health of others. But performing experiments and operations exclusively from the point of view of the patient's own advantage does not prevent their turning out profitably to science.[28]

Likewise, in the wake of the grotesque German experiments of the 1940s, the Nuremberg Code insisted, "No experiment should be conducted where there is an a priori reason to believe that death or disabling injury will occur."[29]

Researchers in the United States have not always followed this moral principle. We have only to think of the Tuskegee syphilis experiments, the deliberate injection of hepatitis virus into mentally retarded children at the Willowbrook home, and the Cold War radiation experiments on unsuspecting Americans in the 1950s.

What is new in recent years is the dominance of a "new ethic" that would justify such abuses *in principle*[30]—a utilitarian calculus that relativizes and demeans human life and other values whenever they may get in the way of the research prize. Tragically, this new ethic of "the end justifies the means" has become virtually the official ethic of those seeking to justify destructive human embryo research and human cloning in both the public and private sectors.

For example, Peter Singer of Princeton University, hailed by some as the most influential ethicist in the world, recently predicted that the old ethic honoring the sanctity of life will effectively be dead by 2040—and that in retrospect, "2005 may be seen as the year in which that

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[28]C. Bernard, *An Introduction to the Study of Experimental Medicine* (1865), quoted in S. Post, *Inquiries in Bioethics* (Washington, DC: Georgetown University Press, 1993), 145.

[29]See "The Nuremberg Code (1947)" *British Medical Journal* 7070: 313 (December 7, 1996): 1448. The Code acknowledges one possible exception to this norm, which if taken absolutely could itself be problematic: "those experiments where the experimental physicians also serve as subjects." Researchers have a moral responsibility to respect their own lives as well.

[30] "The traditional Western ethic has always placed great emphasis on the intrinsic worth and equal value of every human life, regardless of its age or condition. This ethic has had the blessing of the Judeo-Christian heritage and has been the basis for most of our laws and much of our social policy.… This traditional ethic is still clearly dominant but there is much to suggest that it is being eroded at its core and may eventually be abandoned.… It will become necessary and acceptable to place relative rather than absolute values on things such as human lives." "A New Ethic for Medicine and Society," editorial, *California Medicine* 113.3 (September 1970), reprinted at www.bhhrg.org/CountryReport.asp?ChapterID=148&CountryID=18&ReportID=24&keyword=.

position became untenable," because people realize that a sanctity of life ethic would not allow us to benefit from the wonderful new breakthrough in cloning from South Korea![31] Singer is, of course, famous for his logical consistency in realizing that if life is not sacred before birth, it is not sacred afterward either.

Government advisory panels have been forced by the evidence to concede that the early human embryo is a "human life," because the evidence from embryology has only become more and more persuasive on that point.[32] They even concede that this life deserves our "respect."[33] Instead of concluding that experimental destruction of this life is off limits, however, they have used a cost-benefit analysis to argue that this respect is overridden by the health needs of born persons with devastating diseases.

When a member of the NIH Human Embryo Research Panel asked in 1994 whether the panel should really base its recommendations for federally funded embryo research on the principle that "the end justifies the means," the panel's chief ethicist quoted the man known as the father of situation ethics, Joseph Fletcher: "If the end doesn't justify the means, what does?"[34]

As a guide to its ethical approach, the NIH panel cited an article by this ethics co-chair, Prof. Ronald Green of Dartmouth. He argues in this article that there are no realities "out there" in human beings that require us to respect *anyone* as a person. It is the task of the educated and articulate members of society, he wrote, to decide which qualities in others are morally relevant, based on their own enlightened self-interest. If we deny "personhood" or moral worth to too many people, we may risk denying it to ourselves or others we care about; if we bestow it on too many people, we may deprive ourselves and other persons of the benefits of lethal experiments on those people.[35]

By this approach, if respecting a particular kind of human subject would prevent us from pursuing especially promising research, this is sufficient reason for refusing to respect that individual as a person. This approach turns the Nuremberg Code upside down: The dignity of a

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[31] P. Singer, "The Sanctity of Life," *Foreign Policy* (September–October 2005): 40.

[32] "What is clear," says one summary of recent findings, "is that developmental biologists will no longer dismiss early mammalian embryos as featureless bundles of cells." H. Pearson, "Your Destiny, from Day One," *Nature* 418.6893 (July 4, 2002):15.

[33] The National Institutes of Health Human Embryo Research Panel agreed in 1994 that "the preimplantation human embryo warrants serious moral consideration as a developing form of human life." *Report of the Human Embryo Research Panel* (Bethesda, MD: NIH, September 1994), x. And in 1999, the National Bioethics Advisory Commission cited broad agreement in our society that "human embryos deserve respect as a form of human life." *Ethical Issues in Human Stem Cell Research*, vol. I (Rockville, MD: NBAC, September 1999), ii, cf. 2.

[34] Ronald Green, quoted in Proceedings of the NIH Human Embryo Research Panel, Monday, April 11, 1994, transcript, 92.

[35] Ronald Green, "Toward a Copernican Revolution in Our Thinking about Life's Beginning and Life's End," *Soundings* 66.2 (Summer 1983): 152–173, cited in NIH, *Report*, 38 note 13.

human subject will never stop researchers from doing research they think is extremely promising, because the promise of the research justifies defining those subjects out of the community of persons so we can make use of them.

In theory, there are limits to such mistreatment of fellow humans under the New Ethic. In practice, the urge for results tends to swallow up all countervailing values, as it did in Korea. Even NBAC in 1999 conceded that "the derivation of stem cells from embryos remaining following infertility treatments is justifiable only if no less morally problematic alternatives are available for advancing the research."[36] But NBAC and its allies ignored the evidence available even then that such alternatives existed; and as stem cells from adult tissues and umbilical cord blood have saved thousands of lives and begun to treat dozens of conditions, they have only become more hardened against giving due attention to this progress.

In short, once one has used the unique medical promise of a certain approach to justify acts that everyone agrees *would otherwise be unethical*, one has a vested interest in resisting any evidence that may rebut that claim of unique promise. The result is that continuing to justify the initial ethically problematic agenda becomes an end in itself. To some U.S. researchers, therefore, the failure of the Korean experiment only means that they themselves *must* make cloning work, regardless of the human cost.

Dr. Michael West of Advanced Cell Technology, for example, says that the Korean fiasco presents a new opportunity for the United States to "take the lead" and show this can be done "ethically."[37] But as we have seen, this is the company that made the first two undocumented announcements of success in "therapeutic cloning" in 1999 and 2001; it is the company that now sees fetus farming as a new paradigm for human cloning; and the company's ethics committee is chaired by none other than Ronald Green, the leading advocate of "end justifies the means" thinking in this field.

Another U.S. researcher, now considering going back into the cloning field, says, "I have to admit that I decided not to push the efforts here at Stanford because it would have been almost unethical to work with human eggs if [Hwang] had made the process so efficient."[38] Consider this logic. Now that Dr. Hwang has shown that you may bribe or pressure over a hundred women to donate over two thousand eggs, and still have nothing to show for it, this failure may make it *ethical* (or more ethical, since it was only "almost" unethical before) to pursue this route ourselves. The need to reach the goal justifies all.

Even the Korean researchers' willingness to deceive the public about their results is justifiable in principle under the New Ethic. The utilitarian calculus relativizes not only life, but truth as well. The *California Medicine* editorial that hailed the New Ethic in 1970 observed that, since the "old ethic" seeing human life as inviolable had not yet been completely displaced, it was necessary (and therefore, of course, acceptable) to resort to "subterfuge":

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[36] NBAC, *Ethical Issues*, 53.

[37] Monastersky, "Second Life for Cloning," A14.

[38] Dr. Irving Weissman, quoted in Wade and Sang-Hun, "Human Cloning Was All Faked," A12.

> Since the old ethic has not yet been fully displaced it has been necessary to separate the idea of abortion from the idea of killing, which continues to be socially abhorrent. The result has been a curious avoidance of the scientific fact, which everybody knows, that human life begins at conception and is continuous whether intra- or extra-uterine until death. The very considerable semantic gymnastics which are required to rationalize abortion as anything but the taking of a human life would be ludicrous if they were not often put forth under socially impeccable auspices. It is suggested that this schizophrenic sort of subterfuge is necessary because while a new ethic is being accepted the old one has not yet been rejected.[39]

Cloning advocates have brushed aside moral concerns about human life, and the indignity of creating new lives just to destroy them. Even if human embryos are "lives" in a biological sense, we are told, they do not have the value of persons—and they must be sacrificed to help born patients who really matter. Ironically, born patients (and adult women, exploited for their eggs) have joined embryos in being victimized by this agenda. In any case, we should not be surprised when an ethic that dismisses "Thou shalt not kill" in the quest for cures applies the same calculus to "Thou shalt not bear false witness." If the embryo's "merely biological" life can be trampled to benefit more valuable lives, "merely factual" truth can be sacrificed for the higher truth of progress.

While the Hwang scandal itself does not undermine the foundations of science, this ethic—an ethic unfortunately tempting to researchers in this country as well—*does* threaten to undermine those foundations. For science is nothing without an absolute commitment to the facts.

By demeaning life, we learn to demean truth, rendering science itself meaningless. If American ESC researchers have not learned this important lesson, a sound ethical response must come from the broader society and its policymakers. That response should begin with a complete ban on human cloning, and with legislation to prevent the mistreatment of women as egg factories for research or as surrogate incubators for unborn children being grown for their body parts. Only by respecting fellow human beings of every age and condition, and by refusing to treat them as mere instruments for achieving our research goals, will we promote a human progress worthy of the name.

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[39] "New Ethic," *California Medicine*.

Ms. FOXX [presiding]. Thank you.

Dr. Mathews.

STATEMENT OF DEBRA J.H. MATHEWS

Ms. MATHEWS. Hello. Thank you very much for having me here today to share with you some of my thoughts. My name is Debra Mathews. I am a human geneticist by training. I also have training in bioethics and science policy.

The first thing I want to say is that nothing—again, reiterate something that has been said here before today—nothing that Woo Suk Hwang and his collaborators did or didn't do has disproved any of the basic tenets of human embryonic stem cell research, or taken away any of the potential of the research.

When Woo Suk Hwang and his collaborators were doing this research, parallel research in the United States and other places did not stop. And the field did not crash and burn with the unfortunate and reprehensible activities that occurred with Woo Suk Hwang and his collaborator.

Everyone in the embryonic stem cell research field knew that this would take a long time, and were surprised when Hwang came out with the results in 2004 and 2005. And their estimate turned out to be right. It is going to take time. This research did only begin in 1998, and that is not when scientists began attempting to do SCNT. That is when the first human embryonic stem cells were first derived.

I am going to focus most of my comments on the question of fraud and the question of egg donation for research. My primary message here is that oversight is happening, and scientists care about developing oversight for this research.

SCNT does raise the issue of egg donation for research purposes. Last summer the National Academy of Sciences issued guidelines, not only guidelines to govern the research, but also including guidelines relevant to tissue donors and egg donors.

These guidelines have been broadly adopted by research institutions in the United States. And in addition to the national guidelines, the California Institute for Regenerative Medicine has recently issued interim guidelines that go above and beyond the protections provided by the National Academy's in their protection of egg donors.

The California Institute for Regenerative Medicine has also partnered with the Society for Gynecologic Investigation on a scientific conference this May to focus on the risks of egg donation.

I think that the message from the scientific community on this issue is very clear. They understand and are prepared to address the ethical issues raised by stem cell research, including egg donation for research purposes.

With respect to the question of fraud, again, scientists do not embrace fraud. Scientists are slaves to their data, and they want the data to be as pristine as possible. And fraudulent data is of no use to the scientific community.

The process of oversight associated with Federal funding provides some protection against breaches of scientific and ethical integrity. And the National Academy's guidelines add additional—

which, as I mentioned, have been broadly adopted by research institutions in this country—provide additional oversight.

The National Academy has also announced just recently that they will be setting up a committee for oversight of stem cell research. Given the lack of Federal funding and therefore the lack of oversight over this research, the National Academy has taken it upon themselves to set up an oversight committee specifically for stem cell research.

The International Society for Stem Cell Research has also set up a task force to develop internal standards and ethical guidelines for embryonic stem cell research. And they will be presenting their findings at the annual meeting in the end of June/beginning of July.

Finally, recently a group of approximately 60 scientists, ethicists, lawyers, and policymakers got together and developed a consensus statement providing recommendations for fostering the ethical and scientific integrity of embryonic stem cell research in a global context. And I can make those—all of these guidelines available to you.

Scientists in the United States and around the world recognize both the promise and the controversy of stem cell research, and they are willing to step up to the plate and provide and accept ethical guidance to make sure that this science has the scientific and ethical integrity that is necessary.

Thank you very much, and I would be happy to answer any questions.

[The prepared statement of Ms. Mathews follows:]

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TESTIMONY OF DR. DEBRA MATHEWS AT HEARING ENTITLED

"Human Cloning and Embryonic Stem Cell Research After Seoul: Examining Exploitation, Fraud, and Ethical Problems in the Research"

BEFORE THE SUBCOMMITTEE ON CRIMINAL JUSTICE, DRUG POLICY AND HUMAN RESOURCES

MARCH 7, 2006

Chairman and members of the Committee, thank you for this opportunity to share my thoughts. My name is Debra Mathews and I am the Assistant Director for Science Programs at the Phoebe R Berman Bioethics Institute at Johns Hopkins University. I am a human geneticist and also have a degree in bioethics. I am speaking to you today as a scientist and as an ethics and science policy scholar. I have spent the last decade doing scientific research and now spend my life thinking about the scientific community's interactions with and impact on the world outside the laboratory.

While the situation that occurred in and around the laboratory of Dr. Hwang Woo-suk is deeply lamentable, it is not representative of the field of stem cell research, nor a barrier to the progress of this research with ethical and scientific integrity. Scientists throughout the world are actively taking steps to ensure the integrity of their own work and the field more broadly.

No one can promise that stem cell research will produce cell-based cures for currently untreatable diseases; however, scientists who conduct this research do *see* promise in the research for advancing understanding of early human development and human disease and disability. While the lines approved for federal funding by President Bush are suitable for basic studies of, for example, embryonic stem cells themselves, the culture conditions necessary to keep cells healthy and genetically stable, and how to direct the differentiation of pluripotent stem cells into specialized cell types like neurons and islet cells, they are not suitable for many other areas of research. The approved lines were derived very early in the history of human embryonic stem cell science, for example, before optimal – mouse-free – cell culture conditions had been developed. Newly derived lines benefit from almost five years of scientific knowledge and technological advance, ensuring that they are more robust and stable than most approved lines, and uncontaminated by products from non-human animals. Newly derived lines – from IVF embryos in excess of clinical need and from somatic cell nuclear transfer (SCNT) – allow scientists to address a whole set of questions unanswerable through the use of the approved lines. For example, embryos created through IVF in the course of reproductive services, which contain disease-causing genetic mutations and will therefore never be used to create a baby, can be used to derive stem cells that allow scientists to study how the genetic mutation causes disease, providing vital basic information that may help in the development of treatments for that disease. SCNT facilitates the study of conditions for which genetic mutations are not known, or do not

apply, such as schizophrenia, amyotrophic lateral sclerosis (ALS), diabetes and stroke. In addition, SCNT opens the possibility in the (likely distant) future for disease treatments that use a patient's own cells to treat their condition, reducing the likelihood of immune rejection and the need for adjunct immunosuppressive therapy.

SCNT does raise the issue of egg donation for research purposes. This is a complicated and controversial topic, and one that scientists, ethicists and others are working to address. Many argue that egg donation for research purposes can be done ethically. The National Academy of Sciences issued guidelines in 2005 which address not only the oversight of stem cell research, but also provide guidance on egg donation. These guidelines have been broadly adopted by research institutions across the United States. The California Institute for Regenerative Medicine (CIRM) has recently announced their new interim guidelines, in which they go above and beyond the National Academy's guidelines in their attempt to protect from exploitation women who choose to donate eggs. In addition, CIRM has partnered with the Society for Gynecologic Investigation on a scientific conference in May examining the risks of egg donation. The message from the scientific community is very clear – they understand and are prepared to address the ethical issues raised by stem cell research, including egg donation for research purposes.

An issue that is not unique to SCNT or stem cell research broadly is that of fraud. Fraud occurs in all walks of life and in all fields of research. It is fortunately rare and the process of science, involving peer review and replication before findings are accepted, is well equipped to detect fraud when it does occur. However, fraud may not be detected until other scientists attempt to replicate experiments, or many, many scientists have had the opportunity to scrutinize the work. Peer review is equipped to detect bad science and bad fraud, but it is not set up to detect good fraud. If someone wants to intentionally deceive and is clever about it, it is very difficult to detect. While the papers from Dr. Hwang's lab were published, the fraud was quickly recognized by members of the scientific community and the scientific record corrected.

Again, scientists are just as concerned about fraud as non-scientists and they appreciate that in a controversial area like embryonic stem cell research, additional attention must be paid. Usually, the process of oversight associated with federal funding provides some protection against breaches of scientific and ethical integrity. As much embryonic stem cell research in the US does not receive federal funds, other oversight mechanisms must be relied upon, such as university internal review boards (IRBs) and embryonic stem cell research oversight committees (ESCROs), as recommended by the National Academy's guidelines. Recently, the National Academy of Sciences announced that they would set up a committee to provide an additional level of oversight of stem cell research. In addition, groups such as the International Society for Stem Cell Research has established a task force to develop international guidelines to govern stem cell research. Also recently, an international group of scientists, ethicists, journal editors and others issued a consensus statement offering principles by which international collaboration in stem cell research ought to proceed and through which we can foster the ethical and scientific integrity of stem cell science in a global context.

Scientists in the United States and around the world recognize both the promise and the controversy of stem cell research. There will always be bad actors, but they will be the exceptions. Scientists, in collaboration with their institutions, ethicists, journal editors, the public, and others must and are devising guidance and standards to minimize the risk that events such as those that unfolded in South Korea are repeated.

Ms. FOXX. Thank you.

Dr. Mathews, I want to ask you one question. And we are nearly out of time, so we will try to make the questions short and the answers short, too. Has anyone ever created stem cells from cloned human embryos?

Ms. MATHEWS. Not that I'm aware of.

Ms. FOXX. OK. Has it been done even in monkeys?

Ms. MATHEWS. Monkeys have been very difficult to clone, it is true.

Ms. FOXX. OK. Is there anyone on the panel who disagrees with that answer?

Dr. CHOLE. Monkey embryos have been cloned by Gerry Schatten in Pittsburgh. I don't—I am not sure if their stem cells have been extracted and cultured, but the embryos have been made. He is doing that for reproductive purposes for one way to protect endangered species.

Ms. FOXX. Is he the person who was collaborating with Dr. Hwang in Korea?

Dr. CHOLE. That is correct.

Ms. MATHEWS. Is it the case that his embryos were basically in vitro embryos, or were they SCNT embryos?

Dr. CHOLE. They are SCNT embryos. He has had some success with that. But they have not developed. They have implanted but not developed.

Ms. FOXX. Dr. Chole, is there any biological difference between the entity that is created through so-called therapeutic cloning and reproductive cloning?

Dr. CHOLE. No.

Ms. FOXX. Thank you. OK.

Ms. Norsigian, what have other countries done in the area on SCNT and egg donation, and what role did a concern for women's rights have in the passage of these laws? Do you think the conservative movement, as we are typically used to thinking about in the United States, was very active in getting these laws passed? And what reaction would you have to that?

Ms. NORSIGIAN. Well, I have to say I think it is unfortunate that the abortion debate and debates about the moral status of the embryo have clouded the discussion of cloning for research purposes that I focused on in my remarks.

In Canada, interestingly enough, advocates, researchers, people with differing religious views, sat down and they actually came up with something that was acceptable to everyone, including the scientists.

And they are putting a moratorium on SCNT. They are not saying never. They are saying, right now we have so much to learn with other embryo stem cell research. Some of the problems were just raised: the inability to control differentiation so you get the kind of tissue type you want, the inability to control tumorigenicity.

I believe that only John Gearhardt and Johns Hopkins has avoided that by growing the mice embryos to the fetal stage so that germ line cells were harvested. These are not embryo stem cells. And in that instance, he was then able to eliminate the issue of tumorigenicity.

There are many problems that I think may be able to be overcome. And those problems can be possibly solved, and you can use embryo stem cells that would be created from otherwise discarded embryos from IVF clinics. Though there are reasons, and I mention them, that make SCNT advantageous, I don't think they yet justify the known and unknown risks that we are asking women to undergo.

There have been similar concerns expressed in England. And it is interesting. They are allowing this to go forward. The HFEA there has fairly strict regulations. But there is quite a controversy about this, particularly as we see some of the harms that women experience.

Ms. FOXX. We don't have something—I am.

Ms. Watson.

Ms. WATSON. Are you doing an overhead presentation? Is someone doing an overhead?

Ms. FOXX. No. I don't think it is going to work.

Ms. WATSON. OK. I just want to thank the panelists, and of course the Chair. I think this has been very enlightening because it opens up a whole new, I would say, panoply of thought. And I think these are some of the issues that have been brought up today that we are going to have to deal with.

I would definitely hate to see conclusions because of some of the fraud that has been perpetrated stop the serious research that can save lives, limbs, and improve physical conditions. I would hope that we could think through and work through the ethical issues, moral issues, and reach for a higher goal, and that is research that can improve the quality of life.

So I would look forward—not a question, just a statement—to further discussions of this type and to the panelists getting back to us with messages from your research as to the direction the Federal Government should take.

With that, I want to thank you, Madam Chair, and I will have to leave. And thank you very much.

Ms. FOXX. Well, Mr. Doerflinger, I want to share some information and then ask you a question.

In the district that I represent, there is some absolutely fabulous and earth-shaking research going on, Baptist Medical Center, with the use of adult stem cells. The key researcher there said in front of me and another Member of Congress who was visiting there recently that—in response to a question about why he was not using—or why he did not advocate the use of embryonic stem cells, said that—voiced many of the issues that have been voiced here today, aside from—even aside from religious and ethical issues, that these lines of stem cells simply created more problems than they resulted in benefits from.

He and his researchers are able to grow organs that are helping make massive changes in peoples' lives. And they are helping our military people by regeneration of limbs.

Is it your experience, again, that many of the scientists are not using the embryonic stem cells not for religious purposes but because of scientific reasons, so that they do not have to "cloud the issue" by bringing that issue—by bringing the issue of religion into it?

Mr. DOERFLINGER. Well, the ethical issue, which I agree with what was said here earlier about the ethical issue being far broader than any religious issue, is certainly a factor. But I also know of many researchers who do all of their work on non-embryonic stem cells simply because they are easier to work with, easier to control.

In many cases, they do not require lengthy FDA approval because they are the patients' own cells. They are not rejected as foreign tissue. They are in plentiful supply and can be—the research is showing they can be multiplied for clinical use more effectively than used to be the case. And they are working.

Last night, ABC had a premier of its—I guess a new series called "Miracle Workers" featuring a man whose blindness was cured by his sister's adult corneal stem cells. And researchers at the University of South Florida, I think, up at St. Elizabeth's Medical Center in Massachusetts, have all said, it is not that we object to the ethics of the embryonic cells, it is that these are working and we think they are going to work better.

And I think it is important to put this in a context that even in the Clinton administration, the National Bioethics Advisory Commission said that they did realize there is an ethical problem here. They were willing to override the ethical problem because they thought that was the only way to go.

But they said that the pursuit of embryonic stem cell research, even using embryos, spare embryos, from fertility clinics, would not be justifiable if there were less morally problematic alternatives available for pursuing the research.

And I think researchers have shown over and over again that those alternatives are real. They are very promising. And in many cases, they may well make it unnecessary for us to face these terrible ethical dilemmas.

Ms. FOXX. Thank you very much. I believe that—Mr. Brown.

Mr. BROWN. I would just like to make a comment as a patient and as a patient advocate. I heard earlier that there are 60 adult cell cures that have been put in place, some of which I am aware of. One of them that was mentioned was Parkinson's.

First, I question if the acid test has actually been made of replication. I know on some of it, it has—leukemia, for instance. The first time I heard about the Parkinson's was 2003. I know of no Parkinson's patient who is waiting for embryonic stem cells. If adult stem cells in truth were doing the job, I would be one of the happiest people in the world because I would see my wife of 44 years being able to walk 24 hours a day again.

So I think that there is—and I believe that there is a tendency to overstate a great deal of what this science has and has not accomplished from both sides of the issue. I believe there is a great deal of misstatement, a great deal of miseducation—which I think it is very important that we educate. And what I would like to see is a more civil building of consensus and compromise to allow all of this research to go forward; that we close no doors, and see where science can take us.

Ms. FOXX. Thank you all very much for being with us today. The hearing is adjourned.

[Whereupon, at 5 p.m., the subcommittee was adjourned.]

[Additional information submitted for the hearing record follows:]

Who really made Dolly? Tale of British triumph descends into scientists' squabble

- Lead researcher admits his role was overstated
- Technicians complain their contribution ignored

Ian Sample, science correspondent
Saturday March 11, 2006

Guardian

Few stories begin with a cell plucked from the mammary gland of a ewe, go on to shower worldwide acclaim on a team of British scientists and then degenerate into a squabble over who deserves the credit. But then there's nothing ordinary about the tale of Dolly the sheep.

Born on July 5 1996, Dolly propelled Britain to the vanguard of cloning science. For the first time, a sheep had been created from a hollowed-out egg fused with a cell from an adult animal. The provenance of the cell led researchers to name the lamb with a nod to the country singer Dolly Parton.

Dolly brought fame and admiration for Professor Ian Wilmut, the head of the research group at the Roslin Institute in Edinburgh. When the seminal paper describing the work was published in the journal Nature in 1997, he entered the rarefied territory of scientist as household name. Researchers around the world clamoured for details of the group's techniques, eager to repeat the feat.

The boost that Dolly gave British science was incalculable, but the story is not one of collegiate collaboration crowned by shared glory. This week, Prof Wilmut admitted to an employment tribunal in Edinburgh that his involvement was less than may have been portrayed. When asked by a lawyer whether the statement "I did not create Dolly" was accurate, he replied "Yes." The tribunal is hearing a claim from Prim Singh, a biologist, that Prof Wilmut harassed him. The tribunal continues.

The admission from Prof Wilmut raises the question: who did clone Dolly? In the hearing, the scientist said that while he did not develop the technology or conduct the experiments, he instructed the team on the nuclear transfer techniques and coordinated the project. In further evidence, he said Prof Keith Campbell, an expert on the biology of cell cycles, deserved 66% of the credit for Dolly.

The comments have stirred up deep resentments. Some scientists, who spoke to the Guardian under condition of anonymity, believe the group would still be trying to clone an animal were it not for Prof Campbell, who worked out that each egg and cell used in a cloning attempt had to be carefully coordinated for the embryo to have any chance of surviving.

It is understood that Prof Wilmut's handling of the Dolly affair was a factor behind Prof Campbell's decision to quit the institute in 1997 and transfer his skills to another Edinburgh-based research firm.

But the debate does not end there. One member of the Dolly team, a technician called Bill Ritchie, along with Karen Mycock, another technician, was responsible for the intricate and arduous egg and cell manipulation needed to create each clone. At the end of each day, the few successfully cloned embryos were collected and transplanted into ewes. "There were two people doing nuclear transfer that day and it could have been either who created the embryo that made Dolly," said one scientist close to the project.

Mr Ritchie argues that his and Ms Mycock's names should have appeared on the list of authors of the 1997

research paper Instead, the technicians both appear in the small print of acknowledgements at the end of the report's list of references.

The row reveals aspects of the scientific process that will not surprise anyone working in the field. Modern science invariably requires large teams and with the hierarchy come politics. As one scientist put it: "It's one of those scenarios. You have a hierarchy of employment and you need the job. They dictate the rest."

Many scientists say technicians are merely doing what they are told, while the credit - the all-important name on the paper - goes to those whose intellectual thought made the research a success. "You get some papers where the authors haven't done a scrap of work themselves, it's all down to the technicians acknowledged at the back," said one researcher.

Mr Ritchie believes that while Prof Campbell's contribution was crucial for the Dolly project to succeed, the lab work conducted by himself and Ms Mycock was never properly credited. According to Mr Ritchie, Dolly was only born after the two of them put in weeks of labour-intensive lab work. In all, 430 eggs were surgically removed from ewes and given to the technicians. Each one had to have its DNA removed, essentially hollowing out the eggs with a sharpened glass capillary.

Each empty egg was then filled with an adult cell taken from a sheep and zapped with an electric current to fuse the two. Of the original 430, only 270 eggs were successfully hollowed out and fused with other cells and only 29 of those grew into small balls of cells known as blastocysts, the precursors of embryos. Of these, only one that was implanted developed successfully, dividing and growing inside a surrogate female until, five months later, Dolly was born.

According to Mr Ritchie, the technicians did most of the work that led to Dolly, but they got none of the praise. "He [Wilmut] is saying he did a third and Keith did two-thirds. But I don't think I appear in there at all, to be honest" he said.

Scientists contacted by the Guardian said the question of credit is frequently a divisive one. "It can be extremely difficult. The whole cloning process involves a lot of people. It all comes down to how far down the list you want to go," said one.

Earlier this year, Prof Miodrag Stojkovic, who created Britain's first cloned human embryo while working at Newcastle University, admitted that a disagreement with Prof Alison Murdoch, his colleague at the Newcastle Fertility Centre, had been a significant factor in his leaving to take up a post in Spain. He objected to Prof Murdoch announcing the work at a press conference and accused her of taking credit for his team's research work. Newcastle University insists Prof Murdoch's contribution was important.

Prof Wilmut, now at Edinburgh University, heads only the second group in Britain to be granted a licence to clone human embryos by the Human Fertilisation and Embryolgy Authority. Dolly was put down by veterinarians in February 2003 at the age of six after she developed premature progressive lung disease.

EducationGuardian.co.uk © Guardian Newspapers Limited 2006

Source: Do No Harm: The Coalition of Americans for Research Ethics
www.stemcellresearch.org

Potential U.S. Patient Populations for Stem Cell-Based Therapies (according to the National Academy of Sciences)[1]

Condition	Number of Patients
Cardiovascular disease	58 million
Autoimmune diseases	30 million
Diabetes	16 million
Osteoporosis	10 million
Cancers	8.2 million
Alzheimer's disease	5.5 million
Parkinson's disease	5.5 million
Burns (severe)	0.3 million
Spinal-cord injuries	0.25 million
Birth Defects	0.15 million

Total patient population = 133.9 million (10% = 13.4 million)

Assume cloning efficiency at 20%; Assume ES extraction/line establishment at 10%; assume conservatively obtaining 10 eggs per donor.

NEEDED: AT LEAST 670 MILLION EGGS,
DONATED BY AT LEAST 67 MILLION WOMEN.

MEDIA HYPE

"We should also think hard about whether Hwang's deceit went undetected for months because so many scientists and science journalists wanted to believe that ESC research was progressing rapidly, because that would hasten the arrival of miraculous therapies and other biomedical wonders. Extraordinary results need to be held suspect until confirmed independently. Hwang is guilty of raising false expectation, but too many of us held the ladder for him."

- Editors, "Con Men in Lab Coats," Scientific American, February 20, 2006

"To start with, people need a fairy tale. Maybe that's unfair, but they need a story line that's relatively simple to understand."

- Stem Cell researcher Ron McKay, quoted by Rick Weiss, "Stem Cells An Unlikely Therapy for Alzheimer's," The Washington Post, June 10, 2004.

"The drive to succeed was so strong that many top academics and government officials concede they ignored a series of warning signs."

- A. Faiola, "Koreans 'Blinded' to Truth About Claims on Stem Cells," Washington Post, January 13, 2006.

"It makes us (scientists) question peer review, motivation, hype and the media."

- Dr. Stephen Minger, Director of Stem cell Biology Laboratory, King's College, London, quoted by P. Reaney, "S. Korean Clone Scandal is a Tragedy: Scientist," Reuters.com, Jan 12, 2006.

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July 9, 2004

The Honorable Tommy G. Thompson
Secretary
Department of Health and Human Services
200 Independence Avenue, S.W.
Washington, D.C. 20201

Dear Mr. Secretary:

As Chairman Davis and I indicated in our letter dated June 17, 2004, over the past two years the Subcommittee on Criminal Justice, Drug Policy, and Human Resources and the office of Chairman Chris Smith have been in correspondence with the NIH regarding the current status of medical therapies and clinical research using adult and embryonic stem cells.

How the Department has allowed this matter to drag on for nearly two years defies excuse or explanation.

On October 8, 2002, Chairman Smith and I sent a letter to Dr. Elias Zerhouni, Director of the National Institutes of Health (NIH), requesting "a detailed report" providing comprehensive information about the medical applications of adult and embryonic stem cells as well as stem cells from cloned embryos and aborted fetuses.

After almost a year had passed, Subcommittee records indicate that on August 4, 2003, Subcommittee staff inquired into the status of the requested report and were told that the letter had been in the office of the Assistant Secretary for Legislation (ASL) "for some months" and would be out "in a few weeks."

On October 14, 2003, Subcommittee staff again inquired into the status of the report and were assured that although "...the letter is in final draft and is going through the clearance process now."

The written inquiries on the status of this report are recorded below. There were also numerous telephone conversations that are unrecorded here. The dates of correspondence from the Subcommittee to HHS regarding our October 8, 2002, letter are as follows:

August 4, 2003
October 14, 2003
October 27, 2003
November 19, 2003
February 10, 2004
March 25, 2004
April 20, 2004
June 17, 2004

After repeated inquiries about the status of the report by email, I sent a formal, written letter to you, Mr. Secretary, on April 20, 2004.

Remarkably, there was no answer to the April 20 letter.

After waiting several weeks for acknowledgement, on June 17, 2004, Chairman Tom Davis of the House Government Reform Committee and I sent another letter communicating our concern about a number of outstanding correspondence and document requests.

On June 18, 2004, the Subcommittee received a letter signed by Dr. James Battey, Director of the National Institutes on Deafness and Other Communication Disorders (NIDCD) and Director of the Stem Cell Task Force, responding to our request for information regarding stem cell therapies.

However, the letter we received did not respond to the plain meaning of our request on October 8, 2002. Instead of a thorough response, it represented only a sampling of the information we requested. Through subsequent phone and email conversations within hours of receiving the response, Subcommittee staff communicated disappointment regarding the quality and depth of the letter we received and asked that the response be revised and completed by June 30, 2004.

In lieu of sending a revised document, at the close of the day on June 30, an HHS Deputy Assistant Secretary requested a meeting with members of the Subcommittee staff to "discuss the response on adult stem cells and how [NIH] may be able to better respond to your inquiries here."

At this meeting on July 2, Subcommittee staff communicated our frustration about the delay in receiving a response from the Department as well as our disappointment regarding the quality of the letter. In order to assist the Department in responding to the

Subcommittee's inquiry, I have included a summary of the meeting that took place, along with an outline of our agreement about the nature of a forthcoming, revised report in response to our October 8, 2002 written request.

The original letter, dated October 8, 2002 requested (italics added):

- "a *comprehensive* listing of *all* medical therapies" which utilize various types of stem cells,

- "a listing of *all* ongoing clinical trials or experiments involving human subjects using these same categories of stem cells,

- "the findings of *any* studies that utilized stem cells or tissues from embryos or fetuses to treat human patients from Parkinson's disease and juvenile diabetes," and

- "a *listing of alternatives* to stem cells from embryos and fetuses that have shown promise in human subjects for treating juvenile diabetes, Alzheimer's, and Parkinson's disease."

In response to our letter, the NIH stated that there are no treatments or ongoing clinical trials utilizing embryonic stem cells or stem cells from cloned embryos or aborted fetuses. The NIH letter also reported the adverse effects resulting from the two known clinical trials using fetal tissue transplantation to treat Parkinson's disease.

However, instead of a comprehensive listing of all medical therapies and a listing of all ongoing clinical trials in which human patients were being treated with adult stem cell therapies, NIH included a sampling of the work ongoing at some NIH Institutes and a listing of NIH-funded clinical trials.

That is not what was requested.

The Subcommittee identified several obvious omissions in Dr. Battey's letter.

(1) From the NIH website www.clinicaltrials.gov, in the NIH National Library of Medicine *Medline* database, and in the popular press, Subcommittee staff identified extramurally funded clinical trials and clinical research involving human patients which were not included the NIH letter, including some that began as early as 1999 and should have been available to Dr. Battey prior to his submission of the letter to the ASL office in November 2002. A selection of extramurally funded clinical trials not included in the NIH letter are listed below:

• Sponsor: Baylor College of Medicine
Stem Cell Transplant to Treat Patients with Systemic Sclerosis
Phase I H7157
Study start date: June 1999
Date last reviewed: March 2004

•Sponsor: Texas Heart Institute, Houston, Texas
Transendocardial, Autologous Bone Marrow Cell Transplantation for Severe, Chronic Ischemic Heart Failure, announced in media April 16, 2004.
www.genomenewnetwork.org/articles/2004/04/16/stem_cell_trial.php
Circulation. 2003 May 13;107(18):2294-302.

• Sponsor: Caritas St. Elizabeth's Medical Center of Boston
Stem Cell Study for Patients with Heart Disease 00165
Study start date: January 2004
Date last reviewed: April 2004

• Sponsor: Bioheart, Inc.
Autologous Cultured Myoblasts (BioWhittaker) Transplanted via Myocardial Injection
Phase I BMI-US-01-001
Study start date: June 2003
Date last reviewed: December 2003

• Sponsor: Bioheart, Inc.
MYOHEART™ (Myogenesis Heart Efficiency and Regeneration Trial)
Phase I BMI-US-01-002
Study start date: February 2003
Date last reviewed: December 2003

In response, Dr. Battey maintained that the intent of NIH was to provide a comprehensive listing of work funded by NIH, but not by universities or pharmaceutical companies, citing the difficulty of enforcing compliance with a law (PL105-115, signed November, 1997) mandating that privately funded trials also be listed on the www.clincaltrials.gov website.

Nonetheless, Subcommittee staff were also able to identify several intramurally funded clinical trials at www.clinicaltrials.gov, in which human patients are being treated with adult stem cell therapies, which, astonishingly, were not included in the NIH response:

• **NIAMS (National Institute of Arthritis and Musculoskeletal and Skin Diseases)**
Autologous Stem Cell Transplant for Systemic Sclerosis
Phase I N01 AR-9-2239
Study start date: July 2002
Date last reviewed: March 2004

• **NINDS (National Institute of Neurological Disorders and Stroke)**
Investigating Endothelial Precursor Cells 03-N-0269
Study start date: August 1, 2003
Date last reviewed: August 1, 2003

• **NHLBI (National Heart, Lung, and Blood Institute)**
The Effect of Exercise on Stem Cell Mobilization and Heart Function in Patients Undergoing Cardiac Rehabilitation 03-H-0086
Study start date: January 28, 2003
Date last reviewed: December 5, 2003

Stem Cell Mobilization to Treat Chest Pain and Shortness of Breath in Patients with Coronary Artery Disease 02-H-0264
Study start date: August 6, 2002
Date last reviewed: July 17, 2003

• **NIDCR (National Institute of Dental and Craniofacial Research)**
Bone Regeneration Using Stromal Cells 94-D-0188
Study start date: August 3, 1994
Date last reviewed: June 4, 2003

(2) The Subcommittee also identified several reports of clinical research not yet in clinical trials that were also missing from the report. Some of these studies, reported in peer-reviewed journals and in the public media are listed below:

• **Preliminary clinical research using adult skeletal myoblasts to repair injured heart muscle:**

Pagani, et al, 2003. *Autologous skeletal myoblasts transplanted to ischemia-damaged myocardium in humans. Histological analysis of cell survival and differentiation.* J Am Coll Cardiol. Mar 5;41(5):879-88.

Hagege, et al, 2003. *Viability and differentiation of autologous skeletal myoblast grafts in ischaemic cardiomyopathy.* Lancet. Feb 8;361(9356):491-2.

Menasche, et al, 2003. *Autologous skeletal myoblast transplantation for severe postinfarction left ventricular dysfunction.* J Am Coll Cardiol. 2003 Apr 2;41(7):1078-83.

• **Autologous bone marrow or blood cells transplanted into injured heart:**

Dr. Cindy Grines at Beaumont Hospital, Royal Oak, Michigan:
http://www.cnn.com/2003/HEALTH/conditions/03/06/teen.heart.ap/
http://www.sctline.com/info/english_viewarticle.asp?id=1966

Assmus et, al, 2002. *Transplantation of Progenitor Cells and Regeneration Enhancement in Acute Myocardial Infarction (TOPCARE-AMI).* Circulation. 2002 Dec 10;106(24):3009-17.

Dobert, et al, 2004. *Transplantation of progenitor cells after reperfused acute myocardial infarction: evaluation of perfusion and myocardial viability with FDG-PET and thallium SPECT.* Eur J Nucl Med Mol Imaging. 2004 Apr 3 [Epub ahead of print]

(3) Included in the response from NIH was an enclosure from the National Bone Marrow Donor Program entitled "Diseases Treatable by Stem Cell Transplantation," dated 2002. However, this list contained only blood disorders, autoimmune diseases, and related cancers treatable with hematopoietic stem cells. The letter did not include a more updated, comprehensive listing of additional diseases treated with hematopoietic or other adult stem cell types.

When questioned about these omissions, Dr. Battey conceded that the report was not comprehensive. The wide range of information missing from the NIH response to our October 8, 2002 letter demonstrates the need for NIH to review responses to ensure that Congress receives accurate and thorough information in response to its requests.

Dr. Battey also indicated that he had made a decision when responding to the letter to include only NIH information that would be difficult for Congress to obtain through publicly accessible sources.

However, Subcommittee staff reiterated to HHS staff at the meeting that our request for a comprehensive document remained unchanged and unfulfilled.

In response to Subcommittee documentation of the inadequacy and omissions of the NIH response, Dr. Battey apologized.

Dr. Battey agreed he and his colleagues would assemble a comprehensive report as requested on October 8, 2002. Subcommittee staff agreed to give a time extension to the $27 billion agency.

Dr. Battey and Subcommittee staff agreed that the revised report would:

(1) be comprehensive in scope as originally requested, including both NIH funded research as well as privately funded research in the public domain, including studies abroad,

(2) be in a format that is easily accessible and searchable,

(3) include anecdotal reports of clinical research when these reports appear substantive and likely to lead to future clinical research and/or clinical trials, and

(4) include only minimal analysis necessary for translating the factual components of the report into lay terms.

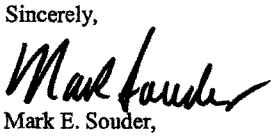
The Subcommittee staff and the Department also agreed that an iterative response would be provided to Senator Brownback in advance of his July 14, 2004, hearing on adult stem cell research.

Subcommittee staff emphasized that this report will be an invaluable resource as Congress seeks to make policy decisions and educate the public based on accurate and in-depth scientific data rather than the often-misleading information that is readily available from the news media and lobbying groups.

I appreciate your attention to this matter and your assurances that the Department will be more responsive to matters of Congressional oversight. This, as you know, is not a peripheral issue of concern only to a small number of people. I would think, on an issue of this magnitude, that HHS would have wanted to have this report available in response not only to Congress but for the President and others to whom such information might be important.

It is my hope that as members of Congress and their staff continue to face critical and complex science policy issues they will be able to draw on accurate, thorough, timely, and up-to-date information from the Department of Health and Human Services.

Sincerely,



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INDEPENDENT

October 20, 2005

Elias A. Zerhouni, M.D.
Director
National Institutes of Health
9000 Rockville Pike
Bethesda, Maryland 20892

Dear Dr. Zerhouni:

This letter is in response to your recent letter, dated October 7, 2005, responding to my inquiry of May 18 raising serious concerns about the ethical and conflicts-of-interest issues surrounding Dr. James Battey's recusal and reinstatement as Chair of the NIH Stem Cell Task Force, while also seeking employment as the President of the California Institute for Regenerative Medicine.

You state in your letter that once Dr. Battey informed NIH officials he was a candidate to head the California Institute for Regenerative Medicine, he was advised "that he would be required to step down [as Chair of the Task Force] to comply with the ethics requirements," and that on March 18, you announced his leave of absence from his position as Chair.

However, during the time Battey was *no longer* Chair of the NIH Stem Cell Task Force, he nonetheless gave several presentations on stem cell research, including one at a California biotech council investors conference. You wrote that Dr. Battey "gave these presentations as an NIH employee," and that they were "part of Dr. Battey's official duties."

I find the justifications for Dr. Battey's continued formal speaking engagements on the subject of stem cell research during this period of "recusal" insupportable.

The presumption is that Dr. Battey, when he is not the Chair of the Stem Cell Task Force, carries only the official NIH title of Director for the National Institute on Deafness and Other Communication Disorders. That being the case, how does giving speeches on the "politics" or the "business" of stem cell research fall within the "official

duties" of the Director for the Institute on Deafness and Other Communication Disorders?[1]

If Dr. Battey's employment negotiations with the California Institute for Regenerative Medicine posed a conflict of interest requiring him to step down as Chair of the NIH Stem Cell Task Force to comply with ethics requirements, wouldn't this require him to forgo speaking opportunities that spring from his role as Chair? Wouldn't it have been more appropriate for the NIH to send one of the acting co-Chairs of the Stem Cell Task Force?

It is rather difficult to see any meaningful difference between Dr. Battey's official activities as Chair of the Stem Cell Task Force, and those when he was supposedly not acting as Chair. For example, Dr. Battey's Powerpoint presentation for speeches on stem cell research was *unchanged* from what he presented as Chair of the Stem Cell Task Force to what he presented when he was not Chair.[2]

Moreover, how has NIH affirmed that Dr. Battey did not stray from the parameters you describe in your letter for his "official" presentations, strictly limiting Dr. Battey's discussions "to previously released information about Federal stem cell policies without discussing any NIH plans or initiatives related to future stem cell research?"

I am confounded by Dr. Battey's appearance – during the time he was *not* Chair because of the conflict of interest arising from his candidacy to head the California Institute for Regenerative Medicine – at a California biomedical *investor* conference. The vague listing that was provided to the Subcommittee of Dr. Battey's appearances (to which Dr. Battey himself contributed and corrected[3]) omits this troubling detail.[4]

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[1] Dr. Battey's speeches during the period when he was *not* Chair of the Stem Cell Task Force include the following events: "The Politics of Stem Cell Research," and "The Business of Stem Cell Research." One press release dated April 7 touting the Business of Stem Cell Research Conference listed as part of its roster of speakers "Dr. James Battey of the National Institute [sic] of Health (NIH) Stem Cell Task Force," to discuss "the current state of the science *and future outlook of stem cell research*" (emphasis added). (Press release vailable at http://www.prnewswire.com/cgi-bin/stories.pl?ACCT=109&STORY=/www/story/04-07-2005/0003338634&EDATE= last visited October 13, 2005.)

[2] In response to the Subcommittee's initial inquiry (May 5, 2005) to HHS requesting a list of appearances and transcripts for Dr. Battey's speeches since March 1, 2005, the Subcommittee received a listing of only two appearances. Although no transcript was provided, a Powerpoint presentation was attached, with the note that Dr. Battey used the slides for presentations on stem cell research on March 4-5 (when he was still Chair of the Stem Cell Task Force) and on March 18 (when Dr. Battey was *not* Chair of the Stem Cell Task Force). Moreover, as we pointed out in our May 18 correspondence on this matter, the Subcommittee was told that "these were the only two presentations [Dr. Battey] made on Stem Cell Research during the time requested." However, Subcommittee staff determined the listing to be incomplete, and after another inquiry (May 9) for Dr. Battey's appearances, the Subcommittee was provided with a listing of twelve appearances. (Flambert, Gemma, email response to "Battey inquiry," May 9, 2005, and "House Government Reform Request," on May 12, 2005. On file with the Subcommittee.)

[3] According to Zerhouni's October 7 letter to the Subcommittee.

[4] The listing for "Public Appearances and speeches on Stem Cell Research, Dr James Battey" provided to the Subcommittee notes an appearance on March 22 for "Workshop on Stem Cell Research, Where is the Beef?" for the "Southern California of Biomedical Council [sic], Los Angeles, CA." The listing failed to

The panel on which he spoke is listed in the program as "Opportunities in Stem Cell Research," "organized in recognition of the importance of the California Stem Cell Research Initiative[5] and to stimulate thinking about its likely impact on healthcare delivery and job creation."[6] This topic does not appear to meet the parameters you described in your letter. Is this the topic on which Dr. Battey spoke?

Considering the ethical and conflict of interest issues raised by Battey's candidacy to head the California Institute for Regenerative Medicine, it is simply absurd:

- that Dr. Battey presented at an *investor's* conference,
- for a California Biomedical Council
- promotionally noted as speaking on the material matter of stem cell research and its relationship to the California Stem Cell Research Initiative,
- as an official of the National Institutes of Health,
- during the time when he was supposedly conflicted out of his role as Chair of the NIH Stem Cell Task Force
- because he was a candidate for the position of President of the California Institute for Regenerative Medicine.

Dr. Zerhouni, I am deeply troubled by the possibility that NIH has not taken seriously the ethical and conflict of interest problems posed by Dr. Battey's activities. I question the level of vigilance against blatant conflicts of interest in light of the following:

If Dr. Battey was strictly limited to presenting "previously released information about the Government's stem cell policy," and not to "discuss any new directions that the NIH may be taking with respect to stem cell research," what was his involvement with the National Institute of General Medical Sciences (NIGMS) workshop, "Human Embryonic Stem Cell Research: Recent Progress and Future Directions of NIGMS Grantees?"[7]

The purpose of this meeting, for which Dr. Battey is a listed participant[8] was "to provide an opportunity for NIGMA grantees conducting human embryonic stem cell (HESC) research to report on their recent progress, to exchange information, and to

---

disclose the fact that the meeting was actually an annual investors conference. See http://www.socalbio.org/investor_conference.htm (last visited October 19, 2005).

[5] The Initiative provided for the establishment of the California Institute for Regenerative Medicine.

[6] SoCalBio Investor Conference brochure, available at http://www.socalbio.org/socalbio2005/2005_brochure1.pdf (last visited October 13, 2005).

[7] Stem Cell Initiatives, National Institute of General Medical Sciences, April 17-19 workshop. A summary and list of participants posted at http://www.nigms.nih.gov/funding/stemcell_human_embryo_meeting.html (last visited October 14, 2005). Sometime on the afternoon of October 14, when the Subcommittee was investigating this matter, the NIGMS webpage listing information about the Stem Cell funding workshop became inactive. The material printed from this webpage prior to its removal is on file with the Subcommittee.

[8] Id.

identify problems, challenges and opportunities associated with this emerging area of research."[9]

Among the sixty-eight participants in this important stem cell research grantee meeting, Dr. Battey is the only Institute Director listed; nine more participants are affiliated with NIH. Of the remaining fifty-eight researcher grantees, ten are California-based. *All of the California researchers' affiliated institutions would have been candidates for multi-million dollar grants from the California Institute for Regenerative Medicine.* (The California Institute for Regenerative Medicine has since awarded $15.9 million in grants to California institutions represented at this workshop.[10])

To the extent that Dr. Battey could have participated in *any* workshop addressing "opportunities" for stem cell research grantees while a candidate to head the California Institute for Regenerative Medicine is quite alarming. That a large percentage of the participating researchers were would-be grantees for the California Institute for Regenerative Medicine shocks the conscience.

Finally, assuming Dr. Battey had at least some contact with representatives from the California Institute for Regenerative Medicine prior to mailing his application seeking the prominent position of President with that group (on March 12, according to your letter), wouldn't this necessarily trigger his recusal as Chair of the Stem Cell Task Force (a minimal gesture), earlier than March 18?

Dr. Zerhouni, based on the activities described above, Dr. Battey's "recusal" as Chair of the Stem Cell Task Force appears to have been utterly meaningless. There does not appear to be any substantive measures against the conflict of interest between Battey's role as a government official and as an applicant to head the California Institute for Regenerative Medicine.

As you may know, I have requested the Inspector General to investigate this matter regarding Dr. Battey's activities. In addition to what appears to be serious ethical and conflict of interest issues, I believe that his activities reveal systemic weaknesses that give rise to opportunities for waste, fraud and abuse.

I have asked a number of serious questions throughout this letter, which merit a response. I do not want to wait almost five months for answers, as with my first letter to you on this matter. Rather, I expect the courtesy of a full response not later than **5:00pm on Friday, December 2, 2005**. This deadline is several weeks from now, and should be adequate time to address these questions posed by the Chairman of your oversight committee.

---

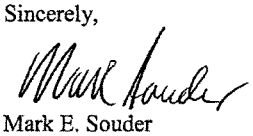
[9] Id.

[10] California Institute for Regenerative Medicine Press Release, September 9, 2005. Available at http://www.cirm.ca.gov/pressreleases/2005/09/09-09-05_ii.asp (last visited October 19, 2005).

In addition to answering the questions posed in this correspondence, please also provide the following:

- All documents relating to Dr. Battey's **removal** and **reinstatement** as Chair of the NIH Stem Cell Task Force, including but not limited to memoranda on March 18, and May 19 to Institute Directors about Dr. Battey's position and duties (see attachment for definition of "documents" and "relating to").
- All documents related to Dr. Battey's affirmation that he adhered to the parameters set forth by ethics officials regarding the scope of his presentations on stem cell research (see attachment for definition of "documents" and "relating to").
- All documents related to NIH's official determination that Dr. Battey adhered to the parameters set forth by ethics officials regarding the scope of his presentations on stem cell research (see attachment for definition of "documents" and "relating to").
- Copies of presentations, transcripts, audio or video recordings for Dr. Battey's presentations on the subject of stem cell research during the period of his "recusal."
- All documents relating to Dr. Battey's notification (1) that he was seeking employment with the California Institute for Regenerative Medicine; and (2) that he was no longer a candidate for any position at the California Institute for Regenerative Medicine (see attachment for definition of "documents" and "relating to").
- All meeting notes, participant lists, and audio recordings, related to the NIGMS Stem Cell Initiatives Research Funding workshop on April 17-19 of this year.

Sincerely,



Mark E. Souder
Chairman
Subcommittee on Criminal Justice, Drug Policy and Human Resources
Government Reform Committee

Attachment: Definitions
Enclosures: Prior correspondence

CC: Hon. Michael Leavitt, Secretary,
Department of Health and Human Services
Claude Allen, Assistant to the President for Domestic Policy
Daniel R. Levinson, Inspector General,
Department of Health and Human Services

ATTACHMENT

1. The term "documents" is to be construed in the broadest sense and shall mean any written or graphic material, however produced or reproduced, of any kind or description, consisting of the original and any non-identical copy (whether different from the original because of notes made on or attached to such copy or otherwise) and drafts and both sides thereof, whether printed or recorded electronically or magnetically or stored in any type of data bank, including, but not limited to, the following: correspondence, memoranda, records, summaries of personal conversations or interviews, minutes or records of meetings or conferences, opinions or reports of consultants, projections, statistical statements, drafts, contracts, agreements, purchase orders, invoices, confirmations, telegraphs, telexes, agendas, books, notes, pamphlets, periodicals, reports, studies, evaluations, opinions, logs, diaries, desk calendars, appointment books, tape recordings, video recordings, e-mails, voice mails, computer tapes, or other computer stored matter, magnetic tapes, microfilm, microfiche, punch cards, all other records kept by electronic, photographic, or mechanical means, charts, photographs, notebooks, drawings, plans, inter-office communications, intra-office and intra-departmental communications, transcripts, checks and canceled checks, bank statements, ledgers, books, records or statements of accounts, and papers and things similar to any of the foregoing, however denominated.

2. The terms "related to" or "relating to" means anything that constitutes, contains, embodies, identifies, deals with, or is in any manner whatsoever pertinent to that subject, including but not limited to records concerning the preparation of other records.

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INDEPENDENT

May 18, 2005

The Honorable Michael Leavitt
Secretary
Department of Health and Human Services
200 Independence Avenue, S.W.
Washington, DC 20201

Dear Mr. Secretary:

We are writing this letter to bring your attention to some matters of concern regarding Dr. James Battey, who allegedly resigned as Chairman of the NIH Stem Cell Task Force, but has since "un-resigned" (if that is the word) his Chairmanship of this important group.

On May 6, Subcommittee staff requested from NIH a list and transcripts of Dr. Battey's speeches or public appearances since March 1 of this year, where the issue of stem cell research was a topic at those events. We received a response on May 9, listing **two** presentations (Smith College on March 4-5; Richmond, VA on March 18). We were told that "[t]hese were the only two presentations [Dr. Battey] made on Stem Cell Research during the time requested."[1]

However, a brief search on the internet revealed at least one additional public appearance where the subject matter was stem cell research, so again on May 9 Subcommittee staff renewed the request for a list of "all public appearances since March 1 of this year" where Dr. Battey spoke on stem cell matters, and transcripts where available.

On May 11, we received a response listing **twelve** presentations.[2] It was in this response that we were also informed that Dr. Battey had "resumed" Chairmanship of the Stem Cell Task Force, a position from which he had resigned on March 18 citing the new NIH conflict of interest rules as prompting his resignation.[3] We were also told that transcripts were not available, except for Dr. Battey's appearance on April 6, 2005 before the Senate Appropriations Subcommittee on Labor, Health and Human Services, Education, and related Agencies.

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[1] Flambert, Gemma, email response to "Battey inquiry," May 9, 2005.
[2] The chart provided to us listing these appearances is attached to this letter.
[3] The new conflict of interest rules were widely reported in the media, and the matter was a significant topic of your April 6 testimony before the Senate Appropriations Subcommittee on Labor, Health and Human Services, Education, and related Agencies.

Important to this matter is the fact that Dr. Battey was a candidate for the position of President of the California Stem Cell Institute, which was widely reported and even referenced during his Senate testimony on April 6, 2005.

Between the period where Dr. Battey formally resigned his Chairmanship of the Stem Cell Task Force (March 18) and when he "resumed" Chairmanship (May 6)[4], he made at least six public speeches or presentations on the subject of stem cell research, and numerous statements to the media on matters related to stem cell research.

The timing and circumstances of Dr. Battey's actions in the last few months raises serious conflict of interest issues. Dr. Battey continued to make formal appearances on the matter of stem cell research as an employee of the NIH, while also publicly a candidate for the California Stem Cell Institute President. We have concerns that "resigning" the Chairmanship and later "un-resigning," while making public speeches and statements related to the central issues of the Stem Cell Task Force appears improper, and perhaps violated the NIH's own ethics guidelines.

First, it is unclear in what capacity Dr. Battey was making public statements and formal appearances dealing with stem cell research: Was it as a representative of NIH, and if so, as head of the Stem Cell Task Force? As the former head of the Stem Cell Task Force? As a job candidate for the California Stem Cell Institute? Obviously, the distinctions are important.

According to the ethics guidelines posted on NIH's website, "an employee may engage in outside activities that require the use of professional qualifications readily identified with his or her NIH position, *provided his/her outside work does not create a real or an apparent conflict of interest* or interfere with regularly assigned official Government duties."[5] The NIH also prohibits activities related to an employee's official duties:

1. **Activities Must Not Be Related to Official Duties:** An employee may not receive compensation for outside activities that relate to his/her official duties and responsibilities as an NIH employee. An activity is considered related to current official work if:
    - it is done as part of official duties or the employee was invited to perform the activity primarily because of the employee's official position, or
    - it deals with any matter to which an employee is presently assigned, or has been assigned during the previous one-year period; or
    - if it deals with any ongoing or announced policy, program or operation of the NIH.[6]

The NIH considers "giving formal speeches or presentations on a scientific or professional topic based on the employee's personal expertise" as an outside activity.[7]

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[4] According to the material provided to us in the response to our request (Flamberg email on May 11, 2005).
[5] National Institutes of Health Ethics Program, Outside Activities, available at http://ethics.od.nih.gov/topics/oa520.htm (last visited May 16, 2005).
[6] Id.
[7] Id.

The Subcommittee is interested in whether Dr. Battey's public statements and appearances between the time he "resigned" and the time he "resumed" his chairmanship were "outside activities" for which he was compensated, and for which he must file a report, in accordance with NIH guidelines. If so, wouldn't such activities, clearly related to Dr. Battey's official duties during the last year, be prohibited by NIH ethics rules?

If Dr. Battey was not compensated, nevertheless the fact that he was speaking on these issues while also a candidate for the California Stem Cell Institute raises concerns. The NIH Ethics Program states that "a 'Conflict of Interest' arises when an employee is involved in a particular matter as part of his/her official duties with an outside organization with which he/she also has a financial interest, or one which is imputed to him/her, i.e.,...a person or organization with which the employee is negotiating for prospective or has an arrangement for prospective employment."[8]

What procedures were followed in approving Dr. Battey's high-profile appearances on a matter that is of such national significance, and for which he held a very prominent position?

Although we were informed that Dr. Battey is no longer a candidate for the California job, it is now unclear whether Dr. Battey has actually "rescinded" his resignation from NIH. In response to our last inquiry regarding Dr. Battey's employment status, we were informed that Dr. Battey "is hoping that the issues that he raised when he stated his intent to resign will be resolved so he can remain in his current position."[9]

Who in the department accepted Dr. Battey's resignation as Chairman of the Stem Cell Task Force? Who accepted Dr. Battey's "un-resignation," and restored him to the said chairmanship? To whom is the resignation reported? What effect does the resignation have on an employee's ethical obligations to the NIH and the Department?

Obviously, considering the importance and controversial nature of the stem cell issue, the appearance of integrity is paramount. However, this situation raises some troubling concerns that we hope you will address.

Finally Mr. Secretary, the last time we sent an oversight request to HHS dealing with critical stem cell research issues, we did not receive a response until after a very unreasonable delay, and the response was inadequate. Specifically, on October 8, 2002, Congressman Chris Smith and I requested "a detailed report" providing comprehensive information about the medical applications of adult and embryonic stem cells as well as stem cells from cloned embryos and aborted fetuses.

Our request was followed by numerous phone calls and a series of eight communications in writing over the subsequent 20 months. The response we finally received on June 18, 2004, stated that there were no treatments or ongoing clinical trials utilizing embryonic stem cells or stem cells from cloned embryos or aborted fetuses. The NIH letter also reported the adverse effects resulting from the two known clinical trials using fetal tissue transplantation to treat

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[8] National Institutes of Health Ethics Program, Conflicts of Interest, available at http://ethics.od.nih.gov/Topics/coi.htm (last visited May 16, 2005).
[9] Flambert, Gemma, email response to "House Government Reform Request," May 12, 2005

Parkinson's disease. This letter was signed by Dr. James Battey. However, the Subcommittee raised numerous material defects in the Department's response, particularly that the response did not address the plain meaning of the Subcommittee's original oversight request. (A copy of our letter to Secretary Thompson regarding this matter is attached.)

We ask that you address the issues raised in this letter regarding Mr. Battey's activities and his employment status, and look forward to receiving your response on these matters by May 27, 2005.

Thank you for your attention to this matter. If you have any questions, please have a member of your staff contact the clerk of the Subcommittee, Malia Holst, at (202) 225-2577.

Sincerely,

Mark E. Souder
Chairman
Subcommittee on Criminal Justice, Drug Policy, and Human Resources

Enclosure

Public Appearances and Speeches on Stem Cell Research
Dr. James Battey

March 1	The Politics of Stem Cell Research: The Stem Cell Controversy	The National Institute of Science, Beta Kappa Chi Honor Society, The Omni Hotel, Richmond, VA
March 4-5	Stem Cell Conference	Smith College, Northampton, MA
March 9	Opening Address: "The Business of Stem Cell Research"	American Enterprise Institute, 1150 17th Street, N.W., Washington, D.C.
March 15	Tribute Reception	Research!America, Tribute Reception, Willard Hotel, 1401 PA, Ave, N.W., Washington, D.C.
March 22	"Workshop on Stem Cell Research, Where is the Beef?"	Southern California of Biomedical Council, Los Angeles, CA.
April 6	Senate Appropriations Hearing	Senate Office Building, Washington, D.C.
April 11	NIH and Stem Cell Research	University of Utah, Genetic Science Learning Center, UT
April 18	Stem Cell Workshop	NIH, NIGMS, Pooks Hill Marriott, Bethesda, MD.
April 25	Business of Stem Cell Research Conference	Bethesda North Marriott Hotel and Conference Center
April 26	Georgetown Chapter of Sigma XI	Georgetown University, School of Medicine, Washington, DC
May 6	Research Dean's Meeting	AAMC, Ritz Carlton, Pentagon City, VA.
May 10	Presentation on Stem Cell Research	National Multiple Sclerosis Society, Mayflower Hotel, Washington, DC

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
Bethesda, Maryland 20892

OCT 7 2005

The Honorable Mark Souder
Chairman, Subcommittee on Criminal Justice,
Drug Policy and Human Resources
Committee on Government Reform
House of Representatives
1227 Longworth House Office Building
Washington, D.C. 20515

Dear Mr. Souder:

I am writing to respond to your concerns regarding Dr. James Battey, Director of the National Institute on Deafness and Other Communication Disorders. As you have noted, Dr. Battey was a candidate for the position of President of the California Institute for Regenerative Medicine during the spring of this year. As you know, seeking prospective employment, as the term is defined for purposes of the Government-wide Standards of Ethical Conduct for Employees of the Executive Branch, triggers certain recusal obligations depending upon the precise facts of the case. Where an employee is seeking employment, but is not yet negotiating for employment, the recusal obligation is regulatory. See, 5 C.F.R. § 2635.604(a). Where, however, such discussions or communications are mutually conducted with a view toward reaching an agreement regarding possible future employment, such employment "negotiations" trigger a disqualification obligation under Section 208 of Title 18 of the United States Code, 18 U.S.C. § 208, because the financial interests of the prospective employer are imputed to the employee. In either case, the employee is prohibited from participating personally and substantially in an official capacity in any particular matter in which, to his knowledge, he will have a direct and predictable effect on the interests of the prospective employer.

The United States Office of Government Ethics (OGE) has opined that a speech given by an employee in his official capacity may be a particular matter under § 208. A speech that solely presents previously released factual information would not, however, likely have a "direct and predictable effect," as the term is defined at 5 C.F.R. § 2640.103(a)(3), on the interests of any entity. An effect is "direct," for these purposes, where there is a close causal link between the decision or action on the matter and any expected effect on the financial interest, and "predictable" where an effect on the financial interest is a real possibility not merely a speculative one. *Id.* Moreover, if the matter at issue in this case is the NIH implementation of the Federal stem cell research program, then presenting previously released factual information on the matter would not constitute "personal and substantial participation," as defined for these purposes at 5 CFR § 2640.103(a)(2), in the matter. Such participation generally occurs when an employee participates through decision, recommendation, or other action. *Id.* While the term is not limited to action or decision that is determinative of the matter, it does require more than perfunctory or administrative involvement, and must be of significance to the matter. *Id.*

I understand that on March 12, 2005, Dr. Battey applied for the position of President of the California Institute for Regenerative Medicine. On March 15, 2005, the first business day after mailing the application, Dr. Battey informed NIH officials that he was a candidate for the position. He was immediately advised that continuing as the Chair of the NIH Stem Cell Task Force during this period would likely result in a conflict of interest and that he would be required to step down to comply with the ethics requirements. By memorandum dated March 18, I then announced to the NIH Institute Directors that Dr. Battey was taking a leave of absence from his position as Chair of the Task Force.

In relation to speaking engagements, Dr. Battey was advised specifically of how delivering speeches in his official capacity could violate the recusal obligation. Ethics officials advised, however, that it would be possible to make a presentation without violating the recusal obligation(s) provided the content was limited strictly to previously released information about the Government's stem cell policy and did not discuss new directions that the NIH may be taking with respect to stem cell research. The parameters included limiting his discussions to previously released information about Federal stem cell policies without discussing any NIH plans or initiatives related to future stem cell research. Once advised, Dr. Battey, like all employees in similar circumstances, was expected to comply with the guidance. Dr. Battey has affirmed that he adhered to these parameters.[1] Dr. Battey gave these presentations as an NIH employee and not in his personal capacity as an outside activity. I am informed that he received no compensation for these duties other than his NIH salary, and because these speeches were part of Dr. Battey's official duties and not outside activities, Dr. Battey was not expected to report them as outside activities.

I understand that in early May, Dr. Battey notified the California Institute for Regenerative Medicine that he was no longer interested in pursuing prospective employment. On May 19, Dr. Zerhouni informed the NIH Institute Directors that Dr. Battey had resumed his duties as Chair of the NIH Stem Cell Task Force.

Please let me know if you have further questions.

Sincerely,

Elias A. Zerhouni, M.D.
Director

Enclosure

[1] Dr. Battey has indicated that the initial list provided to the Subcommittee via email on May 9, and attached to the May 18 letter, contained a minor error regarding the date of one of his public appearances. In addition, one of the appearances listed (March 15, Tribute Reception) did not involve a presentation. Dr. Battey merely attended a reception, referred to under the ethics regulations as a "widely attended gathering." Dr. Battey did not give a presentation at this event, and, consistent with applicable regulations, he attended in his personal capacity. A corrected list of presentations is enclosed.

CORRECTED LIST OF PRESENTATIONS

March 4-5	Stem Cell Conference	Smith College, Northampton, MA
March 9	Opening Address: "The Business of Stem Cell Research"	American Enterprise Institute, 1150 17th Street, N.W., Washington, D.C.
March 18	The Politics of Stem Cell Research: The Stem Cell Controversy	The National Institute of Science, Beta Kappa Chi Honor Society, The Omni Hotel, Richmond, VA
March 22	"Workshop on Stem Cell Research, Where is the Beef?"	Southern California of Biomedical Council, Los Angeles, CA.
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April 26	Georgetown Chapter of Sigma XI	Georgetown University, School of Medicine, Washington, DC
May 6	Research Dean's Meeting	AAMC, Ritz Carlton, Pentagon City, VA.
May 10	Presentation on Stem Cell Research	National Multiple Sclerosis Society, Mayflower Hotel, Washington, D.C.

10/6/05

Follow-up questions from Chairman Mark Souder to James F. Battey, M.D., Ph.D., Chair, NIH Stem Cell Task Force and Director, National Institute on Deafness and Other Communication Disorders, following March 6, 2006, hearing of the Subcommittee on Criminal Justice, Drug Policy and Human Resources entitled, "Human Cloning and Embryonic Stem Cell Research after Seoul: Examining exploitation, fraud, and ethical problems in research"

1. Regarding the scientific process at issue in the Korean scandal:
   - Was it the process of somatic cell nuclear transfer, SCNT (a process for creating cloned embryos), that was supposedly achieved?

ANSWER:

Yes

   - Was it supposedly the same process that was used to create Dolly, the cloned sheep?

ANSWER:

Yes. Dolly, the cloned sheep was created by Somatic Cell Nuclear Transfer, which the Korean research used to create their embryos. The Korean researchers did not, however, propose to take their cloned embryos to live birth but rather to destroy them at an early developmental stage to derive stem cells from them. The first step, the cloning step, is the same, but the intended result is different.

   - And in this case, it was supposedly used to produce cloned human embryos for research purposes?

ANSWER:

Yes. By combining a patient's somatic cell nucleus and an enucleated (nucleus removed) egg, a scientist might create a cloned human embryo that can then be destroyed to harvest embryonic stem cells. Since the embryo is genetically virtually identical to the donor of the somatic cell nucleus, the resulting stem cells could be used to generate tissues that match that patient's body. This means, at least in theory, the tissues created are unlikely to be rejected by that patient's immune system. The researchers did not, however, seek to transfer the cloned embryo into a woman's uterus to develop to birth.

SCNT could presumably be used to accomplish either type of cloning.

2. The results in Korea, which we now know were fraud, were used to tout the promise of cloning for research, by advocates and politicians.
   - Any proof that SCNT has ever been successfully used to produce human embryonic stem cell lines?

ANSWER:

No.

3. The Korean studies were hyped as revolutionary advances. Even putting aside the issue of fraud here, are you concerned that the promise of embryonic stem cell research is being oversold by some advocates and politicians?

ANSWER:

Embryonic stem cell research has shown promise in the laboratory using animal models of human disease. There is the potential for treating diseases in humans. Scientists still have laboratory and clinical research that must be completed before that can be achieved, however. NIH is committed to studying all areas of stem cell research.

4. A common figure tossed around regarding the "promise" of embryonic stem cell research is that it can provide cures for 100 million people.

- Is there any scientific evidence to actually support that claim?

ANSWER:

It is unclear where this statistic came from. Human embryonic stem cell (hESC) research is a relatively new field of science, having been first reported by James Thomson at the University of Wisconsin in 1998. More basic research needs to be conducted in the laboratory before the full potential for treating diseases is clear.

5. Addressing the notion that embryonic stem cells can "become any kind of cell type in the body"

- Is that supported by evidence or current science?
- How many cell types have actually been achieved?

ANSWER:

Scientists report having differentiated embryonic stem cells into many different adult cell types. Some of these include: dopamine-producing nerve cells (the type lost in Parkinson's disease), insulin-producing cells, nerve support cells called glia, other types of nerve cells, blood cells, heart muscle, skeletal muscle, smooth muscle, cartilage, bone, liver, pancreas, sperm and eggs, fat cells, skin, the cells that detect sound in the inner ear, cells that line blood vessels, lung cells, and retinal cells of the eye.

Due to the pace of science, it is difficult to provide a complete list of all cell types derived from hESCs. However, the evidence thus far suggests that hESCs are able to become most, if not all, cell types in the body, under the proper culture conditions.

Another piece of evidence to support the pluripotency of hESCs is the teratoma test. Scientists verify that they have established a hESC line by injecting putative stem cells into mice that lack an immune system. Since the injected cells are not destroyed by the mouse's immune system, they survive and form a multi-layered benign tumor called a teratoma. Even though tumors are not usually a desirable outcome, in this test, the teratomas serve to establish the ability of a stem cell to give rise to all cell types in the body. This is because the teratomas contain cells derived from each of the three **embryonic germ layers** (explained below).

During normal development, the fertilized egg divides to produce cells that eventually make up three layers, called the **embryonic germ layers**. All cells in the body originate from one of these three layers (endoderm, mesoderm, and ectoderm). Teratomas formed by hESCs consist of gut epithelium (endoderm layer derivatives); cartilage, bone, smooth muscle and striated muscle (mesoderm layer derivatives); and neural epithelium, nerve ganglia, and stratified skin (ectoderm layer derivatives). The original injected cells' ability to produce cell types from all germ layers is evidence for pluripotency- the ability to form any cell of the body.

6. How much money was spent on human embryonic stem cell research in 2005? What portion of that went to the University of Pittsburgh researcher Gerald Schatten?

ANSWER:

In FY 2005, NIH-supported approximately $40 million in research involving hESCs. Of this amount, just over $1 million was in support of Dr. Schatten's projects on hESC.

7. University of Pittsburgh researcher Gerald Schatten is doing work on approved Bush stem cell lines as well as on primate embryos.

- How is Schatten's grant award categorized (as being all embryonic stem cell research, is the primate research categorized as something else)?

ANSWER:

In Dr. Schatten's center grant "Pluripotent Stem Cells in Development and Disease" the research is studying both human embryonic stem cells that are eligible for federal funding and non-human primate embryonic stem cells. In FY 2005, approximately 25% ($750,000) of the research focus of this project involves hESCs and 75% ($2,250,000) is devoted to non-human primate embryonic stem cells.

8. Where does Gerald Schatten's $16.1 million grant award fall in terms of how it compares to other large grant awards for all types of embryonic stem cell research?

ANSWER:

NIH awarded a grant (1P01HD047675-01A1) "Pluripotent Stem Cells in Development and Disease" to Dr. Schatten that totaled $16.1 million over 5 years. The portion of the

grant involving hESC research is $750,000 in FY 2005. Dr. Schatten's P01 grant is one of the larger hESC projects awarded by NIH in FY 2005; however, it is not the largest hESC research project. In FY 2005, NIH awarded $4.2 million to WiCell Research Institute to support the National Stem Cell Bank, plus there were eight other projects that were larger in hESC funding than Dr. Schatten's P01 grant.

9. How does Schatten rank in terms of NIH grant awards for ESCR in monkeys and the approved stem cell lines? How many grants has he been awarded? Is he the top single grantee for ESCR grants?

ANSWER:

Dr. Schatten is considered an expert in the field of non-human primate stem cell research, growth of human embryonic stem cells in culture, and non-human primate animal models. The P01 grant is unique in that it involves research involving both non-human primate and human embryonic stem cells; therefore, there are no other NIH-supported projects that have a similar scope. In FY 2005, Dr. Schatten received 3 individual NIH-supported grants that involve hESC research. The cumulative amount of hESC research funding of these grants was $1.1 million. Dr. Schatten is not the top single grantee for NIH-supported hESC research. In FY 2005, there were four other individual scientists who received more NIH funding for hESC research.

10. Gerald Schatten's successful grant application makes reference several times to Korean research.

- Was Schatten's grant contingent upon what was still viewed at the time of the grant application as successful Korean research in these areas?

ANSWER:

No. Dr. Schatten's grant award was not contingent on the stated work of the South Koreans, but instead was based on the results of work with monkeys eventually published in Developmental Biology in December 2004 as Simerly, et al., "Embryogenesis and blastocyst development after somatic cell nuclear transfer in non-human primates; overcoming defects caused by meiotic spindle extraction." That paper showed for the first time that cloned blastocysts can be developed in non-human primates – and most importantly, that unrelated nuclei were successful and transferred into different eggs. Dr. Simerly and other members of Dr. Schatten's lab were leaders of that work. The federal grant application in question was first submitted in 2003, then revised in November 2004 and reviewed by the National Institutes of Health a second time in April 2005. It did not cite the subsequently published (now withdrawn) Hwang Science '05 report. The federal grant application properly referenced the then-existing Hwang, et al., Science '04 article but did not rely on it as sole support for the importance of any of the application's numerous specific aims or even the only aim focused exclusively on deriving non-human primate embryonic stem cells by nuclear transfer (NT-nhpESC).

11. What are the 2005 figures for ESCR grant awards (i.e., how many grants, total dollar amount smallest grant award and largest grant award)?

ANSWER:

In FY 2005, NIH supported 154 individual research projects involving hESCs at the amount of approximately $40 million. In comparison, NIH supported approximately $199 million in human nonembryonic stem cell research in FY 2005. The smallest individual hESC project was a $2,000 effort to intramural scientists at NIH's National Human Genome Research Institute to conduct Genome Instability in Cancer Development. The largest hESC project was $4.2 million awarded to WiCell Research Institute to support the National Stem Cell Bank. In the FY 2005 listing of NIH hESC projects that we provided you after the hearing, some projects were shown with award amounts of less than $2,000. These projects were co-funded by multiple NIH Institutes/Centers (ICs) and the funding levels between the ICs differ.

12. In your oral testimony before the Subcommittee on March 7, 2005, you stated that you had finished a response to the Subcommittee's letter of October 8, 2002, within a "matter of weeks". The Subcommittee was seeking a "detailed report" providing comprehensive information on the medical applications of adult and embryonic stem cells as well as cells from cloned embryos and aborted fetuses. However, the Subcommittee did not receive a response to this letter seeking critical information until twenty months after it was sent, during which time the Subcommittee staff made numerous inquiries and additional Chairman's letters were sent.

You said in your testimony that although you had completed the letter in a matter of weeks, the extreme delay was caused by other officials in the agency. Please provide the names of all employees and/or officials who held up this letter, listing contact information for each person/office with how long they delayed the response and the reasons why. If you are unable to answer this question fully and completely, provide the Subcommittee staff with appropriate names and contact information for the appropriate official/s who can answer this question completely.

ANSWER:

In providing written information to Congress, it is critical that such information be as accurate and complete as possible. This therefore requires review within multiple channels of NIH and HHS to be cleared. We work to respond to inquiries as quickly as possible, and sometimes, additional time is required to collect, review, and summarize the scientific data, as in this situation. The delay was inappropriate, and it is critical that we be as responsive as possible.

13. In May of last year, Chairman Souder inquired with Secretary Leavitt about matters concerning your temporary resignation at the beginning of last year, then "unresignation" as the Chair of the NIH Stem Cell Task Force, while you were a job candidate to head the

California Institute of Regenerative Medicine, the California stem cell center established as the result of the state's controversial Proposition 71.

During the period of "resignation" you continued to make appearances and presentations on stem cell research. At the very least, this gives an appearance of impropriety, but we have concerns that this was a clear conflict of interest, and a violation of HHS's own ethics guidelines, which state the following:

- an employee may engage in outside activities that require the use of professional qualifications readily identified with his or her NIH position, provided his/her outside work does not create a real or apparent conflict of interest or interfere with regularly assigned official Government duties.

Based on information provided to the Subcommittee through a document request, it appears that HHS's own legal counsel advised you against continuing to speak on these matters during your extra-government job candidacy [documented in emails in the Subcommittee's possession]. As the Hwang scandal is demonstrating, it's clear that we have to be vigilant in guarding against impropriety among the leaders working in the field.

- Explain your justification for continuing to make stem cell presentations while at the same time, seeking a high profile job at the California Institute of Regenerative Medicine.

ANSWER:

When I stepped down as Chair of the NIH Stem Cell Task Force during my employment negotiations with the CIRM, I had already accepted several speaking engagements. I had a strong desire to honor these previous commitments. In the weeks that followed, I received invitations from other organizations to speak on stem cell research. Because of my subject matter expertise, I was the best qualified to deliver these talks. I wanted to continue to serve the NIH in this way. Hence, I requested approval from NIH Ethics Officials to accept these invitations, and approval was given subject to the parameters they laid out for me.

I note that the HHS guidelines that you refer to in your question address conflicts that may arise from performing outside activities. Regarding the advice from HHS legal counsel, I did not understand it to advise against giving the speeches. Rather, I understood it to explain parameters in which I was required to stay while delivering these speeches to avoid the appearance of a conflict. In every instance, I believe I adhered to the advice.

14. During the period of your "recusal" as head of the NIH Stem Cell Task Force, and while you were a candidate for the job to head the California Institute of Regenerative Medicine, you gave at least twelve presentations on stem cell research, including one at an investors' Conference for the California Biomedical Council, speaking on a panel listed in the conference brochure as "Opportunities in Stem Cell Research: organized in recognition of the importance of the California Stem Cell Research Initiative and to stimulate thinking about its likely impact on healthcare delivery and job creation."

You were also listed as a participant in the National Institute of General Medical Sciences workshop, "Human Embryonic Stem Cell Research: Recent Progress and Future Directions of NIGMS Grantees?" The purpose of this meeting was "to provide an opportunity for NIGMS grantees conducting human embryonic stem cell research to report on their recent progress, to exchange information, and to identify problems, challenges and opportunities associated with this emerging area of research."

Among the sixty-eight participants in this important stem cell research grantee meeting, you are the only Institute Director listed, and of sixty-eight research grantees participating in the meeting, ten are California-based. All of the California researchers' affiliated institutions would have been candidates for multimillion dollar grants from the California Institute of Regenerative Medicine at the time of this meeting. The California Institute of Regenerative Medicine has since awarded $15.9 million grants to California institutions represented at this workshop.

- Explain your justification for how this does not present a conflict of interest.

ANSWER:

As I understand the law, a conflict of interest would arise if I had participated personally and substantially in a matter that would have a direct and predictable affect on the financial interest of my prospective employer, the California Institute of Regenerative Medicine (CIRM). The matter in which I participated was the NIGMS workshop, not the awarding of grant money by CIRM to some of the workshop's participants. It is unlikely that the NIGMS workshop had any affect on CIRM's financial interest. Even if the workshop did affect CIRM's financial interests, I did not participate in that matter personally and substantially. My participation in the NIGMS workshop was limited to giving opening remarks as a substitute for NIGMS' Director, Dr. Jeremy Berg. (I agreed to this role long before I applied to CIRM.) After introducing the workshop, I left and did not return. These remarks strictly complied with the parameters given to me by ethics officials with respect to stem cell related presentations. Thus, my remarks did not create a conflict of interest with my employment negotiations with CIRM.

I note it is not unusual to have the Director of the sponsoring Institute be the sole Director to attend and address a workshop. As the substitute for NIGMS' Director at a NIGMS workshop, it was very reasonable for me to be the only NIH Institute Director present.

Questions from Chairman Mark Souder
Subcommittee on Criminal Justice, Drug Policy, and Human Resources to

Bernard Schwetz, D.V.M., Ph.D.
Director, Office for Human Research Protections
Department of Health and Human Services
following March 6, 2006 hearing entitled, "Human Cloning and Embryonic Stem Cell Research after Seoul: Examining exploitation, fraud and ethical problems in the research"

1. In your written testimony, you mentioned studies involving research with embryonic stem cells. To clarify:

-- Are there any clinical therapies or clinical trials ongoing using embryonic stem cells, or was this hypothetical?

ANSWER:

The Office for Human Research Protections (OHRP) is not aware of any ongoing clinical therapies or clinical trials conducted or supported by the Department of Health and Human Services (HHS) that involve the use of embryonic stem cells.

2. Upon examining the guidance document you included in your written testimony, we confirmed that nothing is mentioned about whether women who donate their eggs for research are considered Ahuman subjects. In fact, your written testimony suggests that as long as no one could trace whose eggs were whose, IRB protections, etc., would not even apply to women donating eggs.

-- Would women donating their eggs for research in the United States be considered Aresearch subjects@ entitled to federal protections?

ANSWER:

The HHS regulations for the protection of human subjects (45 CFR part 46) apply to all research involving human subjects that is conducted or supported by HHS. Through its assurance of compliance with OHRP, an institution also may voluntarily extend these HHS regulations to all its human subjects research, regardless of funding source. Therefore, if a research study was funded by HHS or conducted at an institution that voluntarily extended these HHS regulations, and involved harvesting eggs from women for the research, then the research would be covered by 45 CFR part 46. In these cases, the woman's informed consent generally would be required before her eggs could be obtained. In addition, if a research study involved the use of eggs that were originally harvested from women for clinical purposes, and the eggs were associated with identifiable information about the women donors, such research would also be covered by the HHS regulations if the research was conducted or supported by HHS, or conducted at an institution that extended these HHS regulations to all human subjects research conducted by the institution.

Note that all clinical research involving drugs, devices, and biological products that is regulated by the Food and Drug Administration (FDA), including cells or test articles regulated as drugs, devices, and biological products, is also subject to FDA regulations governing investigational new drugs (INDs) or devices (IDEs) (Title 21 CFR Parts 312 or 812), regardless of the source of support. Such clinical research is also subject to FDA=s institutional review board (IRB) and informed consent regulations (Title 21 CFR Parts 50 and 56).

3. We know that prior to Hwang's disgrace, the Pacific Fertility Institute in California had entered into an agreement with Hwang to provide eggs from American Women for his research. Of course, given the scandal, the Fertility Institute withdrew from that agreement.

-- If Hwang had been able to continue his fraud, what protections, if any, would these women have had?

ANSWER:

The HHS regulations for the protection of human subjects would have applied if the research involved Ahuman subjects, as defined at 45 CFR 46.102(f), and the research was either conducted or supported by HHS, or conducted at an institution that had extended these HHS regulations to all human subjects research conducted by the institution. In addition, as discussed in the answer above, depending on the nature of the research, the FDA's human subject regulations also might have applied.

4. Since one of the drugs (Lupron) commonly used to hyperstimulate the ovaries so that multiple eggs can be extracted has not been approved for use in egg extraction, what protection does FDA offer women who undergo this procedure solely to donate their eggs for research?

ANSWER:

OHRP is not able to answer this question. We suggest that this question be directed to the FDA.

5. You mention in your written testimony that we regularly conduct research with no known direct benefit to the patient. As you are aware, however, the hoped-for research benefits in clinical research must have some reasonable expectation of success in order for IRBs to approve the assumption of risk on the part of the research subjects.

Along these lines, you may know that shortly after Hwang published his 2005 cloning paper, Stanford bioethicists David Magnus and Mildred Cho (neither of whom are opposed either to ESCR or cloning) argued in article also published in the journal *Science*:

> "It is necessary that prospective [egg] donors recognize the large gap between research and therapy...Because it is likely that oocyte donors [egg donors] will be recruited from individuals with diseases and disabilities or their close family members, researchers must

make every effort to communicate to these volunteers that it is extremely unlikely that their contributions will directly benefit themselves or their loved ones..."

They go on to say:
"The language used to describe the research can reinforce the therapeutic misconception...There is currently no such thing as therapeutic cloning and this [meaning Hwang=s work] is not therapeutic cloning research nor can we say with any certainty that Acell therapy@ is in the near future."

You mentioned the Belmont Report several times in your written testimony. You must also be aware of the Helsinki declaration, which states that:

"Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research" (World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects (Adopted by the World Medical Association General Assembly in June, 1964). Available at http://www.wma.net/e/policy/b3.htm (Last visited March 8, 2006)).

-- Given the above by Professors Magnus and Cho, how would you expect an IRB to view women who volunteer for multiple egg extraction? Are they human subjects? Are they entitled to protections?
-- What level of risk is justified given the speculative nature of cloning research? Would a 15-20% rate of ovarian hyperstimulation syndrome (as was reported in the Hwang scandal) be an appropriate risk for research with purely unknown and untested benefits even in animals?

ANSWER:

As discussed above, women who volunteer for egg extraction for research purposes would be human subjects under the HHS regulations at 45 CFR part 46. If such research were conducted or supported by HHS, or by an institution that had extended these HHS regulations to all human subjects research conducted by the institution, the research would be required to undergo IRB review and approval before it could proceed. As part of an IRB=s review, the IRB must make several determinations before it can approve the research. Included among these determinations is the need to ensure: (1) that risks to subjects are minimized; (2) that risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result; and (3) that the selection of subjects is equitable. Under the HHS regulations, the appropriate balance between risks and benefits is not specified. This assessment must be made by a qualified and appropriately constituted IRB.

In addition, the HHS requirement for informed consent further protects the rights and welfare of

prospective research subjects. The only exception to this requirement for informed consent is if the IRB has determined that specified waiver criteria have been met (45 CFR 46.116(d)). As Dr. Bernard Schwetz stated in his written testimony, as part of the informed consent process, investigators must give prospective research subjects sufficient information about a research study to make an informed decision about whether or not to participate. All reasonably foreseeable risks or discomforts, and reasonably expected benefits of the research must be described. If the research study does not offer subjects the possibility of direct benefit, this must be clearly stated in the informed consent process.

Note that a provision included in the annual HHS appropriations bill specifically prohibits HHS support of "the creation of a human embryo or embryos for research purposes," and that provision (most recently P.L. 109-149, Title V, Section 509) defines human embryo to specifically include embryos created by human cloning.

Questions from Chairman Mark Souder, Subcommittee on Criminal Justice, Drug Policy and Human Resources to Chris B. Pascal, J.D., Director, Office of Research Integrity (ORI), Department of Health and Human Services following March 6, 2006 hearing entitled, "Human Cloning and Embryonic Stem Cell Research after Seoul: Examining exploitation, fraud and ethical problems in the research"

1. It appears that a large grant to the University of Pittsburgh researcher Gerald Schatten was made with at least some consideration of what was still thought to be successful Korean research, in that Korean research is mentioned several times in Schatten's grant application.

What is the process for revisiting federal grant awards when they appear to be based on questionable or fraudulent claims?

ANSWER:

If there is evidence of research misconduct in a Public Health Service (PHS) grant application (whether discovered immediately or later), the institution would follow the process set forth in the PHS Policies on Research Misconduct: an initial inquiry to determine whether misconduct may have occurred; then, if necessary, a formal investigation to determine if misconduct actually occurred and if so, who was responsible and how significant it was. The institution is required to submit an investigation report to ORI, and ORI would then conduct an oversight review of the report.

Is ORI in any way reviewing the grants made to Schatten at the University of Pittsburgh?

ANSWER:

Federal privacy laws and the PHS Policies on Research Misconduct prohibit HHS from admitting or denying the existence of ORI research misconduct proceedings. However, should a grantee institution commence a research misconduct investigation, the institution would be required to report the investigation to ORI, and ORI would conduct an oversight review of the institution's report. In its oversight review, ORI would reach its own conclusions regarding whether misconduct occurred, how serious it was, and what type of administrative actions might be needed to protect biomedical research and the public.

2. You mentioned in your written testimony that when fraud is suspected, an investigation is initiated and conducted at the grantee institution, which must report to ORI when they decide to proceed with a formal investigation, or when admissions are made by accused researchers. This seems to present a conflict of interest for the grantee institution, which investigates one of its own.

Are there any meaningful safeguards in the process to ensure that grantee institutions aren't whitewashing or outright ignoring scientific misconduct when they are acting as the first level of investigation into potential fraud?

ANSWER:

The PHS Polices on Research Misconduct establish a number of checks and balances to make sure the institutional investigation is competent, thorough, and objective. Perhaps the most important safeguard is ORI's authority to conduct an independent oversight review of the institution's investigation report. During an oversight review, ORI conducts a full review of the institutional process, investigation report, and findings. That can include having ORI staff scientists conduct an independent assessment of all of the research data involved, if necessary. ORI can adopt additional findings of misconduct that the institution did not make, or request that the institution reinvestigate aspects of the case. If needed, ORI can request the HHS Office of Inspector General to conduct an independent investigation, using information provided by ORI scientists as needed. If there is evidence of civil or criminal fraud, ORI may ask the Department of Justice to review the case. Research misconduct complainants also have the option of presenting an allegation of wrongdoing directly to ORI, rather than the grantee institution. The PHS Policies on Research Misconduct authorize ORI to implement specific compliance actions against institutions that are found in violation of a regulatory requirement. These remedies include, for very serious non-compliance matters, the suspension or termination of the institution's PHS support.

Questions for the Record Response
Judy Norsigian
Executive Director
Our Bodies Ourselves

Re: Subcommittee Hearing, "Human Cloning and Embryonic Stem Cell Research after Seoul: Examining exploitation, fraud and ethical problems in the research"

1. I do not think that the NAS guidelines go far enough. At this point, until there is a stronger case to be made for SCNT research OR there is FDA review of drugs used routinely during multiple egg extraction procedures (and not currently FDA-approved for these purposes), SCNT research should go forward ONLY with eggs resulting from natural cycling, extraction at the time of an ovariectomy, and similar situations where risks are greatly reduced.

2. Regarding compensation: egg providers should be donors, and all should be treated similarly. No compensation for lost wages is appropriate (as your question even suggests, there is no fair way to do this anyway without producing excessive incentives for poorer women; clinical trial experience to date – especially in other countries – would support this assertion). The attached recent article about Indian women choosing to become gestational mothers for well-to-do American families underscores some of the problems here. As for other compensation, there should be reimbursement for travel, child care expenses, and similar items routinely covered under most research protocols.

3. If oocyte donation were demonstrated to be safe, I do not believe that there is anything inherently exploitive in women choosing to donate eggs for research. The potential for exploitation would exist, but this is sometimes the case with research, and safeguards can be instituted to mitigate against this.

4. A concern for "women's rights" may have been a motivation for some people in other countries who worked on regulations such as those now in Canada, but I don't believe this was ever a primary motivation. I believe that safety concerns as well as concerns about the absence of policies addressing the issue of human germline genetic modification (these go beyond safety questions) were paramount for many advocating for these policies.

5. It is difficult to predict exactly how many eggs would be needed to make progress with this area of research (some of which hopes to eliminate the need for egg donors altogether), but it is certainly in the tens of thousands at least. Obviously, with the intense financial pressures experienced by thousands of women, many would be drawn to this option, and many more would experience adverse health outcomes than do already.

6. It is not at all paternalistic to ask that the basic principles regarding the health and well being of individuals willing to participate in scientific research be followed. There are many things that we are not allowed to do (even if we would like to) because of

considerations more important than individual choice (and safety is certainly a major such consideration).

7. The Dutch study which showed an effect on mice offspring is relevant, because it challenges earlier assumptions that OHS in the mother wouldn't have a direct effect on offspring. Since extra cervical ribs are correlated with increased rates of stillbirth, congenital anomalies and cancer in humans, the possibility that this complex of conditions may be induced by OHS in mammalian species is worrisome.

8. I am not sure I understand Question #8. Those making decisions about this research are free to approve it (although there may be some problems in finding enough women to supply all the eggs desired by researchers). Those of us objecting to SCNT going forward as of this time would like to convince these decision-makers to proceed with greater caution, so I suppose one could refer to us as "obstacles" as well. By the way, we believe that the term "therapeutic cloning" should really be avoided, since there is no evidence yet that therapies are likely to be direct outcomes of this research.

9. There are at least a few documented cases of deaths from OHSS, so the answer is yes. Some of these are written up in the medical literature.

10. Egg extraction for research should take place outside of the IVF context, so that there will be much less likelihood that women will experience pressure to donate eggs for research rather than for reproductive purposes. This could compromise the success of an IVF effort where a woman is seeking to become pregnant. See attached item from a recent issue of Nature –where this same position is taken.

I would be pleased to answer further questions if the need arises.

Sincerely,

Judy Norsigian

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1. *Do the National Academies' recommendations go far enough in protecting women from the dangers of egg extraction for research purposes? What more is needed?*

The National Academies'(NAS) guidelines propose a number of important strategies to protect women's health, but these are merely guidelines intended to encourage responsible practices. They provide no oversight or enforcement and they offer little or no protection against many potential loopholes.

The NAS guidelines are a good beginning, in that they establish a broad consensus on the need for informed consent of the oocyte donor, the inadvisability of cash or in-kind payments for donating oocytes for research purposes, and the importance of limiting reimbursement only to direct expenses incurred as a result of the egg extraction procedure. They also begin to address a very important potential conflict of interest among physicians involved in egg extraction by recommending that the attending physician providing the infertility treatment should not be the same person deriving or proposing to use human embryonic stem (hES) cells.

These guidelines are of limited value, however, in that they place the ultimate responsibility for ensuring that researchers conduct themselves according to professional standards on the investigators themselves and on their institutions. For example, they recommend that all institutions involved in hES cell research establish an Embryonic Stem Cell Research Oversight (ESCRO) committee that includes "representatives of the public and persons with expertise in developmental biology, stem cell research, molecular biology, assisted reproduction, and ethical and legal issues in hES cell research." These ESCRO committees are to provide an additional level of review to existing Institutional Review Boards (IRB). This recommendation for public representation is vague and there is no provision to assure that individuals serving in this capacity, at the discretion of the institution, would have any realistic ability to function independently or to exert any influence.

A significant loophole in the NAS guidelines exists in the recommendation that the attending physician should not be the same person deriving or proposing to use hES cells, because it includes the qualifier, "[w]henever it is practicable."

The existing system of self regulation in institutions that will be conducting egg extraction and hES cell research is already seriously deficient. IRBs are often overburdened and riddled with conflicts of interest. Typically the committee members do not conduct any oversight beyond initial review of the proposals, and violations only come to light through whistleblowers. It was under this existing IRB system of self regulation that the protocols for gene therapy clinical trials at the University of Pennsylvania were approved that led to the death Jesse Gelsinger. Adding another similar layer of mere review without addressing any of the limitations of the first layer simply compounds the problem.

The NAS guidelines cannot solve the ethical problems that egg extraction presents primarily because informed consent is not currently possible given the current limited knowledge about the side effects of egg extraction, as I explained in the body of my testimony. Essentially such guidelines are premature. We must identify more clearly the side effects of ovarian hyperstimulation before we involve young women in this process purely for research.

The California Institute of Regenerative Medicine (CIRM) has recently developed regulations for its hES cell research, and is attempting to reassure the public by stating that CIRM's regulations are based on the NAS guidelines. Yet these regulations approved by CIRM's governing body on February 10 of this year provide an important example of the inadequacy of using NAS guidelines as the standard. A recent analysis by Debra Greenfield, attorney and bioethicist with Prochoice Alliance for Responsible Research (a California-based prochoice women's health advocacy group), demonstrates that ESCRO committees create no central oversight or procedural mechanisms for reviewing or enforcing compliance. Greenfield notes that this approach substitutes disclosure for "the creation of actual, real protections based upon public discussion and perceptions regarding the ethical issues involved in the science." The CIRM's implementation of NAS guidelines results in potential donors being left "with the burden of the decision-making process without adequate knowledge of the science and medicine involved." While these regulations may have been drafted with the best of intentions, they indicate that a "desire to fulfill the needs of the research took precedence" over the need to protect potential participants.

I concur with Greenfield's concerns. The NAS guidelines are only a beginning and following them does not do enough to protect women's health. The multiple dangers posed by expanding egg procurement for research purposes can only adequately be addressed within the context of more research on the health consequences for women and the establishment of an enforceable national system of oversight. This oversight system would move beyond mere disclosure to effectively protect women's health and eliminate conflicts of interest on review committees and among physicians engaging in egg extraction.

2. *Is it possible to fairly compensate women for their eggs? How would an oocyte compensation program protect against the fact that poor women who need the money more than wealthier women would be more likely to put themselves through the unpleasant process of oocyte donation?*

It is difficult to fairly compensate women for undergoing a process that in many cases may have long-term negative health consequences that are unknown at the time the eggs are extracted. If "donors" later acquire ovarian or other cancers, loss of fertility, diminished kidney function, or other such potential side-effects of egg extraction, even guaranteed long-term health care would be inadequate compensation.

Many young women who need money for education or other purposes are currently selling their eggs for use in IVF. Embryo cloning research will only increase the demand for eggs. The best way to protect poor women from putting themselves at risk is to forbid any compensation beyond reimbursement for direct out-of-pocket expenses incurred in the process. The success of this approach depends on strict definitions of "expenses" and strong oversight.

The issue of fair compensation is complicated by the fact that scientists may patent products of donated oocytes in an effort to profit from them. Women donors need to be informed of this so

that they can judge the fairness of their being asked to take significant health risks in such a commercial context.

3. *Even if oocyte donation were safe, do you think it would still be exploitive to use women for their eggs?*

Egg extraction usually involves hormone injections administered daily over a 7-10 day period. According to the Ethics Committee of the American Society for Reproductive Medicine it also requires about "56 hours in the medical setting, undergoing interviewing, counseling, and medical procedures"(Steinbrook, NEJM 1-26-06, vol.354:324-326). In my view, even aside from the health risks, this is exploitive unless the egg provider receives some direct and concrete health benefit. It is particularly exploitive, and emotionally coercive, to appeal to women's altruistic impulses with inflated claims that their eggs will contribute to cures for their loved ones.

It will always be exploitive to take and use biological material from donors to generate products or processes for commercial use. This exploitation becomes even more extreme when these materials are patented, and the patents become barriers to treatments, possibly even to treatments needed by the original donors. This problem is discussed in more detail in Appendix E of my testimony.

4. *Are you aware if a concern for women's rights was a driving force behind other countries' laws regulating egg donation and SCNT (such as Canada's Assisted Human Reproduction Act, which prohibits human cloning as well as the buying and selling of female eggs)?*

Yes, a concern for women's rights was a major driving force behind Canada's Assisted Human Reproduction Act. Canadian feminists lobbied hard for support of this measure because they believe it protects the health and well-being of women and children, and prevents the commercial exploitation of reproduction. The Act establishes the Assisted Human Reproduction Agency of Canada (AHRAC) to develop regulations, license and oversee relevant activities in all public and private clinics and research laboratories. It prohibits the following practices: creation of embryos solely for research; germline genetic engineering; the creation of human/non-human hybrids and chimeras; all use of somatic cell nuclear transfer; sex selection except to prevent, diagnose or treat a sex-linked disorder; commercial surrogate motherhood contracts and the sale of sperm, eggs and embryos. Another indication of the strong concern for women's rights was the recommendation by Senators voting for the bill that at least 50% of the members of AHRAC's governing board should be women.

(See Health Canada's AHRAC website: http://www.hc-sc.gc.ca/hl-vs/reprod/hc-sc/index_e.html. Or for a good summary of AHRAC see: http://www.genetics-and-society.org/policies/other/canada.html.

5. Please see attached information from Do No Harm, which concludes that based on published data, in order to provide genetically matched embryonic stem cells derived from cloning to treat the potential national patient pool, scientists would have to obtain at least 670 million eggs donated by at least 67 million women. *What do you think are the forseeable effect of such a huge demand for oocytes?*

I cannot see any way of dismissing this estimate as unreasonable. I believe that cloning is not a rational or practical way to address the problem of immune response. At best this would be boutique medicine for the most privileged segment of the population at the cost of jeopardizing the health of millions of women.

6. *Some people think that women should be able to decide for themselves whether or not they want to donate their eggs to science. What do you say to the charge that it is being paternalistic to establish a policy, such as a moratorium on SCNT, that essentially deprives women of the choice to do so?*

A moratorium on SCNT is not a permanent ban, but simply a temporary strategy to assure that informed consent is adequate. But even after a moratorium is ended, serious problems with egg extraction need to be addressed at the policy level. A major problem is that egg extraction must be conducted by a medical professional, usually a physician. The doctor/patient relationship has historically been a relationship based on the assumption that the doctor's primary goal and responsibility is to protect or restore the patient's health. When the doctor becomes the agent of a third party, in this case a researcher, and relates to the patient with the researcher's interests in mind, as opposed to those of the patient, the doctor is violating the basic assumptions of the doctor/patient relationship. Abandonment of these traditional assumptions leaves the patient in a particularly vulnerable position. It is not paternalistic to recognize this. Doctors also deserve to be protected from the distortions this creates in their relationship with their patients. It is the appropriate role of policy makers and physicians to see that patients, who often feel a need to please their health providers by being "good patients" to get the best possible care, are not called upon to make decisions that violate the traditional understandings of the important contribution of medical expertise in the doctor/patient relationship.

7. *You mentioned in your written testimony a Dutch study that indicates problems in the offspring of mice that have undergone ovarian hyperstimulation. Could you explain why that is significant for humans?*

For over a century mice have been used in cancer research and drug studies because they possess a surprising biological similarity to humans. Mice have been very important in contributing to our understanding of tumor initiation and growth and the molecular basis of specific gene-associated human diseases, including atherosclerosis and diabetes. They have been widely used to test the cancer-causing ability of substances
as well as therapeutic drugs, and many of these findings have proved relevant to humans. Much of the hope of stem cells as regenerative tools is based on mouse studies. Mouse studies generated many of the earliest warnings of cancer resulting from previous medical misuses of hormones on women in studies of (diethylstilbestrol) DES. Given the long history of significant findings for humans based on mouse studies, and the paucity of research on human offspring after ovarian hyperstimulation, any demonstrated harm to mouse offspring from hormonally perturbing the mothers must be taken very seriously until proven not to apply to humans.

8. *What would be the most difficult problems* to overcome in allowing therapeutic cloning, *SCNT to move forward?*

The most immediate serious problem is the threat to women's health implicit in the harvesting of the vast numbers of human ova required for SCNT. Another serious problem is that the only

difference between SCNT and reproductive cloning is the intent of the researchers, and once we develop and disseminate the technology we have no way of preventing its use for reproductive purposes. We also have no way to prevent or even monitor the misuse of SCNT for inheritable genetic modification, including designer babies, or for the arbitrary proliferation of human-animal hybrids and chimeras.

9. *Do you know of cases where women have been rendered infertile or have died as a result of egg extraction?*

Yes, Gena Correa published the names of three women who died as a result of egg extraction procedures in her book, *The Mother Machine: Reproductive Technologies from Artificial Insemination to Artificial Wombs* (1988:318). They are Senaide Maria Bernardo of Brazil, Aliza Eisenberg of Israel, and Andrea Dominguez of Spain. She reported that another unnamed woman died in Perth, Australia, as well.

I have included in an appendix to my testimony the account by the mother of Jacqueline Rushton who died in 2003 in Dublin, Ireland, as a result of ovarian hyperstimulation syndrome. Another young woman, Temilola Akinbolagbe, died in London in November 2004 of a thrombosis arising out of her recent IVF treatment.

There is no way to know how many women have been made infertile or have died as a result of ovarian hyperstimulation syndrome because there is very little follow-up of egg donors or even IVF patients themselves. This is why we must have more research into the consequences for women of egg extraction so that truly informed consent is possible. The 25 deaths related to Lupron that are on file with the Food and Drug Administration referred to in my testimony may be deaths from ovarian hyperstimulation (OHS). We cannot begin to know the extent of such problems in the virtual absence of systematic follow-up on women who have undergone these procedures.

Two famous cases of women dying of ovarian cancer after undergoing OHS are the comedian Gilda Radner (at age 42) and former Vogue magazine editor Liz Tilberis (at age 51). Barbara Seaman suggested in an article entitled, "The Terrifying Truth About Fertility Drugs" (O Magazine, February 2004), that these drugs may have contributed to their deaths. With the lack of follow-up on women who have undergone OHS it is difficult to know how many other such cases there are and exactly what the role of OHS was in causing them.

10. *Why do you propose separating IVF services from egg extraction for research purposes?*

IVF services are dedicated to promoting fertility. Egg extraction for research purposes threatens fertility. That is, ovarian hyperstimulation can cause infertility. IVF physicians are obligated to inform patients of dangers of egg extraction and minimize risks, which usually involves exercising restraint from harvesting too many eggs. A good IVF physician will try to extract just enough eggs to produce a successful birth. Researchers, in contrast, want to obtain as many eggs as possible. This is an untenable conflict of interest and a perfect setup for exploitation.

Follow-up questions for Richard M. Doerflinger
Hearing of March 7, 2006 on human cloning
House Government Reform Subcommittee on Criminal Justice, Drug Policy and Human Resources

1. Are you familiar with the new consensus document recently released by an international consortium on stem cells, ethics, and law, known as the "Hinxton Group?"

- *What are your comments about the principles listed in the document and the ethicists who authored it?*

I am familiar with this document. Its seven "principles" are so vague, and so completely avoid the most basic ethical issues, that they are virtually useless. The text does not even discuss the central moral problem in cloning and embryonic stem cell research, the misuse of human embryos, but simply assumes that embryonic human beings can be treated as "research materials" to be donated, used and destroyed. The document says researchers should follow the law, but then exhorts governments to make laws as few and "flexible" as possible to accommodate researchers. While the text's first principle is that stem cell research should minimize harm, and "any risk of harm should be commensurate with expected overall benefit," this vague language could be used to justify grave harm to human subjects -- in cases where *other* people can be expected to reap "overall benefit" in the future.

Such loopholes are not surprising in light of the list of Steering Committee members, which includes scientists interested in the research and ethicists notorious for promoting utilitarian or "end justifies the means" reasoning. One author, John Harris, has said that infanticide may be justified to prevent the survival of children with disabilities (See E. Day, "Infanticide is justifiable in some cases, says ethics professor," *The Telegraph*, Jan. 25, 2004, www.telegraph.co.uk/news/main.jhtml?xml=/news/2004/01/25/nbaby25.xml&sSheet=/news/2004/01/25/ixhome.html). Another author, Julian Savulescu, defends the deliberate creation of human/animal hybrids (e.g., half human, half chimpanzee), and says the availability of genetic enhancement technologies will create a moral *obligation* on parents to have "the best child possible." See: J. Savulescu, "Human-Animal Transgenesis and Chimeras Might Be an Expression of Our Humanity,"
The American Journal of Bioethics, August 2003, pp. 22-25; A. Dunn and T. Noble, "Should science reshape the human race?", *The Age* (Australia), June 5, 2005, http://theage.com.au/news/Science/Should-science-reshape-the-human-race/2005/06/04/1117825100891.html. If society through its elected representatives does not set limits, this will be the ethic shaping our biotechnological future.

2. You mention in your written testimony that researchers are heading down the road of implanting the cloned embryos.

- *Would you explain a little further what the longrange implications are of this research moving forward?*

As documented in footnote 7 of my written statement, several animal studies in "therapeutic cloning" suggest that safe clinical use of stem cells from cloning may require implanting the

cloned embryos in a womb and developing them to a later (fetal) stage before harvesting stem cells. Clearly the biotechnology lobby and its political allies believe this expansion may be necessary in humans, because they have crafted some new state cloning laws to allow "therapeutic cloning" up to the moment before birth. Thus what used to be called "reproductive cloning" (implanting cloned embryos in women's wombs) would become an integral step in "therapeutic cloning." Ethically it means that this agenda may have to exploit human beings well beyond the embryonic stage: growing cloned unborn children into the fetal stage in order to destroy them, and exploiting women to be surrogate "incubators" for these children (in addition to exploiting them as egg factories to produce cloned embryos in the first place).

3. *Do you think Institutional Review Boards do an effective job of protecting human subjects in research?*

Often they do, but they are by no means foolproof. Grave flaws in the IRB system were dramatized by the death of Jessie Gelsinger in 1999 during a clinical trial at the University of Pennsylvania, and of Ellen Roche during an NIH-funded study at Johns Hopkins University in 2000.

In a case involving the deliberate exposure of poor minority children to the dangers of lead paint in Baltimore in 2001, the Maryland Court of Appeals found that Johns Hopkins University's IRB had "abdicated" its responsibility to protect children from research risks and had shown that it "was willing to aid researchers in getting around federal regulations designed to protect children used as subjects in nontherapeutic research." *Grimes v. Kennedy Krieger Institute*, 366 Md. 29, 782 A.2d 807, 813-14 (2001). More generally the court observed: "The Institutional Review Boards, IRBs, are, primarily, in-house organs. In our view, they are not designed, generally, to be sufficiently objective in the sense that they are as sufficiently concerned with the ethicality of the experiments they review as they are with the success of the experiments." Id. at 817.

These abuses occurred when IRBs were supposedly acting under clear federal guidelines, involving types of research that are eligible for federal funding. Any institution now pursuing human cloning or embryo destruction for research purposes is already disregarding the guidelines for federally funded research, which forbid such abuses; such an institution would also surely be willing to violate less principled and less persuasive federal guidelines for opening up research in this field while struggling to conduct it "ethically."

4. The Tuskegee syphilis experiment was referenced by Members at the hearing. You also mentioned the Tuskegee experiment in your written testimony. *Please clarify your point about federal government oversight of the Tuskegee experiment in light Members' concerns that were expressed at the hearing.*

During the hearing, subcommittee members made several inaccurate remarks about the Tuskegee syphilis experiment, which deliberately left poor African-Americans from Alabama without treatment for syphilis from 1932 to 1972 in order to study the untreated condition.

First, this abuse did not occur due to the absence of oversight by a public agency. In fact it was conducted for forty years *by* a public agency, the U.S. Public Health Service. The researchers even used their official clout to make sure that subjects enlisting in the armed forces during World War II did not receive the syphilis screening and treatment mandated for all other recruits. No one should cite this study to argue that federal supervision necessarily ensures proper ethical limits on human experimentation.

Second, this study was not just about white racism in the Old South. While racism was surely a factor, black physicians and nurses were among those conducting the study. One of them, Eunice Rivers, had the most direct contact with the subjects and was lead author of the researchers' self-congratulatory "follow-up" article in Public Health Reports in 1953, which concluded: "As public health workers accumulate experience and skill in this type of study, not only should the number of such studies increase, but a maximum of information will be gained from the efforts expended." E. Rivers et al., "Twenty Years of Followup Experience in a Long-Range Medical Study," *Public Health Reports*, Vol. 68, No. 4 (April 1953), 391-395.

Third, this study did not involve deliberately injecting the subjects with syphilis. Rather, they already had syphilis, and were deliberately misinformed about their condition and deprived of proper treatment for decades, until long after safe and reliable treatments were widely available. However, our nation's history does contain episodes in which even that abuse was practiced and defended, as when retarded children at the Willowbrook State School in New York were deliberately injected with hepatitis virus to study how to prevent and treat the infection in other children in the future, or when chronically ill and debilitated patients at Jewish Chronic Disease Hospital were deliberately injected with cancer cells without their consent. See: Paul Ramsey, *The Patient as Person* (Yale University Press 1970), 47-55; *Zeleznik v. Jewish Chronic Disease Hosp.*, 47 App.Div. 2d 199, 366 NYS 2d 163 (1975).

As the Maryland Court of Appeals said in the case cited above, after citing a litany of unethical human experiments conducted in this and other countries in the 20th century: "These programs were somewhat alike in the vulnerability of the subjects; uneducated African-American men, debilitated patients in a charity hospital, prisoners of war, inmates of concentration camps and others falling within the custody and control of the agencies conducting or approving the experiments. In the present case, children, especially young children, living in lower economic circumstances ...are...vulnerable as well." Id. at 817. Today the new disfavored class, the new set of coveted guinea pigs for harmful experiments, consists of members of the human species who are very young and very vulnerable indeed. But the same utilitarian ethic that endangered other marginalized human beings in the past endangers the embryonic and fetal human being today, and will expand to demean others tomorrow.

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RESPONSE TO POST-HEARING QUESTIONS BASED ON HEARING ENTITLED

"Human Cloning and Embryonic Stem Cell Research After Seoul: Examining Exploitation, Fraud, and Ethical Problems in the Research"

BEFORE THE SUBCOMMITTEE ON CRIMINAL JUSTICE, DRUG POLICY AND HUMAN RESOURCES

MARCH 7, 2006

QUESTIONS:

1. "Would you say the current peer review process is thorough enough in its treatment of alluring scientific papers such as Hwang's?"

The scientific peer review process for academic journals is designed to detect good science and bad fraud; it is not designed to detect good fraud. The peer review process for the Hwang *et al.* (2005) paper was the same as other papers reviewed at *Science*, but a bit faster. Journals are not predisposed to suspect that submitted manuscripts contain fraudulent data, nor are they designed to be investigative bodies. Reviewers did not detect the fraud because the fraud was done with care, not because the peer reviewers were careless. Moreover, scientists and ethicists who serve as peer reviewers do so as volunteers. A certain amount of trust will always be required.

Scientific peer reviewers should be expected, for example, to ask for a different control for a given experiment, request data on additional biochemical markers, or request additional tests, such as DNA fingerprinting. These reviewers cannot be reasonably expected to review the entire literature of all contributing authors or ask for proof that each experiment and each result is what the authors claim it to be, nor can they be expected to travel to each laboratory and repeat reported experiments. Experimental replication is the role of the broader scientific community after the initial experiments have been published – this is the manner in which science self-corrects. Science advances through small, progressive steps, each of which builds on that which came before; it is in no one's interest to have fraudulent data in the literature.

Ethics peer reviewers should be expected to, for example, ask for translations of foreign consent documents or to request that consent documents include additional information on risk. Such reviewers cannot be reasonably expected to obtain signed affidavits from all research participants stating that their participation was free and informed, interview lab members about participation/coercion, or obtain bank statements to investigate potential receipt of payment for participation.

I am including for your review the "Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication," as codified by the International Committee of Medical Journal Editors.

2. "Among the dozens of signers on [the Hinxton Group consensus statement], are you aware of any of them having a public record that is critical of embryonic stem cell research or cloning?"

The meeting in Hinxton, UK, was convened to explore the ethical and policy challenges that scientists, universities, and scientific journals face as a consequence of national variations in policy governing embryo research and stem cell sciences. Our goal was to foster international and interdisciplinary collaboration in this area of scholarship. Our specific aims were to 1) Identify the primary challenges faced by scientists, universities, and journal editors with respect to international collaboration in stem cell research, 2) Determine the extent to which it may be possible to develop guidance for conduct that could be useful across national boundaries and national legal regimes, 3) Explore the role of oversight and data sharing in international research, 4) Explore the question of oocyte donation and related issues, and 5) Identify forward-looking strategies to foster the scientific and ethical integrity of research in a global context. The meeting started from the premise that international collaborations in embryonic stem cell research will occur and, given that, the belief that such research ought to take place with ethical and scientific integrity. Signers of the Hinxton Group statement are all committed to fostering the ethical and scientific integrity of embryonic stem cell research.

I am including for your review the Hinxton Group consensus document as released on 24 February 2006.

3. "Do you currently serve, or have you served, on the Institutional Review Board at Johns Hopkins University for reviewing human subjects research? Do you think such boards do an effective job of protecting human subjects in research?"

I have not served on an institutional review board (IRB), but have sat in on IRB meetings and submitted applications to IRBs. I do believe that IRBs, as governed in the US by the Common Rule (45 CRF 46), do a thoughtful and effective job of protecting human subjects in research. Members of IRBs, my colleagues among them, take very seriously their role on IRBs and in the service of current and potential human research subjects. Science and medicine cannot make progress, improving human health and relieving human suffering, without well-designed research and clinical trials and human research subjects willing to enroll in such studies. IRBs are an effective mechanism for protecting human subjects in this process.

4. "In light of [the Genetics and Public Policy Institute's polling data on embryonic stem cell research] do you think it is justified to call the Hinxton document, endorsed by all appearances solely by supporters of research cloning, a true 'consensus'?"

As stated in Question #2 above, the meeting in Hinxton was convened to deliberate the ethical issues raised by international collaboration in embryonic stem cell research, given that 51 countries and regions (including 10 states in the US) have policies that are supportive of embryonic stem cell research (16 of these permit somatic cell nuclear transfer, including 6 states in the US). We were concerned with all embryonic stem cell research, not just that which involves somatic cell nuclear transfer. We were able to come to a true consensus on the specific set of issues we were charged to address.

With respect to the broader debate on somatic cell nuclear transfer, the 2005 report of the Genetics and Public Policy Center (GPPC), *Cloning: A Policy Analysis*, which you cite, concludes,

> "Our survey, together with several others that have been conducted on the subject, demonstrate that differences in question wording and context result in a great deal of variation in survey results, and consequently an unclear picture of Americans' opinions about cloning. In our survey, the questions regarding research and reproductive cloning were asked within the

> context of a larger poll to assess American attitudes toward reproductive genetic technologies. The questions preceding those on cloning queried attitudes about preimplantation genetic diagnosis, prenatal genetic testing, in-vitro fertilization, scientific research, and the moral worth of human embryos. This survey did not include information regarding the benefits or harms of various applications of cloning, nor did it use the term "stem cell," a term that most Americans are now familiar with.
>
> Americans are unclear about what is currently possible in existing cloning technology. The multiple surveys of American attitudes toward cloning show that a vast majority opposes reproductive cloning and that this view has been relatively consistent over time. At the same time, these surveys show significant variability in levels of approval for research cloning, making it difficult to know where the American public truly stands on this issue. These differences in findings likely are attributable to the wording of survey questions, as well as the socio-political environment at the time of the survey. It could be argued that Americans' opinions about research cloning are not firmly held and survey questions are tapping into and reflecting positions on more familiar issues such as abortion and the value of biomedical research." (p. 53)

In a survey conducted by the GPPC in September of 2005, *Values in Conflict: Public Attitudes on Embryonic Stem Cell Research* (included for your review), 67% of the representative sample of Americans polled approve or strongly approve of embryonic stem cell research. In addition, a "clear majority of those in all religion groups, except Fundamentalist and Evangelical Christians, approve of ESC research", while "Fundamentalist and Evangelical Christians were divided, with 50 percent approving or strongly approving and 48 percent disapproving or strongly disapproving of ESC research." The study concludes that public opinion is much more nuanced than the "polarized, deep moral divide" expressed by political debates and the media.

The GPPC is part of the Phoebe R. Berman Bioethics Institute, but was not involved in the Hinxton meeting and is not involved in the Hinxton Group.

ATTACHMENTS: ICMJE "Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication";
Hinxton Group Consensus Statement, 24 February 2006;
Values in Conflict: Public Attitudes on Embryonic Stem Cell Research, Genetics and Public Policy Center, 2005.

Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication

Updated October 2005

International Committee of Medical Journal Editors

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I. Statement Of Purpose

I. A. About the Uniform Requirements

A small group of editors of general medical journals met informally in Vancouver, British Columbia, in 1978 to establish guidelines for the format of manuscripts submitted to their journals. The group became known as the Vancouver Group. Its requirements for manuscripts, including formats for bibliographic references developed by the National Library of Medicine, were first published in 1979. The Vancouver Group expanded and evolved into the International Committee of Medical Journal Editors (ICMJE), which meets annually. The ICMJE gradually has broadened its concerns to include ethical principles related to publication in biomedical journals.

The ICJME has produced multiple editions of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals. Over the years, issues have arisen that go beyond manuscript preparation, resulting in the development of a number of Separate Statements on editorial policy. The entire Uniform Requirements document was revised in 1997; sections were updated in May 1999 and May 2000. In May 2001, the ICMJE revised the sections related to potential conflict of interest. In 2003, the committee revised and reorganized the entire document and incorporated the Separate Statements into the text. The committee prepared this revision in 2005.

The total content of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals may be reproduced for educational, not-for-profit purposes without regard for copyright; the committee encourages distribution of the material.

Journals that agree to use the Uniform Requirements are encouraged to state in their instructions to authors that their requirements are in accordance with the Uniform Requirements and to cite this version. Journals that wish to be listed on www.ICMJE.org as a publication that follows the Uniform Requirements should contact the ICMJE secretariat office.

The ICMJE is a small working group of general medical journals not an open membership organization. Occasionally, the ICMJE will invite a new member or guest when the committee feels that the new journal or organization will provide a needed perspective that is not already available within the existing committee. Open membership organizations for editors and others in biomedical publication include the World Association of Medical Editors www.WAME.org and the Council of Science Editors www.councilofscienceeditors.

I.B. Potential Users of the Uniform Requirements

The ICMJE created the Uniform Requirements primarily to help authors and editors in their mutual task of creating and distributing accurate, clear, easily accessible reports of biomedical studies. The initial sections address the ethical principles related to the process of evaluating, improving, and publishing manuscripts in biomedical journals and the relationships between editors and authors, peer reviewers, and the media. The latter sections address the more technical aspects of preparing and submitting manuscripts. The ICMJE believes the entire document is relevant to the concerns of both authors and editors.

The Uniform Requirements can provide many other stakeholders—peer reviewers, publishers, the media, patients and their families, and general readers—with useful insights into the biomedical authoring and editing process.

I. C. How to Use the Uniform Requirements

The Uniform Requirements state the ethical principles in the conduct and reporting of research and provide recommendations relating to specific elements of editing and writing. These

recommendations are based largely on the shared experience of a moderate number of editors and authors, collected over many years, rather than on the results of methodical, planned investigation that aspires to be "evidence-based." Wherever possible, recommendations are accompanied by a rationale that justifies them; as such, the document serves an educational purpose.

Authors will find it helpful to follow the recommendations in this document whenever possible because, as described in the explanations, doing so improves the quality ity and clarity of reporting in manuscripts submitted to any journal, as well as the ease of editing. At the same time, every journal has editorial requirements uniquely suited to its purposes. Authors therefore need to become familiar with the specific instructions to authors published by the journal they have chosen for their manuscript—for example, the topics suitable for that journal, and the types of papers that may be submitted (for example, original articles, reviews, or case reports)—and should follow those instructions. The Mulford Library at the Medical College of Ohio maintains a useful compendium of instructions to authors.

II. Ethical Considerations in the Conduct and Reporting of Research

II.A Authorship and Contributorship

II.A.1. Byline Authors

An "author" is generally considered to be someone who has made substantive intellectual contributions to a published study, and biomedical authorship continues to have important academic, social, and financial implications. (1) In the past, readers were rarely provided with information about contributions to studies from those listed as authors and in acknowledgments. (2) Some journals now request and publish information about the contributions of each person named as having participated in a submitted study, at least for original research. Editors are strongly encouraged to develop and implement a contributorship policy, as well as a policy on identifying who is responsible for the integrity of the work as a whole.

While contributorship and guarantorship policies obviously remove much of the ambiguity surrounding contributions, it leaves unresolved the question of the quantity and quality of contribution that qualify for authorship. The International Committee of Medical Journal Editors has recommended the following criteria for authorship; these criteria are still appropriate for those journals that distinguish authors from other contributors.

- Authorship credit should be based on 1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. Authors should meet conditions 1, 2, and 3.

- When a large, multi-center group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript (3). These individuals should fully meet the criteria for authorship defined above and editors will ask these individuals to complete journal-specific author and conflict of interest disclosure forms. When submitting a group author manuscript, the corresponding author should clearly indicate the preferred citation and should clearly identify all individual authors as well as the group name. Journals will generally list other members of the group in the acknowledgements. The National Library of Medicine indexes the group name and the names of individuals the group has identified as being directly responsible for the manuscript.

- Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.

- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.

- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

Some journals now also request that one or more authors, referred to as "guarantors," be identified as the persons who take responsibility for the integrity of the work as a whole, from inception to published article, and publish that information.

Increasingly, authorship of multi-center trials is attributed to a group. All members of the group who are named as authors should fully meet the above criteria for authorship.

The order of authorship on the byline should be a joint decision of the co-authors. Authors should be prepared to explain the order in which authors are listed.

II.A.2. Contributors Listed in Acknowledgments

All contributors who do not meet the criteria for authorship should be listed in an acknowledgments section. Examples of those who might be acknowledged include a person who provided purely technical help, writing assistance, or a department chair who provided only general support. Financial and material support should also be acknowledged.

Groups of persons who have contributed materially to the paper but whose contributions do not justify authorship may be listed under a heading such as "clinical investigators" or "participating investigators," and their function or contribution should be described—for example, "served as scientific advisors," "critically reviewed the study proposal," "collected data," or "provided and cared for study patients."

Because readers may infer their endorsement of the data and conclusions, all persons must give written permission to be acknowledged.

II.B Editorship

II.B.1. The Role of the Editor

The editor of a journal is the person responsible for its entire content. Owners and editors of medical journals have a common endeavor—the publication of a reliable and readable journal, produced with due respect for the stated aims of the journal and for costs. The functions of owners and editors, however, are different. Owners have the right to appoint and dismiss editors and to make important business decisions in which editors should be involved to the fullest extent possible. Editors must have full authority for determining the editorial content of the journal. This concept of editorial freedom should be resolutely defended by editors even to the extent of their placing their positions at stake. To secure this freedom in practice, the editor should have direct access to the highest level of ownership, not only to a delegated manager.

Editors of medical journals should have a contract that clearly states the editor's rights and duties in addition to the general terms of the appointment and that defines mechanisms for resolving conflict.

An independent editorial advisory board may be useful in helping the editor establish and maintain editorial policy.

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addition to the general terms of the appointment and that defines mechanisms for resolving conflict.

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II.B.2. Editorial Freedom

The ICMJE adopts the World Association of Medical Editors' definition of editorial freedom. This definition states that editorial freedom or independence is the concept that editors-in chief should have full authority over the editorial content of their journal. Journal owners should not interfere in the evaluation; selection or editing of individual articles either directly or by creating an environment that strongly influences decisions. Editors should base decisions on the validity of the work and its importance to the journal's readers not on the commercial success of the journal. Editors should be free to express critical but responsible views about all aspects of medicine without fear of retribution, even if these views might conflict with the commercial goals of the publisher. Editors and editors' organizations have the obligation to support the concept of editorial freedom and to draw major transgressions of such freedom to the attention of the international medical, academic, and lay communities.

II.C. Peer Review

Unbiased, independent, critical assessment is an intrinsic part of all scholarly work, including the scientific process. Peer review is the critical assessment of manuscripts submitted to journals by experts who are not part of the editorial staff. Peer review can therefore be viewed as an important extension of the scientific process. Although its actual value has been little studied, and is widely debated (4), peer review helps editors decide which manuscripts are suitable for their journals, and helps authors and editors in their efforts to improve the quality of reporting. A peer reviewed journal is one that submits most of its published research articles for outside review. The number and kind of manuscripts sent for review, the number of reviewers, the reviewing procedures, and the use made of the reviewers' opinions may vary. In the interests of transparency, each journal should publicly disclose its policies in its instructions to authors.

II.D. Conflicts of Interest

Public trust in the peer review process and the credibility of published articles depend in part on how well conflict of interest is handled during writing, peer review, and editorial decision making. Conflict of interest exists when an author (or the author's institution), reviewer, or editor has financial or personal relationships that inappropriately influence (bias) his or her actions (such relationships are also known as dual commitments, competing interests, or competing loyalties). These relationships vary from those with negligible potential to those with great potential to influence judgment, and not all relationships represent true conflict of interest. The potential for conflict of interest can exist whether or not an individual believes that the relationship affects his or her scientific judgment. Financial relationships (such as employment, consultancies, stock ownership, honoraria, paid expert testimony) are the most easily identifiable conflicts of interest and the most likely to undermine the credibility of the journal, the authors, and of science itself. However, conflicts can occur for other reasons, such as personal relationships, academic competition, and intellectual passion.

All participants in the peer review and publication process must disclose all relationships that could be viewed as presenting a potential conflict of interest. Disclosure of these relationships is also important in connection with editorials and review articles, because it is can be more difficult to detect bias in these types of publications than in reports of original research. Editors may use information disclosed in conflict of interest and financial interest statements as a basis for editorial decisions. Editors should publish this information if they believe it is important in judging the manuscript.

II.D.1. Potential Conflicts of Interest Related to Individual Authors' Commitments

When authors submit a manuscript, whether an article or a letter, they are responsible for disclosing all financial and personal relationships that might bias their work. To prevent ambiguity, authors must state explicitly whether potential conflicts do or do not exist. Authors should do so in the manuscript on a conflict of interest notification page that follows the title page, providing additional detail, if necessary, in a cover letter that accompanies the manuscript. (*See Section IV.A.3. Conflict of Interest Notification Page*)

Investigators must disclose potential conflicts to study participants and should state in the manuscript whether they have done so.

Editors also need to decide when to publish information disclosed by authors about potential conflicts. If doubt exists, it is best to err on the side of publication.

II.D.2. Potential Conflicts of Interest Related to Project Support

Increasingly, individual studies receive funding from commercial firms, private foundations, and government. The conditions of this funding have the potential to bias and otherwise discredit the research.

Scientists have an ethical obligation to submit creditable research results for publication. Moreover, as the persons directly responsible for their work, researchers should not enter into agreements that interfere with their access to the data and their ability to analyze it independently, to prepare manuscripts, and to publish them. Authors should describe the role of the study sponsor(s), if any, in study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the report for publication. If the supporting source had no such involvement, the authors should so state. Biases potentially introduced when sponsors are directly involved in research are analogous to methodological biases of other sorts. Some journals, therefore, choose to include information about the sponsor's involvement in the methods section.

Editors may request that authors of a study funded by an agency with a proprietary or financial interest in the outcome sign a statement such as, "I had full access to all of the data in this study and I take complete responsibility for the integrity of the data and the accuracy of the data analysis." Editors should be encouraged to review copies of the protocol and/or contracts associated with project-specific studies before accepting such studies for publication. Editors may choose not to consider an article if a sponsor has asserted control over the authors' right to publish.

II.D.3. Potential Conflicts of Interest Related to Commitments of Editors, Journal Staff, or Reviewers

Editors should avoid selecting external peer reviewers with obvious potential conflicts of interest, for example, those who work in the same department or institution as any of the authors. Authors often provide editors with the names of persons they feel should not be asked to review a manuscript because of potential conflicts of interest, usually professional. When possible, authors should be asked to explain or justify their concerns; that information is important to editors in deciding whether to honor such requests.

Reviewers must disclose to editors any conflicts of interest that could bias their opinions of the manuscript, and they should disqualify themselves from reviewing specific manuscripts if they believe it to be appropriate. As in the case of authors, silence on the part of reviewers concerning potential conflicts may mean either that such conflicts exist that they have failed to disclose, or that conflicts do not exist. Reviewers must therefore also be asked to state explicitly whether conflicts do or do not exist. Reviewers must not use knowledge of the work, before its publication, to further

their own interests.

Editors who make final decisions about manuscripts must have no personal, professional, or financial involvement in any of the issues they might judge. Other members of the editorial staff, if they participate in editorial decisions, must provide editors with a current description of their financial interests (as they might relate to editorial judgments) and disqualify themselves from any decisions where they have a conflict of interest. Editorial staff must not use the information gained through working with manuscripts for private gain. Editors should publish regular disclosure statements about potential conflicts of interests related to the commitments of journal staff.

II.E. Privacy and Confidentiality

II. E.1. Patients and Study Participants

Patients have a right to privacy that should not be infringed without informed consent. Identifying information, including patients' names, initials, or hospital numbers, should not be published in written descriptions, photographs, and pedigrees unless the information is essential for scientific purposes and the patient (or parent or guardian) gives written informed consent for publication. Informed consent for this purpose requires that a patient who is identifiable be shown the manuscript to be published.

Identifying details should be omitted if they are not essential. Complete anonymity is difficult to achieve, however, and informed consent should be obtained if there is any doubt. For example, masking the eye region in photographs of patients is inadequate protection of anonymity. If identifying characteristics are altered to protect anonymity, such as in genetic pedigrees, authors should provide assurance that alterations do not distort scientific meaning and editors should so note.

The requirement for informed consent should be included in the journal's instructions for authors. When informed consent has been obtained it should be indicated in the published article.

II.E.2. Authors and Reviewers

Manuscripts must be reviewed with due respect for authors' confidentiality. In submitting their manuscripts for review, authors entrust editors with the results of their scientific work and creative effort, on which their reputation and career may depend. Authors' rights may be violated by disclosure of the confidential details of the review of their manuscript. Reviewers also have rights to confidentiality, which must be respected by the editor. Confidentiality may have to be breached if dishonesty or fraud is alleged but otherwise must be honored.

Editors must not disclose information about manuscripts (including their receipt, content, status in the reviewing process, criticism by reviewers, or ultimate fate) to anyone other than the authors and reviewers. This includes requests to use the materials for legal proceedings.

Editors must make clear to their reviewers that manuscripts sent for review are privileged communications and are the private property of the authors. Therefore, reviewers and members of the editorial staff must respect the authors' rights by not publicly discussing the authors' work or appropriating their ideas before the manuscript is published. Reviewers must not be allowed to make copies of the manuscript for their files and must be prohibited from sharing it with others, except with the permission of the editor. Reviewers should return or destroy copies of manuscripts after submitting reviews. Editors should not keep copies of rejected manuscripts.

Reviewer comments should not be published or otherwise made public without permission of the reviewer, author, and editor.

Opinions differ on whether reviewers should remain anonymous. Authors should consult the information for authors of the journal they have chosen to learn whether the reviews are anonymous. When comments are not signed the reviewers' identity must not be revealed to the author or anyone else without the reviewer's permission.

Some journals publish reviewers' comments with the manuscript. No such procedure should be adopted without the consent of the authors and reviewers. However, reviewers' comments should be sent to other reviewers of the same manuscript, which helps reviewers learn from the review process, and reviewers may be notified of the editor's decision.

II.F. Protection of Human Subjects and Animals in Research

When reporting experiments on human subjects, authors should indicate whether the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5). If doubt exists whether the research was conducted in accordance with the Helsinki Declaration, the authors must explain the rationale for their approach, and demonstrate that the institutional review body explicitly approved the doubtful aspects of the study. When reporting experiments on animals, authors should be asked to indicate whether the institutional and national guide for the care and use of laboratory animals was followed.

III. Publishing and Editorial Issues Related to Publication in Biomedical Journals

III.A. Obligation to Publish Negative Studies

Editors should consider seriously for publication any carefully done study of an important question, relevant to their readers, whether the results are negative (that is, convincingly allow the null hypothesis to be accepted) or positive (that is, allow the null hypothesis to be rejected). Failure to submit or publish negative studies, in particular, contributes to publication bias. Many studies that purport to be negative are, in fact, inconclusive; publication of inconclusive studies is problematic, since they add little to biomedical knowledge and consume journal resources. The Cochrane Library may be interested in publishing inconclusive trials.

III.B. Corrections, Retractions and "Expressions of Concern"

Editors must assume initially that authors are reporting work based on honest observations. Nevertheless, two types of difficulty may arise.

First, errors may be noted in published articles that require the publication of a correction or erratum of part of the work. The corrections should appear on a numbered page, be listed in the contents page, include the complete original citation, and link to the original article and vice versa if online. It is conceivable that an error could be so serious as to vitiate the entire body of the work, but this is unlikely and should be handled by editors and authors on an individual basis. Such an error should not be confused with inadequacies exposed by the emergence of new scientific information in the normal course of research. The latter require no corrections or withdrawals.

The second type of difficulty is scientific fraud. If substantial doubts arise about the honesty or integrity of work, either submitted or published, it is the editor's responsibility to ensure that the question is appropriately pursued, usually by the authors' sponsoring institution. However, it is not ordinarily the task of editors to conduct a full investigation or to make a determination; that responsibility lies with the institution where the work was done or with the funding agency. The editor should be promptly informed of the final decision, and if a fraudulent paper has been published, the journal must print a retraction. If this method of investigation does not result in a

satisfactory conclusion, the editor may choose to conduct his or her own investigation. As an alternative to retraction, the editor may choose to publish an expression of concern about aspects of the conduct or integrity of the work.

The retraction or expression of concern, so labeled, should appear on a numbered page in a prominent section of the print journal as well as in the online version, be listed in the contents page, and include in its heading the title of the original article. It should not simply be a letter to the editor. Ideally, the first author should be the same in the retraction as in the article, although under certain circumstances the editor may accept retractions by other responsible persons. The text of the retraction should explain why the article is being retracted and include a full original citation reference to it.

The validity of previous work by the author of a fraudulent paper cannot be assumed. Editors may ask the author's institution to assure them of the validity of earlier work published in their journals or to retract it. If this is not done editors may choose to publish an announcement expressing concern that the validity of previously published work is uncertain.

III.C. Copyright

Many biomedical journals ask authors to transfer copyright to the journal. However, an increasing number of "open access" journals do not require authors to transfer copyright to the journal. Editors should make their position on copyright transfer clear to authors and to others who might be interested in using editorial content from their journals. The copyright status of articles in a given journal can vary: some content cannot be copyrighted (articles written by employees of the U.S. and some other governments in the course of their work, for example); editors may agree to waive copyright on others; still others may be protected under serial rights (that is, use in publications other than journals, including electronic publications, is permitted).

III.D. Overlapping Publications

III.D.1. Duplicate Submission

Most biomedical journals will not consider manuscripts that are simultaneously being considered by other journals. Among the principal considerations that have led to this policy are: 1) the potential for disagreement when two (or more) journals claim the right to publish a manuscript that has been submitted simultaneously to more than one; and 2) the possibility that two or more journals will unknowingly and unnecessarily undertake the work of peer review and editing of the same manuscript, and publish same article.

However, editors of different journals may decide to simultaneously or jointly publish an article if they believe that doing so would be in the best interest of the public's health.

III.D.2. Redundant Publication

Redundant (or duplicate) publication is publication of a paper that overlaps substantially with one already published in print or electronic media.

Readers of primary source periodicals, whether print or electronic, deserve to be able to trust that what they are reading is original unless there is a clear statement that the article is being republished by the choice of the author and editor. The bases of this position are international copyright laws, ethical conduct, and cost-effective use of resources. Duplicate publication of original research is particularly problematic, since it can result in inadvertent double counting or inappropriate weighting of the results of a single study, which distorts the available evidence.

Most journals do not wish to receive papers on work that has already been reported in large part in a published article or is contained in another paper that has been submitted or accepted for publication elsewhere, in print or in electronic media. This policy does not preclude the journal considering a paper that has been rejected by another journal, or a complete report that follows publication of a preliminary report, such as an abstract or poster displayed at a professional meeting. Nor does it prevent journals considering a paper that has been presented at a scientific meeting but not published in full or that is being considered for publication in a proceedings or similar format. Press reports of scheduled meetings will not usually be regarded as breaches of this rule, but additional data or copies of tables and illustrations should not amplify such reports.

When submitting a paper, the author must always make a full statement to the editor about all submissions and previous reports that might be regarded as redundant or duplicate publication of the same or very similar work. The author must alert the editor if the manuscript includes subjects about which the authors have published a previous report or have submitted a related report to another publication. Any such report must be referred to and referenced in the new paper. Copies of such material should be included with the submitted paper to help the editor decide how to handle the matter.

If redundant or duplicate publication is attempted or occurs without such notification, authors should expect editorial action to be taken. At the least, prompt rejection of the submitted manuscript should be expected. If the editor was not aware of the violations and the article has already been published, then a notice of redundant or duplicate publication will probably be published with or without the author's explanation or approval.

Preliminary reporting to public media, governmental agencies, or manufacturers, of scientific information described in a paper or a letter to the editor that has been accepted but not yet published violates the policies of many journals. Such reporting may be warranted when the paper or letter describes major therapeutic advances or public health hazards such as serious adverse effects of drugs, vaccines, other biological products, or medicinal devices, or reportable diseases. This reporting should not jeopardize publication, but should be discussed with and agreed upon by the editor in advance.

III.D.3. Acceptable Secondary Publication

Certain types of articles, such as guidelines produced by governmental agencies and professional organizations, may need to reach the widest possible audience. In such instances, editors sometimes choose deliberately to publish material that is also being published in other journals, with the agreement of the authors and the editors of those other journals. Secondary publication for various other reasons, in the same or another language, especially in other countries, is justifiable, and can be beneficial, provided all of the following conditions are met.

1. The authors have received approval from the editors of both journals; the editor concerned with secondary publication must have a photocopy, reprint, or manuscript of the primary version.

2. The priority of the primary publication is respected by a publication interval of at least one week (unless specifically negotiated otherwise by both editors).

3. The paper for secondary publication is intended for a different group of readers; an abbreviated version could be sufficient.

4. The secondary version faithfully reflects the data and interpretations of the primary version.

5. The footnote on the title page of the secondary version informs readers, peers, and

documenting agencies that the paper has been published in whole or in part and states the primary reference. A suitable footnote might read: "This article is based on a study first reported in the [title of journal, with full reference]."

Permission for such secondary publication should be free of charge.

6. The title of the secondary publication should indicate that it is a secondary publication (complete republication, abridged republication, complete translation, or abridged translation) of a primary publication. Of note, the National Library of Medicine does not consider translations to be "republications," and does not cite or index translations when the original article was published in a journal that is indexed in MEDLINE.

III.D.4. Competing Manuscripts Based on the Same Study

Publication of manuscripts to air co-investigators disputes may waste journal space and confuse readers. On the other hand, if editors knowingly publish a manuscript written by only some of a collaborating team, they could be denying the rest of the team their legitimate co authorship rights; they could also be denying the journal's readers access to legitimate differences of opinion about the interpretation of a study.

Two kinds of competing submissions are considered: submissions by coworkers who disagree on the analysis and interpretation of their study, and submissions by coworkers who disagree on what the facts are and which data should be reported.

Setting aside the unresolved question of ownership of the data, the following general observations may help editors and others dealing with these problems.

III. D.4.a. Differences in Analysis or Interpretation

If the dispute centers on the analysis or interpretation of data, the authors should submit a manuscript that clearly presents both versions. The difference of opinion should be explained in a cover letter. The normal process of peer and editorial review of the manuscript may help the authors to resolve their disagreement regarding analysis or interpretation.

If the dispute cannot be resolved and the study merits publication, both versions should be published. Options include publishing two papers on the same study, or a single paper with two analyses or interpretations. In such cases it would be appropriate for the editor to publish a statement outlining the disagreement and the journal's involvement in attempts to resolve it.

III.D.4. b. Differences in Reported Methods or Results

If the dispute centers on differing opinions of what was actually done or observed during the study, the journal editor should refuse publication until the disagreement is resolved. Peer review cannot be expected to resolve such problems. If there are allegations of dishonesty or fraud, editors should inform the appropriate authorities; authors should be notified of an editor's intention to report a suspicion of research misconduct.

III.D.5. Competing Manuscripts Based on the Same Database

Editors sometimes receive manuscripts from separate research groups that have analyzed the same data set, e.g., from a public database. The manuscripts may differ in their analytic methods, conclusions, or both. Each manuscript should be considered separately. Where interpretations of the same data are very similar, it is reasonable but not necessary for editors to give preference to the manuscript that was received earlier. However, editorial consideration of multiple submissions may

be justified in this circumstance, and there may even be a good reason for publishing more than one manuscript because different analytical approaches may be complementary and equally valid.

III.E. Correspondence

Biomedical journals should provide its readership with a mechanism for submitting comments, questions, or criticisms about published articles, as well as brief reports and commentary unrelated to previously published articles. This will likely, but not necessarily, take the form of a correspondence section or column. The authors of articles discussed in correspondence should be given an opportunity to respond, preferably in the same issue in which the original correspondence appears. Authors of correspondence should be asked to declare any competing or conflicting interests.

Published correspondence may be edited for length, grammatical correctness, and journal style. Alternatively, editors may choose to publish correspondence unedited for length or style, as for example in rapid response sections on the Internet; the journal should declare its editorial practice in this regard. Authors should approve editorial changes that alter the substance or tone of a letter or response.

Although editors have the prerogative to sift out correspondence material that is irrelevant, uninteresting, or lacking in cogency, they have a responsibility to allow a range of opinion to be expressed. The correspondence column should not be used merely to promote the journal's, or the editors', point of view. In all instances, editors must make an effort to screen out discourteous, inaccurate, or libelous statements, and should not allow ad hominem arguments intended to discredit opinions or findings.

In the interests of fairness and to keep correspondence within manageable proportions, journals may want to set time limits for responding to articles and correspondence, and for debate on a given topic. Journals should also decide whether they would notify authors when correspondence bearing on their published work is going to appear in standard or rapid response sections. Journals should also set policy with regard to the archiving of unedited correspondence that appears on line. These policies should be published both in print and electronic versions of the journal.

III.F. Supplements, Theme Issues, and Special Series

Supplements are collections of papers that deal with related issues or topics, are published as a separate issue of the journal or as part of a regular issue, and are usually funded by sources other than the journal's publisher. Supplements can serve useful purposes: education, exchange of research information, ease of access to focused content, and improved cooperation between academic and corporate entities. Because funding sources can bias the content of supplements through the choice of topics and viewpoints, journals should consider adopting the following principles. These same principles apply to theme issues or special series that have external funding and/or guest editors.

- The journal editor must take full responsibility for the policies, practices, and content of supplements, including complete control of the decision to publish all portions of the supplement. Editing by the funding organization should not be permitted.

- The journal editor must retain the authority to send supplement manuscripts for external peer review and to reject manuscripts submitted for the supplement. These conditions should be made known to authors and external supplement editors before beginning editorial work on the supplement.

- The journal editor must approve the appointment of any external editor of the supplement and take responsibility for the work of the external editor.

- The sources of funding for the research, publication, and the products the funding source make that are considered in the supplement should be clearly stated and prominently located in the supplement, preferably on each page. Whenever possible, funding should come from more than one sponsor.

- Advertising in supplements should follow the same policies as those of the rest of the journal.

- Journal editors must enable readers to distinguish readily between ordinary editorial pages and supplement pages.

- Journal editors and supplement editors must not accept personal favors or personal remuneration from sponsors of supplements.

- Secondary publication in supplements (republication of papers previously published elsewhere) should be clearly identified by the citation of the original paper. Supplements should avoid redundant or duplicate publication. Supplements should not republish research results, but the republication of guidelines or other material in the public interest might be appropriate.

- The principles of authorship and potential conflict of interest disclosure articulated elsewhere in this document should apply to supplements.

III.G. Electronic Publishing

Most biomedical journals are now published in electronic as well as print versions, and some are published in electronic form only. Electronic publishing (which includes the Internet) is publishing. In the interests of clarity and consistency, the medical and health information published on the Internet should follow the recommendations in this document whenever possible.

The nature of electronic publication requires some special considerations, both within and beyond this document. At a minimum, websites should indicate the following: names, appropriate credentials, affiliations, and relevant conflicts of interest of editors, authors, and contributors; documentation and attribution of references and sources for all content; information about copyright; disclosure of site ownership; and disclosure of sponsorship, advertising, and commercial funding.

Linking from one health or medical Internet site to another may be perceived as an implicit recommendation of the quality of the second site. Journals thus should exercise caution in linking to other sites; when users are linking to another site, it may be helpful to provide an explicit message to that they are leaving the journal's site. If links to other sites are posted as a result of financial considerations, such should be clearly indicated. All dates of content posting and updating should be indicated. In electronic layout as in print, advertising and promotional messages should not be juxtaposed with editorial content, and commercial content should be clearly identifiable as such.

Electronic publication is an area that is in flux. Editors should develop, make available to authors, and implement policies on issues unique to electronic publishing. These issues include archiving, error correction, version control, and choice of the electronic or print version of the journal as the journal of record, publication of ancillary material, and electronic publication.

In no instance should a journal remove an article from its website or archive. If an article needs to be corrected or retracted, the explanation must be labeled appropriately and communicated as soon as possible on a citable page in a subsequent issue of the journal.

Preservation of electronic articles in a permanent archive is essential for the historical record. Access to the archive should be immediate and it should be controlled by a third party, such as a library,

instead of a publisher. Deposition in multiple archives is encouraged.

III.H. Advertising

Most medical journals carry advertising, which generates income for their publishers, but advertising must not be allowed to influence editorial decisions. Journals should have formal, explicit, written policies for advertising in both print and electronic versions; website advertising policy should parallel policy for the print version as much as possible. Editors must have full and final authority for approving advertisements and enforcing advertising policy.

Where independent bodies for reviewing advertising exist editors should make use of their judgments. Readers should be able to distinguish readily between advertising and editorial material. The juxtaposition of editorial and advertising material on the same products or subjects should be avoided. Interleafing advertising pages within articles discourages readers by interrupting the flow of editorial content, and should be discouraged. Advertising should not be sold on the condition that it will appear in the same issue as a particular article.

Journals should not be dominated by advertising, but editors should be careful about publishing advertisements from only one or two advertisers, as readers may perceive that these advertisers have influenced the editor.

Journals should not carry advertisements for products that have proved to be seriously harmful to health—for example, tobacco. Editors should ensure that existing regulatory or industry standards for advertisements specific to their country are enforced, or develop their own standards. The interests of organizations or agencies should not control classified and other non-display advertising, except where required by law. Finally, editors should consider all criticisms of advertisements for publication.

III. I. Medical Journals and the General Media

The public's interest in news of medical research has led the popular media to compete vigorously to get information about research as soon as possible. Researchers and institutions sometimes encourage the reporting of research in the non-medical media before full publication in a scientific journal by holding a press conference or giving interviews.

The public is entitled to important medical information without unreasonable delay, and editors have a responsibility to play their part in this process. Biomedical journals are published primarily for their readers, but the general public has a legitimate interest in their content; an appropriate balance should therefore guide journals' interaction with the media between these complementary interests. Doctors in practice need to have reports available in full detail before they can advise their patients about the reports' conclusions. Moreover, media reports of scientific research before the work has been peer reviewed and fully published may lead to the dissemination of inaccurate or premature conclusions.

An embargo system has been established in some countries to prevent publication of stories in the general media before the original paper on which they are based appears in the journal. The embargo creates a "level playing field," which most reporters appreciate since it minimizes the pressure on them to publish stories which they have not had time to prepare carefully. Consistency in the timing of public release of biomedical information is also important in minimizing economic chaos, since some articles contain information that has great potential to influence financial markets. On the other hand, the embargo system has been challenged as being self-serving of journals' interests, and impeding the rapid dissemination of scientific information.

Editors may find the following recommendations useful as they seek to establish policies on these

issues.

- Editors can foster the orderly transmission of medical information from researchers, through peer-reviewed journals, to the public. This can be accomplished by an agreement with authors that they will not publicize their work while their manuscript is under consideration or awaiting publication and an agreement with the media that they will not release stories before publication in the journal, in return for which the journal will cooperate with them in preparing accurate stories.

- Editors need to keep in mind that an embargo system works on the honor system; no formal enforcement or policing mechanism exists. The decision of any significant number of media outlets, or of biomedical journals, not to respect the embargo system would therefore lead to its rapid dissolution.

- Very little medical research has such clear and urgently important clinical implications for the public's health that the news must be released before full publication in a journal. In such exceptional circumstances, however, appropriate authorities responsible for public health should make the decision and should be responsible for the advance dissemination of information to physicians and the media. If the author and the appropriate authorities wish to have a manuscript considered by a particular journal, the editor should be consulted before any public release. If editors accept the need for immediate release, they should waive their policies limiting prepublication publicity.

- Policies designed to limit prepublication publicity should not apply to accounts in the media of presentations at scientific meetings or to the abstracts from these meetings (see Redundant Publication). Researchers who present their work at a scientific meeting should feel free to discuss their presentations with reporters, but they should be discouraged from offering more detail about their study than was presented in their talk.

- When an article is soon to be published, editors should help the media prepare accurate reports by providing news releases, answering questions, supplying advance copies of the journal, or referring reporters to the appropriate experts. Most responsible reporters find this assistance should be contingent on the media's cooperation in timing their release of stories to coincide with the publication of the article.

- Editors, authors, and the media should apply the above stated principles to material released early in electronic versions of journals.

III.J. Obligation to Register Clinical Trials

The ICMJE believes that it is important to foster a comprehensive, publicly available database of clinical trials. The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like.

The ICMJE member journals will require, as a condition of consideration for publication in their journals, registration in a public trials registry. The details of this policy are contained under editorials. The ICMJE encourages editors of other biomedical journals to adopt similar policy.

The ICMJE does not advocate one particular registry, but its member journals will require authors to register their trial in a registry that meets several criteria. The registry must be accessible to the public at no charge. It must be open to all prospective registrants and managed by a not-for-profit

organization. There must be a mechanism to ensure the validity of the registration data, and the registry should be electronically searchable. An acceptable registry must include at minimum the data elements in the following table. Trial registration with missing fields or fields that contain uninformative terminology is inadequate.

The ICMJE recommends that journals publish the trial registration number at the end of the Abstract.

Minimal Registration Data Set*

	Item	Comment
1.	Unique trial number	The unique trial number will be established be the primary registering entity (the registry).
2.	Trial registration date	The date of registration will be established by the primary registering entity.
3.	Secondary IDs	May be assigned by sponsors or other interested parties (there may be none).
4.	Funding source(s)	Name of the organization(s) that provided funding for the study.
5.	Primary sponsor	The main entity responsible for performing the research.
6.	Secondary sponsor(s)	The secondary entities, if any, responsible for performing the research.
7.	Responsible contact person	Public contact person for the trial, for patients interested in participating.
8.	Research contact person	Person to contact for scientific inquiries about the trial.
9.	Title of the study	Brief title chosen by the research group (can be omitted if the researchers wish).
10.	Official scientific title of the study	This title must include the name of the intervention, the condition being studied, and the outcome (e.g., The International Study of Digoxin and Death from Congestive Heart Failure).
11.	Research ethics review	Has the study at the time of registration received appropriate ethics committee approval (yes/no)? (It is assumed that all registered trials will be approved by an ethics board before commencing.)
12.	Condition	The medical condition being studied (e.g., asthma, myocardial infarction, depression).
13.	Intervention(s)	A description of the study and comparison/control intervention(s) (For a drug or other product registered for public sale anywhere in the world, this is the generic name; for an unregistered drug the generic name or company serial number is acceptable). The duration of the intervention(s) must be specified.
14.	Key inclusion and exclusion criteria	Key patient characteristics that determine eligibility for participation in the study.
15.	Study type	Database should provide drop-down lists for selection. This would include choices for randomized vs. non-randomized, type of masking (e.g., double-blind, single-blind), type of controls (e.g., placebo, active), and group assignment, (e.g., parallel, crossover, factorial).
16.	Anticipated trial start date	Estimated enrollment date of the first participant.
17.	Target sample size	The total number of subjects the investigators plan to enroll before closing the trial to new participants.
18.	Recruitment status	Is this information available (yes/no) (If yes, link to information).
19.	Primary outcome	The primary outcome that the study was designed to evaluate Description should include the time at which the outcome is measured (e.g., blood pressure at 12 months)
20.	Key secondary outcomes	The secondary outcomes specified in the protocol. Description should include time of measurement (e.g., creatinine clearance at 6 months).

*The data fields were specified at a meeting convened by the WHO in April 2004; the explanatory comments are largely from the ICMJE.

IV. Manuscript Preparation and Submission

IV.A. Preparing a Manuscript for Submission to a Biomedical Journal

Editors and reviewers spend many hours reading manuscripts, and therefore appreciate receiving with manuscripts that are easy to read and edit. Much of the information in journals' instructions to authors is designed to accomplish that goal in ways that meet each journal's particular editorial needs. The guidance that follows provides a general background and rationale for preparing manuscripts for any journal.

IV.A.1.a. General Principles

The text of observational and experimental articles is usually (but not necessarily) divided into sections with the headings Introduction, Methods, Results, and Discussion. This so-called "IMRAD" structure is not simply an arbitrary publication format, but rather a direct reflection of the process of scientific discovery. Long articles may need subheadings within some sections (especially the Results and Discussion sections) to clarify their content. Other types of articles, such as case reports, reviews, and editorials, are likely to need other formats.

Publication in electronic formats has created opportunities for adding details or whole sections in the electronic version only, layering information, cross-linking or extracting portions of articles, and the like. Authors need to work closely with editors in developing or using such new publication formats and should submit material for potential supplementary electronic formats for peer review.

Double spacing of all portions of the manuscript— including the title page, abstract, text, acknowledgments, references, individual tables, and legends—and generous margins make it possible for editors and reviewers to edit the text line by line, and add comments and queries, directly on the paper copy. If manuscripts are submitted electronically, the files should be double spaced, because the manuscript may need to be printed out for reviewing and editing.

During the editorial process reviewers and editors frequently need to refer to specific portions of the manuscript, which is difficult unless the pages are numbered. Authors should therefore number all of the pages of the manuscript consecutively, beginning with the title page.

IV.A.1.b. Reporting Guidelines for Specific Study Designs

Research reports frequently omit important information. The general requirements listed in the next section relate to reporting essential elements for all study designs. Authors are encouraged in addition to consult reporting guidelines relevant to their specific research design. For reports of randomized controlled trials authors should refer to the CONSORT statement. This guideline provides a set of recommendations comprising a list of items to report and a patient flow diagram. Reporting guidelines have also been developed for a number of other study designs that some journals may ask authors to follow. Some of these reporting guidelines can also be found at www.consort-statement.org. Authors should consult the information for authors of the journal they have chosen.

IV.A.2. Title Page

The title page should carry the following information:

- The title of the article. Concise titles are easier to read than long, convoluted ones. Titles that are too short may, however, lack important information, such as study design (which is particularly important in identifying randomized controlled trials). Authors should include all information in the title that will make electronic retrieval of the article both sensitive and specific.

- Authors' names and institutional affiliations. Some journals publish each author's highest academic degree(s), while others do not.

- The name of the department(s) and institution(s) to which the work should be attributed.

- Disclaimers, if any.

- Corresponding authors. The name, mailing address, telephone and fax numbers, and e-mail address of the author responsible for correspondence about the manuscript (the "corresponding author;" this author may or may not be the "guarantor" for the integrity of the study as a whole, if someone is identified in that role. The corresponding author should indicate clearly whether his or her e-mail address is to be published.

- The name and address of the author to whom requests for reprints should be addressed or a statement that reprints will not be available from the authors.

- Source(s) of support in the form of grants, equipment, drugs, or all of these.

- A running head. Some journals request a short running head or foot line, usually of no more than 40 characters (count letters and spaces) at the foot of the title page. Running heads are published in most journals, but are also sometimes used within the editorial office for filing and locating manuscripts.

- Word counts. A word count for the text only (excluding abstract, acknowledgments, figure legends, and references) allows editors and reviewers to assess whether the information contained in the paper warrants the amount of space devoted to it, and whether the submitted manuscript fits within the journal's word limits. A separate word count for the Abstract is also useful for the same reason.

- The number of figures and tables. It is difficult for editorial staff and reviewers to tell if the figures and tables that should have accompanied a manuscript were actually included unless the numbers of figures and tables that belong to the manuscript are noted on the title page.

IV.A.3. Conflict of Interest Notification Page

To prevent the information on potential conflict of interest for authors from being overlooked or misplaced, it is necessary for that information to be part of the manuscript. It should therefore also be included on a separate page or pages immediately following the title page. However, individual journals may differ in where they ask authors to provide this information and some journals do not send information on conflicts of interest to reviewers. (***See Section II.D. Conflicts of Interest***)

IV.A.4. Abstract and Key Words

An abstract (requirements for length and structured format vary by journal) should follow the title page. The abstract should provide the context or background for the study and should state the study's purposes, basic procedures (selection of study subjects or laboratory animals, observational and analytical methods), main findings (giving specific effect sizes and their statistical significance, if possible), and principal conclusions. It should emphasize new and important aspects of the study or

observations.

Because abstracts are the only substantive portion of the article indexed in many electronic databases, and the only portion many readers read, authors need to be careful that abstracts reflect the content of the article accurately. Unfortunately, many abstracts disagree with the text of the article (6). The format required for structured abstracts differs from journal to journal, and some journals use more than one structure; authors should make it a point prepare their abstracts in the format specified by the journal they have chosen.

Some journals request that, following the abstract, authors provide, and identify as such, 3 to 10 key words or short phrases that capture the main topics of the article. These will assist indexers in cross-indexing the article and may be published with the abstract. Terms from the Medical Subject Headings (MeSH) list of Index Medicus should be used; if suitable MeSH terms are not yet available for recently introduced terms, present terms may be used.

IV.A.5. Introduction

Provide a context or background for the study (i.e., the nature of the problem and its significance). State the specific purpose or research objective of, or hypothesis tested by, the study or observation; the research objective is often more sharply focused when stated as a question. Both the main and secondary objectives should be made clear, and any pre-specified subgroup analyses should be described. Give only strictly pertinent references and do not include data or conclusions from the work being reported.

IV.A.6. Methods

The Methods section should include only information that was available at the time the plan or protocol for the study was written; all information obtained during the conduct of the study belongs in the Results section.

IV.A.6.a. Selection and Description of Participants

Describe your selection of the observational or experimental participants (patients or laboratory animals, including controls) clearly, including eligibility and exclusion criteria and a description of the source population. Because the relevance of such variables as age and sex to the object of research is not always clear, authors should explain their use when they are included in a study report; for example, authors should explain why only subjects of certain ages were included or why women were excluded. The guiding principle should be clarity about how and why a study was done in a particular way. When authors use variables such as race or ethnicity, they should define how they measured the variables and justify their relevance.

IV.A.6.b. Technical information

Identify the methods, apparatus (give the manufacturer's name and address in parentheses), and procedures in sufficient detail to allow other workers to reproduce the results. Give references to established methods, including statistical methods (see below); provide references and brief descriptions for methods that have been published but are not well known; describe new or substantially modified methods, give reasons for using them, and evaluate their limitations. Identify precisely all drugs and chemicals used, including generic name(s), dose(s), and route(s) of administration.

Authors submitting review manuscripts should include a section describing the methods used for locating, selecting, extracting, and synthesizing data. These methods should also be summarized in the abstract.

IV.A.6.c. Statistics

Describe statistical methods with enough detail to enable a knowledgeable reader with access to the original data to verify the reported results. When possible, quantify findings and present them with appropriate indicators of measurement error or uncertainty (such as confidence intervals). Avoid relying solely on statistical hypothesis testing, such as the use of P values, which fails to convey important information about effect size. References for the design of the study and statistical methods should be to standard works when possible (with pages stated). Define statistical terms, abbreviations, and most symbols. Specify the computer software used.

IV.A.7. Results

Present your results in logical sequence in the text, tables, and illustrations, giving the main or most important findings first. Do not repeat in the text all the data in the tables or illustrations; emphasize or summarize only important observations. Extra or supplementary materials and technical detail can be placed in an appendix where it will be accessible but will not interrupt the flow of the text; alternatively, it can be published only in the electronic version of the journal.

When data are summarized in the Results section, give numeric results not only as derivatives (for example, percentages) but also as the absolute numbers from which the derivatives were calculated, and specify the statistical methods used to analyze them. Restrict tables and figures to those needed to explain the argument of the paper and to assess its support. Use graphs as an alternative to tables with many entries; do not duplicate data in graphs and tables. Avoid non-technical uses of technical terms in statistics, such as "random" (which implies a randomizing device), "normal," "significant," "correlations," and "sample."

Where scientifically appropriate, analyses of the data by variables such as age and sex should be included.

IV.A.8. Discussion

Emphasize the new and important aspects of the study and the conclusions that follow from them. Do not repeat in detail data or other material given in the Introduction or the Results section. For experimental studies it is useful to begin the discussion by summarizing briefly the main findings, then explore possible mechanisms or explanations for these findings, compare and contrast the results with other relevant studies, state the limitations of the study, and explore the implications of the findings for future research and for clinical practice.

Link the conclusions with the goals of the study but avoid unqualified statements and conclusions not adequately supported by the data. In particular, authors should avoid making statements on economic benefits and costs unless their manuscript includes the appropriate economic data and analyses. Avoid claiming priority and alluding to work that has not been completed. State new hypotheses when warranted, but clearly label them as such.

IV.A.9. References

IV.A.9.a. General Considerations Related to References

Although references to review articles can be an efficient way of guiding readers to a body of literature, review articles do not always reflect original work accurately. Readers should therefore be provided with direct references to original research sources whenever possible. On the other hand, extensive lists of references to original work on a topic can use excessive space on the printed page. Small numbers of references to key original papers will often serve as well as more exhaustive lists, particularly since references can now be added to the electronic version of published papers, and

since electronic literature searching allows readers to retrieve published literature efficiently.

Avoid using abstracts as references. References to papers accepted but not yet published should be designated as "in press" or "forthcoming"; authors should obtain written permission to cite such papers as well as verification that they have been accepted for publication. Information from manuscripts submitted but not accepted should be cited in the text as "unpublished observations" with written permission from the source.

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Some journals check the accuracy of all reference citations, but not all journals do so, and citation errors sometimes appear in the published version of articles. To minimize such errors, authors should therefore verify references against the original documents.

IV.A.9.b. Reference Style and Format

The Uniform Requirements style is based largely on an ANSI standard style adapted by the National Library of Medicine (NLM) for its databases. (7) For samples of reference citation formats, authors should consult National Library of Medicine web site.

References should be numbered consecutively in the order in which they are first mentioned in the text. Identify references in text, tables, and legends by Arabic numerals in parentheses. References cited only in tables or figure legends should be numbered in accordance with the sequence established by the first identification in the text of the particular table or figure. The titles of journals should be abbreviated according to the style used in Index Medicus. Consult the list of Journals Indexed for MEDLINE, published annually as a separate publication by the National Library of Medicine. The list can also be obtained through the Library's web site. Journals vary on whether they ask authors to cite electronic references within parentheses in the text or in numbered references following the text. Authors should consult with the journal that they plan to submit their work to.

Journals vary on whether they ask authors to cite electronic references within parentheses in the text or in numbered references following the text. Authors should consult with the journal that they plan to submit their work to.

IV.A.10. Tables

Tables capture information concisely, and display it efficiently; they also provide information at any desired level of detail and precision. Including data in tables rather than text frequently makes it possible to reduce the length of the text.

Type or print each table with double spacing on a separate sheet of paper. Number tables consecutively in the order of their first citation in the text and supply a brief title for each. Do not use internal horizontal or vertical lines. Give each column a short or abbreviated heading. Authors should place explanatory matter in footnotes, not in the heading. Explain in footnotes all nonstandard abbreviations. For footnotes use the following symbols, in sequence:

*,†,‡,§,||,¶,**,††,‡‡

Identify statistical measures of variations, such as standard deviation and standard error of the mean.

Be sure that each table is cited in the text.

If you use data from another published or unpublished source, obtain permission and acknowledge them fully.

Additional tables containing backup data too extensive to publish in print may be appropriate for publication in the electronic version of the journal, deposited with an archival service, or made available to readers directly by the authors. In that event an appropriate statement will be added to the text. Submit such tables for consideration with the paper so that they will be available to the peer reviewers.

IV.A.11. Illustrations (Figures)

Figures should be either professionally drawn and photographed, or submitted as photographic quality digital prints. In addition to requiring a version of the figures suitable for printing, some journals now ask authors for electronic files of figures in a format (e.g., JPEG or GIF) that will produce high quality images in the web version of the journal; authors should review the images of such files on a computer screen before submitting them, to be sure they meet their own quality standard.

For x-ray films, scans, and other diagnostic images, as well as pictures of pathology specimens or photomicrographs, send sharp, glossy, black-and-white or color photographic prints, usually 127 x 173 mm (5 x 7 inches). Although some journals redraw figures, many do not. Letters, numbers, and symbols on Figures should therefore be clear and even throughout, and of sufficient size that when reduced for publication each item will still be legible. Figures should be made as self-explanatory as possible, since many will be used directly in slide presentations. Titles and detailed explanations belong in the legends, however, not on the illustrations themselves.

Photomicrographs should have internal scale markers. Symbols, arrows, or letters used in photomicrographs should contrast with the background.

If photographs of people are used, either the subjects must not be identifiable or their pictures must be accompanied by written permission to use the photograph (*see Section III.D.4.*a). Whenever possible permission for publication should be obtained.

Figures should be numbered consecutively according to the order in which they have been first cited in the text. If a figure has been published, acknowledge the original source and submit written permission from the copyright holder to reproduce the material. Permission is required irrespective of authorship or publisher except for documents in the public domain.

For illustrations in color, ascertain whether the journal requires color negatives, positive transparencies, or color prints. Accompanying drawings marked to indicate the region to be reproduced might be useful to the editor. Some journals publish illustrations in color only if the author pays for the extra cost.

Authors should consult the journal about requirements for figures submitted in electronic formats.

IV.A.12. Legends for Illustrations (Figures)

Type or print out legends for illustrations using double spacing, starting on a separate page, with Arabic numerals corresponding to the illustrations. When symbols, arrows, numbers, or letters are used to identify parts of the illustrations, identify and explain each one clearly in the legend. Explain the internal scale and identify the method of staining in photomicrographs.

IV.A.13. Units of Measurement

Measurements of length, height, weight, and volume should be reported in metric units (meter, kilogram, or liter) or their decimal multiples.

Temperatures should be in degrees Celsius. Blood pressures should be in millimeters of mercury, unless other units are specifically required by the journal.

Journals vary in the units they use for reporting hematological, clinical chemistry, and other measurements. Authors must consult the information for authors for the particular journal and should report laboratory information in both the local and International System of Units (SI). Editors may request that the authors before publication add alternative or non-SI units, since SI units are not universally used. Drug concentrations may be reported in either SI or mass units, but the alternative should be provided in parentheses where appropriate.

IV.A.14. Abbreviations and Symbols

Use only standard abbreviations; the use of non-standard abbreviations can be extremely confusing to readers. Avoid abbreviations in the title. The full term for which an abbreviation stands should precede its first use in the text unless it is a standard unit of measurement.

IV.B Sending the Manuscript to the Journal

An increasing number of journals now accept electronic submission of manuscripts, whether on disk, as attachments to electronic mail, or by downloading directly onto the journal website. Electronic submission saves time as well as postage costs, and allows the manuscript to be handled in electronic form throughout the editorial process (for example, when it is sent out for review). When submitting a manuscript electronically, authors should consult with the instructions for authors of the journal they have chosen for their manuscript.

If a paper version of the manuscript is submitted, send the required number of copies of the manuscript and figures; they are all needed for peer review and editing, and editorial office staff cannot be expected to make the required copies.

Manuscripts must be accompanied by a cover letter, which should include the following information.

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- A statement of financial or other relationships that might lead to a conflict of interest, if that information is not included in the manuscript itself or in an authors' form.

- A statement that the manuscript has been read and approved by all the authors, that the requirements for authorship as stated earlier in this document have been met, and that each author believes that the manuscript represents honest work, if that information is not provided in another form (see below); and

- The name, address, and telephone number of the corresponding author, who is responsible for communicating with the other authors about revisions and fi- nal approval of the proofs, if that information is not included on the manuscript itself.

The letter should give any additional information that may be helpful to the editor, such as the type or format of article in the particular journal that the manuscript represents. If the manuscript has been submitted previously to another journal, it is helpful to include the previous editor's and

reviewers' comments with the submitted manuscript, along with the authors' responses to those comments. Editors encourage authors to submit these previous communications and doing so may expedite the review process.

Many journals now provide a pre-submission checklist that assures that all the components of the submission have been included. Some journals now also require that authors complete checklists for reports of certain study types (e.g., the CONSORT checklist for reports of randomized controlled trials). Authors should look to see if the journal uses such checklists, and send them with the manuscript if they are requested.

Copies of any permission to reproduce published material, to use illustrations or report information about identifiable people, or to name people for their contributions must accompany the manuscript.

V. References

A. References Cited in this Document

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2. Yank V, Rennie D. Disclosure of researcher contributions: a study of original research articles in The Lancet. Ann Intern Med. 1999 Apr 20;130(8):661-70.

3. Flanagin A, Fontanarosa PB, DeAngelis CD. Authorship for research groups. JAMA. 2002;288:3166-68.

4. Peer Review in Health Sciences. F Godlee, T Jefferson. London: BMJ Books, 1999.

5. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA. 2000 Dec 20;284(23):3043-5.

6. Pitkin RM, Branagan MA, Burmeister LF. Accuracy of data in abstracts of published research articles. JAMA. 1999 Mar 24-31;281(12):1110-1.

7. Patrias K. National Library of Medicine recommended formats for bibliographic citation. Bethesda (MD): The Library; 1991.

B. Other Sources of Information Related to Biomedical Journals

World Association of Medical Editors (WAME) www.WAME.org

Council of Science Editors (CSE) www.councilscienceeditors.org

European Association of Science Editors (EASE) www.ease.org.uk

Cochrane Collaboration www.cochrane.org

The Mulford Library, Medical College of Ohio www.mco.edu/lib/instr/libinsta.html

VI. About The International Committee of Medical Journal Editors

The International Committee of Medical Journal Editors (ICMJE) is a group of general medical journal editors whose participants meet annually and fund their work on the Uniform Requirements for Manuscripts. The ICMJE invites comments on this document and suggestions for agenda items.

VII. Authors of The Uniform Requirements for Manuscripts Submitted to Biomedical Journals

The ICMJE participating journals and organizations and their representatives who approved the revised Uniform Requirements for Manuscripts in July 2005 include *Annals of Internal Medicine, British Medical Journal, Canadian Medical Association Journal, Croatian Medical Journal, Journal of the American Medical Association, The Dutch Medical Journal (Nederlands Tijdschrift voor Geneeskunde), New England Journal of Medicine, New Zealand Medical Journal, The Lancet, The Medical Journal of Australia, Tidsskrift for Den Norske Laegeforening, Journal of the Danish Medical Association (Ugeskrift for Laeger),* and the U.S. National Library of Medicine.

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IX. Inquiries

Inquiries about the Uniform Requirements should be sent to Christine Laine, MD, MPH at the ICMJE Secretariat office, American College of Physicians, 190 N. Independence Mall West, Philadelphia, PA 19106-1572, USA. fax 215-351-2644; e-mail claine@acponline.org. Please do not direct inquiries about individual journal styles or policies to the ICMJE secretariat office.

The Hinxton Group

An International Consortium on Stem Cells, Ethics and Law

Consensus Statement[i]

February 24, 2006

Stem cell and related research holds out immense promise for good. This research has the potential to dramatically increase our understanding of human biology from which may come new treatments for many serious diseases and injuries. The moral reason to conduct stem cell and nuclear reprogramming research thus comes from both the possibility of advancing knowledge and the values of relieving suffering and promoting human welfare. Furthermore, intra- and international scientific collaboration are vital to the success and advancement of science.

While we strive for consensus on a fundamental ethical framework for stem cell research, we acknowledge the reality of cultural diversity and moral disagreement about some elements of stem cell research. Inconsistent and conflicting laws prevent some scientists from engaging in this research and hinder global collaboration. Societies have the authority to regulate science, and scientists have a responsibility to obey the law. However, policy makers should refrain from interfering with the freedom of citizens unless good and sufficient justification can be produced for so doing. As scientists, philosophers, bioethicists, lawyers, clinicians, journal editors and regulators involved in this field, we have reached consensus that if humankind is to have the very best chance of realizing the benefits of stem cell research in an ethically acceptable manner, the following principles should govern the ethical and legal regulation and oversight of stem cell and related research and its clinical applications. This is by no means a comprehensive list of principles, but rather a declaration of those discussed and agreed upon by our group:

1. Stem cell research should seek to minimize harm, and any risk of harm should be commensurate with expected overall benefit. Scientists and clinicians should conduct research according to ethically acceptable norms. For example, research should be conducted so as to protect the well-being, liberty and rights of cell and tissue donors as well as research participants. Research participants and donors of human materials must provide valid informed consent, and conflicts of interest should be appropriately addressed.

2. The law carries great power to facilitate or restrict scientific exploration in the area of stem cell research. Law makers should be circumspect when regulating science. When enacted, laws or regulations governing science nationally and internationally ought to be flexible, so as to accommodate rapid scientific advance.

3. Scientists and clinicians have a responsibility to obey the law. However, they also have the right to know through clear and explicit laws, what is and is not permitted with

respect to their research, the jurisdiction of any prohibitions, and related penalties, so that they can regulate their behavior accordingly.

4. In countries with laws that restrict elements of human embryonic stem cell (hESC) research but that do not expressly prohibit international collaborations, research institutions should neither discriminate against nor restrict the freedom of their investigators who want to travel to do work that is undertaken with scientific and ethical integrity.

5. Law makers should be similarly circumspect in restricting citizens' conduct extraterritorially with regard to stem cell research. So long as scientifically and ethically defensible hESC research is undertaken in a country in which it is legally permissible, scientists should be free to participate in that research without fear of being liable to prosecution, restriction, or discrimination in another jurisdiction.

6. It is essential that scientists and policy makers consult each other and the public in the attempt to develop regulatory regimes for stem cell research that strike the best possible balance between free scientific inquiry and social values.

7. Journal editors should encourage authors to include in manuscripts explicit descriptions of their roles in the published research so as to clarify the appropriateness of their participation, in particular for researchers residing in countries with more restrictive laws and collaborating with researchers residing in countries with more permissive laws.

In addition, we reached consensus on the following forward-looking strategies to foster the scientific and ethical integrity of research in a global context:

8. Insofar as ESC lines are a precious resource and replication and scientific collaboration are vital to scientific advancement, we encourage scientists conducting stem cell research to submit any stem cell lines they derive to national or international depositories that subscribe to internationally accepted standards of quality and make cell lines and data (e.g. DNA fingerprinting and micro satellite data) publicly available.

9. Journal editors should support and promote high standards for scientific peer review. For studies generating new ESC lines described in manuscripts submitted for publication, we encourage journal editors to require that authors submit data verifying the authenticity of the ESC line(s), and an explanation of how the authors have complied with accepted standards of good cell culture practice[ii]. We further urge journal editors to require that the source of the cells used in the research be clearly specified.

10. Journal editors should also support and promote high standards for ethical integrity in stem cell science. Journal editors should require a statement from scientists that their research conforms to local laws and policies, and that, where applicable, it has been approved by all appropriate oversight committees. Authors should provide statements of all conflicts of interest that affect their research. On request from editors, authors should provide protocols approved by ethics review committees, consent forms, information

provided to potential human subjects and tissue donors, and other related documents or information that may bear on the ethics of the research.

11. For the purposes of oversight, regulations and applications to ethics review boards and funding agencies, etc., human materials donors in the context of human ESC research ought to be treated as human research subjects.

12. We encourage the creation of a public database for the deposition of statements of ethical conduct and guidance, research protocols, consent forms, information provided to potential human subjects and tissue donors and other related documents that bear on the ethics of stem cell research.

13. As the science evolves, academies of science and relevant professional organizations, in consultation with the public, should continue to develop guidelines for the ethical conduct of stem cell research and clinical trials. Insofar as possible, these guidelines should be applicable to stem cell research internationally and should continue to address the challenges of international collaboration.

14. Funding bodies must take adequate steps to satisfy themselves that those they fund intend to carry out their research ethically and in accordance with relevant national regulations and appropriate international guidance as it emerges.

15. Research institutions and laboratories are encouraged to provide opportunity for researchers to engage in ethical discussion, review, and education.

While we believe we have accomplished much, we believe there is much work to be done. For example:

16. Insofar as donors of human materials are treated as human subjects, many of the ethical issues raised by hESC research can be adequately addressed through existing international codes of ethics and policy documents governing research involving human subjects. However, new ethical challenges in the conduct of stem cell research that are on the horizon cannot be adequately addressed by existing international ethical codes or practices. Examples are gametes derived from hESC, and human-non human chimeras. At least one national effort is currently underway to anticipate such challenges[iii]. However, it is imperative that international efforts to address these new issues be initiated as soon as possible in order to ensure that science proceeds in an ethically acceptable fashion and to reduce the likelihood that diversity in international response will result in obstacles to ethical conduct similar to those raised by existing differences in national policies governing hESC research and nuclear transfer.

17. Steps should be taken to develop consensus in ethical standards and practices in hESC research for international collaboration to proceed with confidence and for research from anywhere in the world that adheres to these standards and practices to be accepted as valid and valuable by the scientific community and academic journals.

18. To achieve this goal, it will be necessary to specify what these standards and practices should be through the international efforts of scientists, philosophers, bioethicists, lawyers, clinicians, journal editors and regulators involved in this field, in collaboration and consultation with the public. It is imperative that scientists in particular actively and honestly engage with the public about the promises and limitations of this research.

19. This process of identification of international ethical standards and practices should include concerted efforts to engage people throughout the world in honest and realistic conversations about the science and ethics of stem cell research and its emerging applications.

The Hinxton Group

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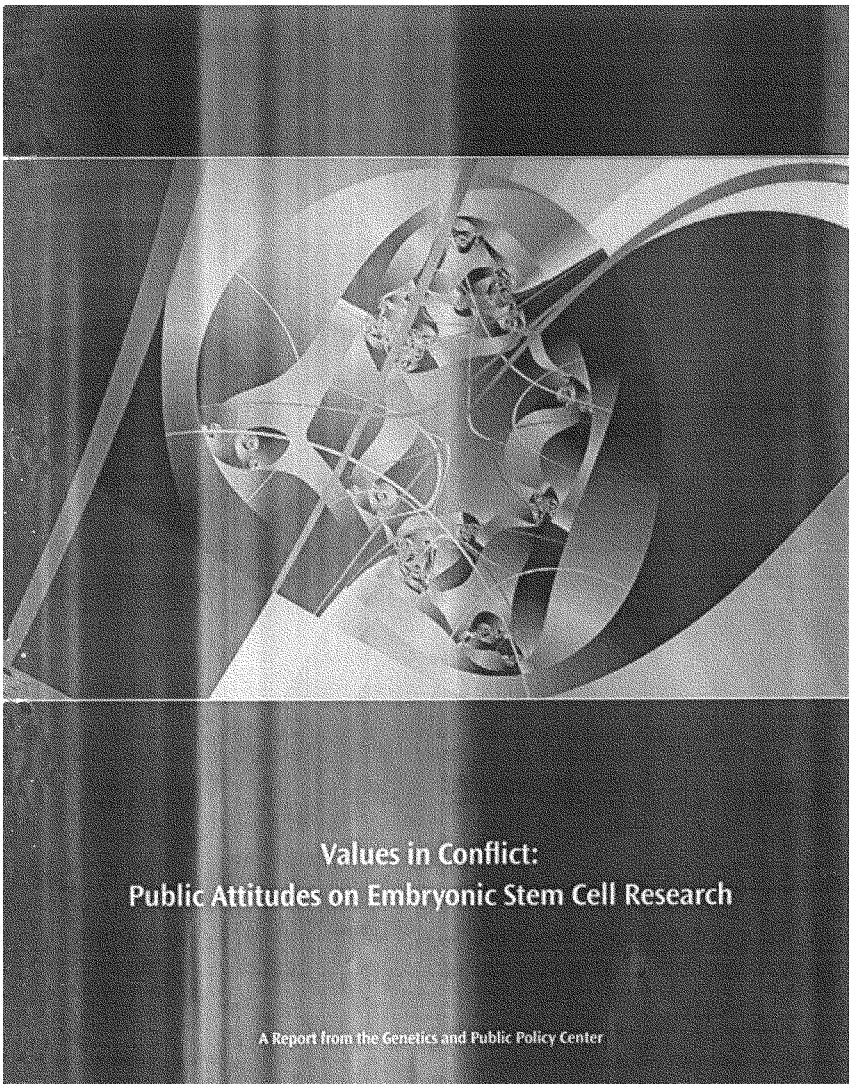
[i] Uncorrected advance copy.
[ii] Coecke S, et al. Guidance on good cell culture practice: A report of the second ECVAM task force on good cell culture practice. ATLA: 2005; 33: 261-287.
[iii] The Human Fertilization and Embryology Authority (HFEA) is conducting at least one national effort to anticipate to these challenges.


Values in Conflict:
Public Attitudes on Embryonic Stem Cell Research
A Report from the Genetics and Public Policy Center

Values in Conflict: Public Attitudes on Embryonic Stem Cell Research

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Introduction

Embryonic stem cell (ESC) research has raised profound moral issues that have become the focus of a polarized policy debate. Some believe that human life at all stages of development – including embryos – holds the same moral value and therefore deserves the same respect and protection as a born child. Others have argued that human embryos are not morally equivalent to born babies but are nevertheless deserving of more respect than cells in a Petri dish. Still others hold that a human embryo in a Petri dish is "just a clump" of cells with no more moral status than any other cells growing in the laboratory.

Some surveys and social science research have sought to tap into how the public feels about ESC research. However, how the public lines up along the continuum of available policy options concerning ESC research is much less clear.

Our goal was to field a credible, unbiased, comprehensive survey to assess the awareness and approval or disapproval of human embryonic stem cell (ESC) research. We also aimed to identify values underlying these attitudes as well as the public's policy preferences for ESC research.

The Attitudes Towards Stem Cell Research Survey collected data from 2,212 Americans between September 9 and 19, 2005. The respondents were sampled randomly from Knowledge Network's web-enabled research panel designed to be representative of the entire U.S. population. The panel is representative because it was selected using high-quality probability sampling techniques, and was not limited to current Web users or computer owners. Households were selected using random digit dialing (RDD) and each household was provided with free hardware and Internet access as needed for research participation. Three thousand ninety-nine panel members were sampled and 2,254 cases completed the survey for a completion rate of 73 percent. Forty-two cases were excluded from final analysis because they did not answer more than one-third of the survey questions. Statistical results were weighted to correct for sampling error for characteristics highly correlated with population benchmarks. For the results based on all 2,212 qualified completions, there is a 95 percent confidence that the maximum margin of sampling error is +/- 2.5 percentage points. For more details about the methodology go to: www.knowledgenetworks.com/ganp/index.html

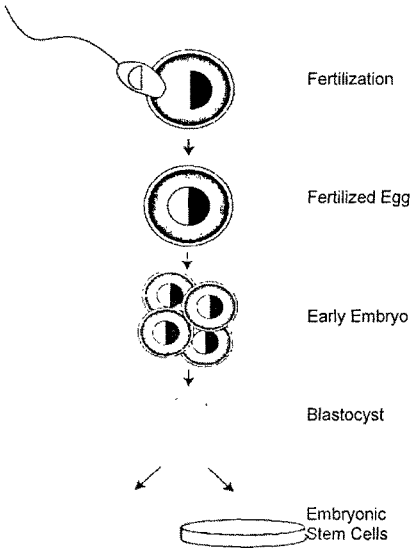
The survey questions on embryonic stem cell research used in this report are available at www.DNApolicy.org.

Scientific and Policy Environment

Stem cells are unique cells found all over the human body. They can, in theory, divide indefinitely to produce more of the same cells and also can, when coaxed, develop into specialized cell types such as muscle, skin, or nerve. Stem cells generally exist in the body to replace cells normally lost due to age, damage, normal wear and tear, injury, or disease.

There are several types of stem cells, defined mainly by the tissue from which they are isolated – embryos or adult tissues. Adult stem cells have been found in several tissues in the body. They are limited in their ability to develop into specialized cell types; generally they only can develop into the cell types of the tissue from which they were isolated. Embryonic stem cells, however, are believed to be able to develop into all adult human cell types. ESCs are isolated from human embryos early in development.

A fertilized human egg will divide and form two cells; each of those cells will divide, forming four cells, and so on. If one cell of a two-cell embryo is destroyed, the remaining cell can produce an entire embryo. Or, if the two cells become separated, each cell can give rise to an individual embryo, resulting in identical twins. Thus, early embryonic cells can give rise to all the cells in an adult.



At five to seven days after fertilization, the cells of the embryo undergo physical changes to prepare it for implantation into the uterine wall. However, if these cells are isolated and grown under lab conditions in a Petri dish, they can continue to divide and remain stem cells capable of giving rise to all cell types for long periods of time. These cells are the embryonic stem cells that are used in research.

The ability of embryonic stem cells to develop into more cell types than adult stem cells is what makes them more promising for research and for future therapies and cures. Although adult stem cells and umbilical cord blood stem cells can provide research material and already have demonstrated

promising success with patients, most scientists think that embryonic stem cells will give rise to better results.

The ESCs currently available were generated by isolating and culturing cells from week-old human embryos. Because ESCs currently only can be created by destroying human embryos, the debate surrounding their creation and use turns, at least in part, on how people assign moral status to a human embryo.

Some consider it immoral under any circumstance to destroy an embryo for any purpose, including for medical research. Others consider it acceptable to destroy embryos to isolate ESCs only if the embryos are remaining after in vitro fertilization (IVF), since such embryos would likely be discarded anyway. Still others believe that the science to develop cures and therapies from stem cell research is too important to be hindered and they consider the destruction of embryos in order to pursue stem cell research to be not only acceptable but necessary.

Key Events in Science:

1978 – First "test tube" baby, Louise Brown, born in Manchester, UK.

1981 – First American IVF baby, Elizabeth Carr, born in Norfolk, VA.

1997 – First successful cloning of a mammal, Dolly the sheep, by Dr. Ian Wilmut's group of the Roslin Institute in Edinburgh, Scotland.

1998 – Dr. James A. Thomson of University of Wisconsin, Madison and colleagues are the first to report the isolation of human embryonic stem cells.

2004 – Korean scientists led by Dr. Woo Suk Hwang of Seoul National University in Korea report the cloning of 30 human embryos. The embryos were destroyed after one week to harvest human embryonic stem cells. Only one cell line was generated successfully.

2005 – Dr. Woo Suk Hwang's group of Seoul National University in Korea reports the creation of 11 human embryonic stem cell lines from cloned human embryos to be used to study human disease and therapies.

Key Events in Policy

1978 – The US establishes an Ethics Advisory Board (EAB) whose review is required for federal funding of in vitro fertilization research. Failure of the Department of Health and Human Services to name members to the EAB results in a "de facto" moratorium on federal funding for this research.

1993 – The NIH Revitalization Act nullifies the requirement for EAB review.

1994 – The National Institutes of Health (NIH) establishes the Human Embryo Research Panel, which recommends federal funding for embryo research using either "spare" embryos from IVF with parental consent, or embryos created solely for research purposes.

1994 – President Clinton responds to the NIH recommendations announcing that he did "not believe that federal funds should be used to support the creation of human embryos for research purposes" and directs the NIH not to support such research.

1996 – Congress passes the Dickey-Wicker Amendment banning NIH-funding of human embryo research.

1999 – The Department of Health and Human Services concludes that public funds can be used for research on human embryonic stem cells derived using only private funds.

2000 – The NIH, with support from President Clinton, releases final guidelines allowing federally funded research on human embryonic stem cells derived in the private sector.

2001 – President Bush allows federal funding of human embryonic stem cell research to proceed but only on cell lines already in existence worldwide, which were derived from leftover embryos from fertility clinics. President Bush also establishes the President's Council on Bioethics to study ethical issues in biomedical and behavioral sciences, and oversee all federally funded human embryonic stem cell research.

2004 – H.R. 4682, the Stem Cell Research Enhancement Act of 2004, is introduced into the House that would relax limits on federal funding of human embryonic stem cell research.

2004 – Californians pass Proposition 71, allowing the state to spend $3 billion over 10 years to fund human embryonic stem cell research.

2005 – A number of bills on stem cell research are introduced in Congress that support alternatives to embryonic stem cell research funding including H.R. 596, the Cord Blood Stem Cell Act of 2005; H.R. 2541, the Joe Testaverde Adult Stem Cell Research Act of 2005; and S.1557, the Respect for Life Pluripotent Stem Cell Act of 2005.

2005 January – The state of New Jersey announces it will fund a $150 million stem cell research center with promise of a future ballot initiative to allocate another $230 million toward the center.

2005 May – The President's Council on Bioethics publishes "Alternative Sources of Pluripotent Stem Cells" describing theoretical methods for obtaining embryonic stem cells without destroying embryos.

2005 May – The House approves, by a vote of 238 to 194, H.R. 810, that would to loosen restrictions on federal funding for human embryonic stem cell research. A similar bill, S. 471, is introduced in the Senate.

2005 May – Connecticut lawmakers earmark $100 million for stem cell research over 10 years to compete with biotech industries in California and New Jersey.

2005 July – Illinois Governor Rod Blagojevich uses an executive order to circumvent the state legislature to dedicate $10 million for stem cell research.

2005 July – Senate Majority Leader Bill Frist (R-TN) breaks with President Bush and announces his support to loosen federal restrictions on human embryonic stem cell research.

Survey Findings

Awareness

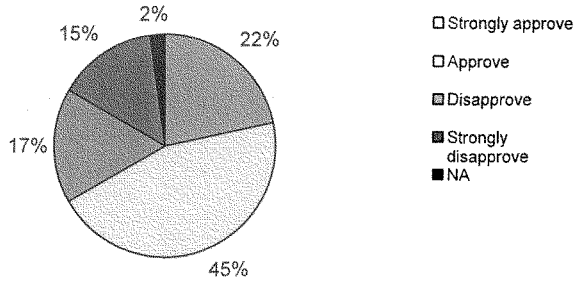
Most survey respondents (81 percent) indicated they had heard of ESC research prior to the survey. Survey respondents also were presented with three images and asked to identify the image of a one-week-old embryo. More than two-thirds (72 percent) correctly identified the image of a one-week embryo while 25 percent misidentified a 4-week fetus as a one-week embryo and 1 percent misidentified a 16-week fetus. There was almost no variation among demographic variables in respondents' abilities to correctly identify which image was that of a one-week embryo.

Approval

After reviewing a definition of ESC research (below), respondents were asked, "in general, do you strongly approve, approve, disapprove, or strongly disapprove of embryonic stem cell research?" Two-thirds of respondents indicated that they approve or strongly approve of ESC research.

- A majority of respondents of both sexes and all ages, education levels, political affiliations, and racial/ethnic groups approve or strongly approve of ESC research.

Approval of Embryonic Stem Cell Research



- Women are more likely than men to disapprove or strongly disapprove of ESC research (35 percent vs. 27 percent).

- More Democrats (75 percent) than Republicans (55 percent) approve or strongly approve of ESC research with independents falling in between (66 percent).

- No significant difference was observed in approval/disapproval by race/ethnicity.

- Those with a college degree or higher were twice as likely as those with no college degree to strongly approve of ESC research (33 percent vs. 16 percent).

- A clear majority of those in all religion groups, except Fundamentalist and Evangelical Christians, approve of ESC research.
- More than two-thirds of Catholics approve or strongly approve of ESC research.

- Fundamentalist and Evangelical Christians were divided, with 50 percent approving or strongly approving and 48 percent disapproving or strongly disapproving of ESC research.

- The highest levels of approval were among "non-Christians" (85 percent approve or strongly approve) and those with no religious affiliation (80 percent approve or strongly approve).

- Fundamentalist and Evangelical Christians were 10 times more likely than those with no religious affiliation to strongly disapprove of embryonic stem cell research (25 percent vs. 2.5 percent respectively).

Embryonic Stem Cell Definition

Stem cells are cells that are able to give rise both to more stem cells and to specialized cell types (e.g. muscle cells, blood cells, liver cells). The next few questions will be about one type of stem cells called embryonic stem cells. For the purposes of today's questions, here is a definition of embryonic stem cells.

Embryonic stem cells are obtained from early embryos and can give rise to all cell types in the human body. When stem cells are obtained from embryos, the embryo is destroyed. Most scientists believe that human embryonic stem cell research holds great promise for understanding human disease and developing new treatments for diseases such as diabetes, heart disease and Parkinson disease. Stem cells can be obtained from embryos that were created through IVF for couples trying to have a baby. Sometimes there are embryos remaining after IVF. Couples can donate these embryos to stem cell research in which the embryo will be destroyed.

Stem cells also can be obtained from bone marrow and umbilical cord blood. These stem cells are useful in treating some diseases such as some cancers and blood diseases. However, most scientists believe that developing new treatments for many diseases from these stem cells will take longer and is less certain than using embryonic stem cells.

Approval/Disapproval of ESC Research

		Approve (Net)	Strongly Approve	Approve	Disapprove	Strongly Disapprove	Disapprove (Net)	Don't know/ No Answer
	Total	66.6	21.6	45.0	16.7	14.6	31.2	2.1
Sex	Male	71.6	24.7	46.8	15.2	11.7	26.9	1.5
	Female	62.1	18.8	43.3	18.0	17.3	35.5	2.6
Age	18-29	68.8	19.6	49.3	18.0	12.0	30.0	1.2
	30-49	65.2	22.4	42.7	18.3	13.9	32.2	2.6
	50+	66.8	22.0	44.8	14.6	16.5	31.0	2.1
Education	No College	63.0	15.6	47.5	17.3	17.7	34.0	3.0
	Some College/Tech	65.4	21.2	44.2	18.0	15.8	33.8	0.07
	Bachelor's degree	74.2	29.6	44.6	13.8	9.5	23.3	2.4
	Post-Grad	75.1	40.0	35.2	14.6	9.2	23.8	1.0
Political Affiliation	Republican	54.8	13.8	41.0	21.8	21.0	42.8	2.4
	Democrat	75.1	28.1	47.0	12.2	10.8	23.0	1.8
	Indep/other /NA	66.3	13.8	52.5	19.1	11.4	30.5	3.2
Religion	Protestant*	73.9	22.4	51.4	13.3	10.5	23.8	2.3
	Roman* Catholic	68.9	22.7	46.3	14.5	15.2	29.7	1.4
	Other* Christian	57.2	13.6	43.6	21.3	18.9	40.0	2.8
	Fund/Evan	49.6	8.6	41.0	23.0	24.9	48.0	2.4
	Non-Christian	84.7	37.9	46.8	7.3	6.6	13.9	1.4
	None	79.5	40.8	38.8	16.0	2.5	18.5	2.0
Race/Ethnicity	White	66.5	23.3	43.2	16.9	15.0	31.9	1.6
	Black	64.1	13.2	50.9	18.8	12.9	31.7	4.2
	Hispanic	64.1	21.7	42.4	17.3	15.6	32.9	3.0

* not Fundamentalist/Evangelical

Conflicting Values

Survey respondents were asked a series of five questions, in random order, that sought to unearth the relative value respondents placed on pursuing ESC research and protecting embryonic life.

All three of the statements supporting protecting embryonic life garnered lower levels of agreement than the two statements supporting ESC research (see below).

Responses to these five statements were evaluated to determine the extent to which respondents consistently favored one side or the other. A small number of respondents (6 percent) strongly agreed with the three statements supportive of embryonic life and strongly disagreed with the two statements supportive of ESC research. An equal number (6 percent) of respondents strongly agreed with the two statements supportive of ESC research and strongly disagreed with the three statements supportive of protecting embryonic life. In some respects, these two groups represent the extremes of the debate, with consistent and strongly held views.

Thirteen percent agreed or strongly agreed with the embryo protection statements and disagreed or strongly disagreed with the statements promoting ESC research. Twenty-one percent disagreed or strongly disagreed with the embryo protection statements and agreed or strongly agreed with the statements supporting ESC research.

ESC Research: Protecting Embryos or Pursuing Research

Survey Question	Net Agree	Strongly agree	Agree	Disagree	Strongly Disagree	Net Disagree	DK/NA
Using embryos for research is dehumanizing and turns embryos into commodities.	41.0	16.8	24.2	40.0	16.0	56.0	3.0
It is really important to protect human embryos, even if it will delay the development of new medicines.	47.5	16.9	30.6	34.3	15.8	50.1	2.4
It would be terrible if embryos were destroyed because of policies that promote embryonic stem cell research.	53.2	17.3	35.9	30.6	13.3	43.9	3.0
It is really important to find cures for diabetes, heart disease, and Parkinson as quickly as possible, even if it means destroying embryos to do so.	56.1	21.2	34.9	26.5	14.9	41.4	2.6
It would be terrible if cures were delayed because of policies that make embryonic stem cell research difficult.	67.3	24.2	43.1	20.1	10.2	30.3	2.4

These respondents also had consistent views but expressed them less strongly then the respondents at the poles. Fifty-two percent of respondents agreed with one or more statements supportive of embryonic life AND one or more statements supporting ESC research. It is likely that these respondents have moral concerns about the destruction of human embryos but also wish to see important research proceed.

On balance, the responses to this series of questions evidenced somewhat higher support for pursuit of research than for protection of embryos. This finding was supported by responses to the single item: "All in all, which is more important to you, conducting embryonic stem cell research that might result in new medical cures OR not destroying the human embryos involved in this research?" A majority, 61 percent, indicated that conducting ESC research was more important, while 37 percent indicated that not destroying embryos was more important[1].

[1] Question from an earlier survey by the Pew Research Center for the People and the Press http://people-press.org/commentary/display.php3?AnalysisID=111

Policy Preferences

Survey respondents were asked to review the following four possible approaches the government could take towards embryonic stem cell research using embryos remaining after IVF and select the one that they thought is the best government policy.

Ban: The government should prohibit all research to create or study embryonic stem cells.

Current: The government should keep the current policy that allows federal funding for research to study a small number of embryonic stem cells created before August 2001.

Proposed: The government should not fund research to create new embryonic stem cells, but if private funding is used to create new embryonic stem cells then the government should fund research to study these cells.

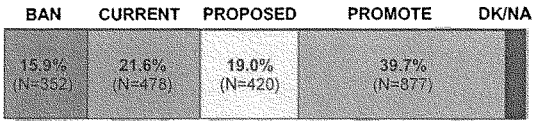
Promote: The government should fund research to both create and study new embryonic stem cells.

Survey Text Preceding Policy Questions

There is a public debate about embryonic stem cell research and disagreement about the public policies that should be put in place regarding this research. Some believe embryonic stem cell research is morally acceptable because research to find cures for diseases is extremely important. Others believe embryonic stem cell research is morally unacceptable because it requires the destruction of human embryos.

A number of proposals have been put forward for embryonic stem cell research policy. The current policy of the US government has three components: 1) it allows federal funding of research using a limited number of embryonic stem cells that were created before August 2001 (because those IVF embryos had already been destroyed); 2) it prohibits federal funding to create new embryonic stem cells or to study new embryonic stem cells created with private funds; and 3) it permits private funds to be used to create and study new embryonic stem cells. Some feel the current policy is a good compromise because of the controversy about destroying embryos. Others feel that federal funding is essential to spur important medical research.

The responses are shown below:



- Sixteen percent of Americans want a more restrictive policy than is currently in place.

- Twenty-two percent of Americans support the current human embryonic stem cell policy.

- Fifty-nine percent support policies that are more permissive toward embryonic stem cell research than the current policy.

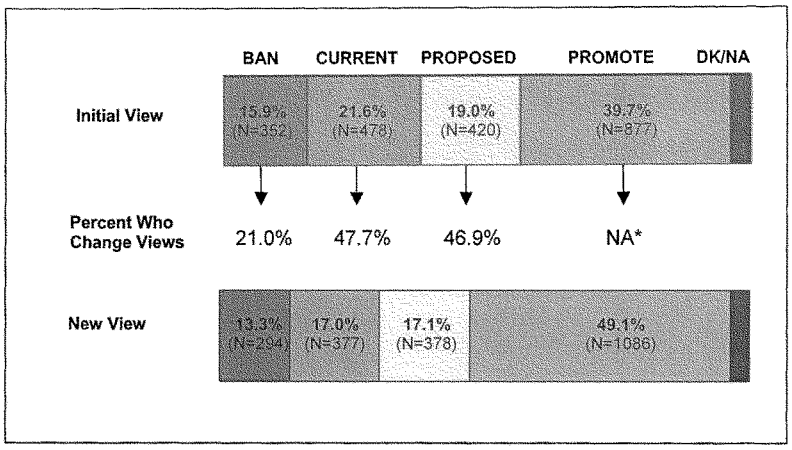
- More Americans support a government policy of funding both creation and study of new embryonic stem cells than support any other policy.

To get a sense of how "fixed" or "fluid" these policy preferences are and how they might shift in response to potential scientific advances in embryonic stem cell research, respondents were presented with two hypothetical scenarios. In the first scenario, the *treatment scenario*, respondents were asked to "imagine that in a year from now scientists report results from new research showing that embryonic stem cells are an effective treatment for a serious disease like diabetes."

In the second scenario, the *alternative scenario*, respondents were asked to "imagine that in a year from now scientists report results from new research in which new embryonic stem cells are created from embryos without harming or destroying the embryo. The embryos that provided the stem cells could still be transferred to a woman's womb and produce healthy babies."

Following each scenario, survey respondents were asked, "Would such a development change your views about government policy about research using embryonic stem cells from embryos donated by couples after IVF?"

In response to the treatment scenario, a significant number of respondents indicated this new information would change their view. Those that selected "ban" as their initial policy preference were least likely to change their view in response to the treatment scenario. Nearly half of those who preferred the current or proposed ESC policy said that the treatment scenario would change their view.



* Those who initially selected "promote" were not asked about the treatment scenario since they already held the most permissive of the four ESC policy options.

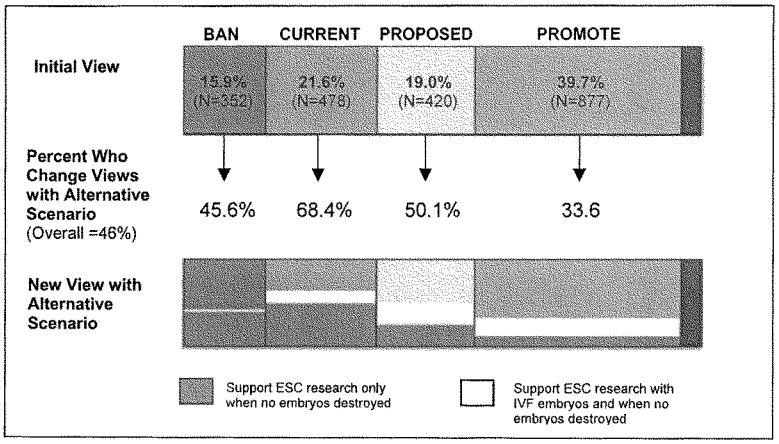
Those who said their view would change were then asked what their policy preference would be based on the new information. In fact, 30 percent reaffirmed their original policy preference. Of those who did change their position in response to the treatment scenario, most selected a more permissive policy. In particular, 25 percent of respondents who initially supported either a complete ban or the current policy, would, in response to the treatment scenario, now support the proposed or promote policy options. The new distribution of policy preferences following the treatment scenario is shown above.

In response to the alternative scenario, nearly half (46 percent) of respondents indicated they would change their minds. Those who originally favored current policy were mostly likely to say they would change their views in response to the alternative scenario (68 percent) while those who selected the promote option were least likely to say the alternative scenario would change their minds (34 percent).

Those indicating the alternative scenario would change their views were asked whether, based on this new information, they would support ESC research "only when embryos are not destroyed" or if they would support embryonic stem cell research "using embryos from both sources."

After being presented with the alternative scenario, 41 percent of respondents who initially preferred a complete ban on ESC research were willing to support ESC research if no embryos are destroyed. Similarly, 52 percent of those who initially supported the "current" policy would support ESC research only if embryos would not be destroyed.

The prospect that ESC research could be pursued without embryo destruction had a less pronounced effect on the views of respondents who favored government policies more supportive of ESC research. Twenty-four percent of those who initially supported the "proposed" policy and 12 percent of those who supported the "promote"



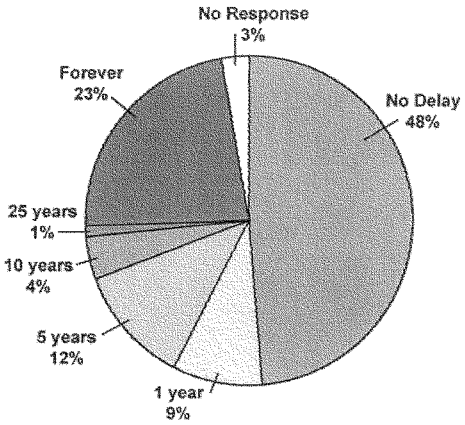
policy of funding both the creation and study of new ESCs would then only support ESC research if embryos are not destroyed. Thus, 16 percent of respondents favoring one of the two more permissive polices would, in response to the alternative scenario, only favor ESC research if embryos were not destroyed.

Although progress is being made in the development of techniques for creating ESCs without destroying embryos, the alternative scenario does not yet exist. Survey respondents were asked whether they would be willing to delay research to find alternative sources.

Those who said "yes" were asked how long they would be willing to delay progress in medical research. The results are shown in the chart below.

The responses were almost equally divided between those who said they would accept a delay in medical research and those who would not, with nearly a quarter saying they would be willing to delay progress in medical research "forever."

Would you be willing to delay progress in medical research in order to find sources of stem cells that do not involve embryo destruction? If so, for how long?



More than Moral Status

Survey respondents were provided with a description of moral status (below) and then asked to indicate on a continuum from no moral status to maximum moral status, what moral status they would accord to a one-week-old embryo in a Petri dish. There was a significant grouping of responses at maximum moral status (maximum) and another significant grouping at or near no moral status (none/low). The remaining responses were distributed across the continuum and were divided into two groups on either side of the midpoint (high and moderate).

Survey Text for Moral Status

There is debate about the "moral status" of human eggs, embryos and fetuses. Moral status is a term people use to capture the extent to which "something" should be given the protections and the level of respect that society gives to each of us. For example, some people believe that an embryo has "maximum moral status" which means that it is always morally wrong to destroy an embryo. By contrast, other people believe that an embryo has no moral status, which would mean that there are no moral problems in destroying an embryo. Still others believe that the moral status of an embryo falls somewhere in between. These people believe that under some circumstances it might be morally permissible to destroy an embryo.

More than half of the respondents either ranked the embryo as having maximum moral status (28 percent) or as having no/low moral status (30 percent).

Levels of disapproval of ESC research (63 percent) were considerably higher among those who believe that a one-week embryo in a Petri dish has maximum moral status than among those who granted the embryos high, moderate, or no/low moral status.

For some respondents, attitudes towards ESC research could not be explained by their views about the moral status of embryos. For example, more than one-third (36 percent) of respondents who accorded the embryo maximum moral status nevertheless approved of ESC research. Moreover, 33 percent of those assigning maximum moral status to the embryo preferred an ESC research policy that is more permissive than current policy. Among the respondents who accorded the embryo no or low moral status, 17 percent disapproved of ESC research and 22 percent preferred either the current policy on ESC research or a total ban.

		ESC Research			Policy Preference		
Embryo Moral Status	Total	Approve	Disapprove	Ban	Current	Proposed	Promote
Maximum	27.7	35.5	63.0	34.0	29.8	14.0	18.5
High	25.7	70.1	27.7	7.6	32.4	18.6	39.1
Moderate	14.5	85.4	12.4	6.7	17.4	23.4	49.6
None/Low	29.5	81.3	16.6	10.1	12.0	20.1	53.0

Intent vs. Use

In the policy debate on embryo research, a distinction often is made between using embryos remaining after IVF and creating embryos specifically for research. Some hold the position that it is ethically acceptable to destroy embryos in ESC research if they were created with the intent of using them in fertility treatment, are not needed for that purpose, and likely will be discarded, but that it is not ethically acceptable to create embryos with the intent of destroying them in research.

This idea of the intent behind the creation of embryos has become more prominent in public discourse about ESC research and about research cloning in particular.

However, little previous work has been done to determine how the American public feels about this issue.

Survey respondents were presented with the following text about this issue:

Survey Text: Intent vs. Use

In addition to embryos donated by couples after infertility treatment with IVF, it is possible for people to donate sperm and eggs specifically to create embryos to be used to make embryonic stem cells. Some scientists believe that stem cells from these embryos would be particularly useful in research. Some people oppose creating embryos specifically to be used to make stem cells because they believe it is wrong to create embryos only to destroy them.

A majority (60 percent) responded that they do not see a moral difference between creating embryos for research and using those remaining after IVF.

	Yes	No	DK/NA
In your view, is there a moral difference between creating embryos specifically for research and using embryos remaining after IVF for research?	37.9%	60.2%	1.8%

Respondents were divided on whether they approve (49 percent) or disapprove (48 percent) of using embryos specifically created to be used in ESC research.

	Net Approve	Strongly Approve	Approve	Disprove	Strongly Disapprove	Net Disapprove	DK/NA
In general, do you strongly approve, approve, disapprove or strongly disapprove of using embryos specifically created to be used in to make embryonic stem cells in which the embryo will be destroyed?	48.6%	10.2%	38.4%	26.5%	21.3%	47.8%	3.6%

Conclusion

Stem cells are unique among human cells in that they possess the uncanny ability to develop into virtually any other cell of the body, offering a hypothetical tool kit for repairing diseased hearts, mending broken spinal cords, or correcting genetic diseases, among other hoped-for benefits. Stem cells derived from very early embryos show the most promise in research to date, but the embryo is destroyed in the process of acquiring the cells themselves. This outcome is not acceptable to individuals and institutions that believe human life at all stages of development deserves protection and should not be destroyed.

Much current debate focuses on whether other sources of stem cells – blood from the umbilical cord removed at birth, for example – might be as useful without the need to destroy embryos, but the scientific consensus so far is that embryos remain the best research choice. Typically, the embryos used are those remaining at the conclusion of fertility treatments that would otherwise be discarded or kept in frozen storage; a ban on the use of Federal funds to create new stem cells using these embryos currently is in effect, and various pieces of legislation pending in Congress would either extend this ban or relax it.

A survey of 2,212 Americans conducted September 9-19, reveals a public opinion landscape that bears little resemblance to the polarized, deep moral divide expressed on the floor of the Congress and in the op-ed pages of American newspapers.

The survey found wide support for embryonic stem cell research that cut across political, religious and socio-economic lines, with two-thirds of respondents either approving or strongly approving of human embryonic stem cell research. Even Fundamentalist and Evangelical Christians – long considered the most hard-line opponents of embryonic stem cell studies – split evenly on approval for embryonic stem cell research.

Respondents were given a choice of four ESC research policy options: banning all embryonic stem cell research, retaining the current Bush administration policy, relaxing restrictions along the lines of some Congressional proposals that would allow federal funding of research using embryonic stem cell lines created using private funds, and unqualified Federal support for embryonic stem cell creation and research.

Twenty-two percent of respondents expressed support for the current Bush administration policy; fewer still (16 percent), would ban embryonic stem cell research altogether. A majority favor relaxing embryonic stem cell restrictions, including 40 percent who would support federal funding for both the creation of new embryonic stem

cell lines and further research using them.

The survey also explored how potential future changes in the scientific landscape might affect public opinion. Respondents were asked to imagine two scenarios – the development of a technique to isolate ESCs without destroying embryos, or a major advance in treating disease based on embryonic stem cell technologies. About 25 percent of respondents who initially favored the current policy or a complete ban of ESC research indicated that if the treatment scenario were to materialize, they would support a public policy for ESC research that is more supportive than their initial policy position. Similarly, if the alternative scenario were to materialize, 16 percent of respondents who currently endorse a public policy towards ESC research that is more permissive than the current public policy would then support ESC research only if embryos were not destroyed.

The survey looked beyond overall attitudes toward ESC research to explore the competing values that underlie them. Survey respondents were asked a series of questions designed to ascertain the value placed on progress in ESC research and protecting early human embryos. The survey revealed a subtle topography of the public's attitudes with only a small fraction (6 percent at each pole) of the public occupying the extreme positions that so frequently characterize the public and policy debate. Fully half expressed agreement both with statements that placed high priority on protecting human embryos *and* with statements that placed high priority on searching for medical cures through ESC research. When asked in a single item which was more important, 60 percent selected ESC research and 37 percent selected not destroying embryos.

While the moral status of human embryos has been the centerpiece of the political debate about ESC research, often articulated as an all-or-nothing proposition that is fully predictive of all of an individual's other views on embryonic stem cell research, the public's views about the moral status of embryos and the relationship of those views to ESC research policy preferences has not been fully explored.

The survey showed that nearly the same number of Americans believe that an embryo in a Petri dish has no or low moral status (30 percent) or maximum moral status (28 percent). The remainder (42 percent) accord embryos some intermediate moral status.

A third of those who believe an embryo in a Petri dish has maximum moral status nonetheless approve of ESC research. Similarly, a third support ESC research policies more permissive than the current policy and which involve funding for research using new ESCs.

In a parallel fashion, 17 percent of those who accord an embryo in a Petri dish no or low moral status nevertheless disapprove of ESC research and support the current ESC policy or an all-out ban (22 percent). Thus, even for a sizeable number of respondents who fall at the polar ends of the moral status continuum, the commonly held expectation that they will support the corresponding policy extreme does not hold true.

Ethics of using employees' eggs in cloning research

SIR — The Hwang case highlights issues in human egg donation that were not addressed in your Editorial "Standards for papers on cloning" (*Nature* **439,** 243; 2006). Developing clones with eggs obtained from one's employees raises serious ethical concerns (see D. Magnus and M. K. Cho *Science* **308,** 1747–1748; 2005).

First, there is considerable risk that the decision to donate is made under pressure and is not entirely voluntary. Second, donors may not be adequately informed. For example, if donated eggs are sought purely for research purposes, the donor must know that they will not be used to develop therapies. Scientists, like all professionals, have an ethical imperative to serve certain socially valued goals, but they must not violate others' autonomy in the pursuit of those goals.

Human eggs are not easily obtained: the process involves trips to a clinic, ultrasound scans, injections to stimulate egg production and, when appropriate, having a probe with an attached needle guided by ultrasound inserted through the vaginal wall into the ovary to remove the eggs. Researchers using human eggs should be independent of any fertility clinics treating the women from whom the eggs came. That way, women are less likely to feel coerced into donating their eggs, and it helps ensure that clinical decisions are not motivated by either scientific or financial gain in the pursuit of these unique stem-cell lines. Cloning publications should include clear information about the steps taken to ensure that egg donors gave their informed and voluntary consent to donation.

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Ethics: China already has clear stem-cell guidelines

SIR — As scientists and ethicists who care about stem-cell research in China, we disagree with the statement in your News story "Panel clarifies stem-cell rules" (*Nature* **440,** 9; 2006) that "China lacks clear national policies, with different institutes following different rules".

In fact, China's government has issued several guidelines to regulate human stem-cell research. These include guidelines on human assisted-reproductive technologies, issued by the Ministry of Health in July 2003, and ethical guidelines for research on human embryonic stem cells, jointly issued by the Ministry of Science and Technology and the Ministry of Health in December 2003. Both explicitly prohibit human reproductive cloning, and the latter is similar in principle to the guidelines proposed by the US National Academies (www.nap.edu/books/0309096537/html).

It is true that national policies on human stem-cell research in China are not laws. With some further improvement, however, we think they are adequate, as nearly all scientific research in China relies on government funding. There have been cases in China where a few medical practitioners have used human fetal tissues or cells to treat patients, without required government approvals or appropriate clinical trials. We believe that this practice is against commonly accepted principles of modern scientific research. Infringements are a matter of law enforcement against unapproved medical practices, as in any lawful and civilized country, and should not be viewed as unethical examples of human stem-cell research in China.

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Eastern European science needs sweeping changes

SIR — Your News story "Ukraine scientists grow impatient for change" (*Nature* **440,** 132–133; 2006) touches on the situation and potential growth of scientific research in a single country, but the issues are relevant to all of the former Soviet bloc.

The facts are sobering. Although the average gross national product per capita in these countries is only a few times lower than in the rest of Europe, the average university ranking is an order of magnitude poorer: in the latest Academic Ranking of World Universities, only 4 of the top 123 European universities are from the former Soviet bloc. Pumping extra money into the system would make little difference. As a member of the Independent Academic Forum (www.nauka-edukacja.tubaza.pl) — a group of Polish scientists aiming to promote changes in higher education, leading to the US model — I believe the only real hope lies in creating a new generation of dynamic scientists to set the pace for academic life, which means supporting the best of the best. But much of the old guard, who attained their positions and influence under the old regime, are not up to the scientific challenges of today and resist any real change.

I believe that what we need is transparency and competitiveness: transparent records of achievements, including full publication lists, and fair and open competition for academic positions. An academic ombudsman would facilitate open discussion, and special grants for young scientists could also help. Major political and legislative decisions are called for. The Independent Academic Forum is doing its best to press for such changes.

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Reviewers peering from under a pile of 'omics' data

SIR — An increasing problem for reviewers, in providing adequate reviews for science journals, is not simply fraudulent data submission or manipulation (see Correspondence *Nature* **439,** 782–784; 2006), but the information density and sheer bulk of data that now have to be supplied as part of publishing modern biological science. This is particularly true with 'omics'-type data sets (transcriptomics, proteomics, metabonomics and so on), which are now collected in parallel in systems-biology studies.

Many referees are experienced and learned scientists, but they are also very busy people who may well get several papers a week to referee. Do we really have time to read the 60-plus pages of supplementary data that often accompany a major paper? Do we even have the tools and expertise needed to analyse and check the veracity of raw 'omics' data sets? A typical data set formatted to meet MIAME (minimum information about a microarray experiment) requirements may contain millions of discrete data.

To check whether these data have been scaled, normalized and processed correctly — within a data set that might have taken a couple of postdocs two years to process — is a difficult task, even if the referee has the time, the knowledge and the right software.

In the data-rich 'omics world' of today, the referee's task has become more complex and challenging than could have been envisaged only a few years ago.

Furthermore, there is increasing demand for integrative papers that cover many types of bioanalytical measurement and multivariate statistics at different levels of biomolecular organization. The scientific community needs to reassess the way it addresses the peer-review problem, taking into account that referees are only human and are now being asked to do a superhuman task on a near-daily basis.

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Wombs for rent in India
Women are getting paid as surrogate mothers to help Western couples with infertility problems.
Is such outsourcing a logical outgrowth of India's fast economic growth or an ethically troubling trend?
Apr. 20, 2006. The Toronto Star. http://www.thestar.com

ANAND, INDIA--As temp jobs go, Saroj Mehli has landed what she feels is a pretty sweet deal. It's a nine-month gig, no special skills needed and the only real labour comes at the end ‹ when she gives birth. If everything goes according to plan, Mehli, 32, will deliver a healthy baby early next year.
But rather than join her other three children, the newborn will be handed over to a U.S. couple who are unable to bear a child on their own and are hiring Mehli to do it for them. She'll be paid about $5,000 (U.S.) for acting as a surrogate mother, a bonanza that would take her more than six years to earn on her salary as a schoolteacher in a village near here. "I might renovate or add to the house, or spend it on my kids' education or my daughter's wedding," Mehli said. Beyond the money, she added, there is the reward of bringing happiness to a childless couple from the United States, where such a service would cost them thousands and thousands of dollars more, not to mention the potential legal hassles.

Driven by many of the same factors that have led Western businesses to outsource some of their operations to India in recent years, an increasing number of infertile couples from abroad are coming here in search of women willing, in effect, to rent out their wombs. The trend is evident to doctors such as Indira Hinduja, perhaps India's most prominent fertility specialist, who receives an inquiry from overseas every other week. It can also be detected on the Internet, where a young Indian woman recently posted an ad on a help-wanted website offering to carry a child for an expatriate husband and wife.

Then there is the dramatic example of Mehli's family. Two of her sisters have already served as surrogates -- one of them for foreigners -- and so has a sister-in-law. Mehli finally decided to join in, with the enthusiastic consent of her husband, a barber. She is under the care of a local physician who has become a minor celebrity after arranging more than a dozen surrogacies in the past two years, for both Indian and non-Indian couples.

For some, the practice is a logical outgrowth of India's fast-paced economic growth and liberalization of the last 15 years, a perfect meeting of supply and demand in a globalized marketplace. Payment usually ranges from about $2,800 to $5,600, a fortune in a country where annual per capita income hovers around $500.

"It's win-win," said S.K. Nanda, a former health secretary here in Gujarat state. "It's a completely capitalistic enterprise. There is nothing unethical about it. If you launched it somewhere like West Bengal or Assam"
-- both poverty-stricken states -- "you'd have a lot of takers.''

Others aren't so sure about the moral implications, and are worried about the exploitation of poor women and the risks in a land where 100,000 women die every year as a result of pregnancy and childbirth. Rich couples from the West paying Indian women for the use of their bodies, they say, is distasteful at best, unconscionable at worst. "You're subjecting the life of that woman who will be a surrogate to some amount of risk," said C.P. Puri, director of the National

Institute for Research in Reproductive Health in Mumbai (formerly Bombay). "That is where I personally feel it should not become a trade."

Both sides of the debate agree that the fertility business in India, including "reproductive tourism" by foreigners, is potentially enormous.
Current figures are tough to pin down, but the Indian Council of Medical Research estimates that helping residents and visitors beget children could bloom into a nearly $6 billion-a-year industry. "It's definitely going to increase with education and literacy, especially in a country like India,"
said Gautam Allahbadia, a fertility specialist in Mumbai who recently helped a Singaporean couple find an Indian surrogate. He has received similar inquiries from the U.S., Israel and Spain.

In the vanguard of the nascent industry is this small city, where gynecologist Nayna H. Patel is presiding over a mini baby boom. But eight of her recent and imminent arrivals won't be adding to Anand's population of
100,000: Three of the infants are destined for the U.S., two for Britain and three for other parts of India. (Six more surrogacy attempts were
unsuccessful.)

Before Patel's practice began attracting national and international notice, Anand was famous for decades as the milk capital of India, home to the country's most successful dairy farmer co-operative. Now the town also boasts about 20 young women who have volunteered to be implanted with embryos at Patel's clinic. A few have already gone through the process once and are eager for a second go-round.

Prospective foreign clients hear of Patel through word of mouth or informal online networks and websites dealing with infertility issues. By the time they contact her, and spend the time, energy and money to get here, they are usually desperate for children and often emotionally battered from long years of trying and failing.

Patel has set some criteria for those she'll help: only couples for whom the baby would be their first and where the wife is either infertile or cannot physically carry a child to term. Likewise, potential surrogates must be between 18 and 45, and in good health. They also must already be mothers, so that they know what awaits their bodies during pregnancy and are less likely to be troubled about giving up the new baby because they already have kids at home. The egg that contributes to the embryo is never one of their own, coming instead from an anonymous donor or the intended mother, and then usually fertilized in vitro.

Both parties sign a contract under which the intended parents pay for medical care and the surrogate renounces rights to the baby, a provision that relieves the fears of many foreign couples. In the U.S., for example, where laws vary from state to state, the surrogate sometimes has a window of opportunity after birth to stake a claim on the child. In Anand, volunteers are repeatedly reminded by Patel and her staff that the fetuses in their wombs are not theirs. They give up the newborns within one to two days after delivering. Patel said no problems have arisen yet with too strong a bond forming between surrogate and child.

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