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Lawyers praise classic defense as 'a powerful legal argument'

By Tony Mauro
USA TODAY

WASHINGTON — White House counsel Charles Ruff served up on Tuesday a classic criminal defense lawyer's argument, in which he raised doubts about the prosecutors' facts and leveled new charges that the case against President Clinton is constitutionally defective.

The array of arguments, delivered blandly and relatively briefly, was generally praised by legal experts as an effective opening shot to counter last week's forceful presentation by House impeachment managers.

"The job of the defense is to create reasonable doubts," said Notre Dame law professor Jimmy Gurule, a former federal prosecutor. "If you can create sufficient doubts or confusion, you've won."

Ruff's strongest assault might have been his claim that the two articles of impeachment against Clinton are too vague and all-encompassing to produce a constitutionally sound verdict. "It's a powerful legal argument," said lawyer David Stewart, who defended former federal judge Walter Nixon, the last person to be impeached.

"There is not a court anywhere, from highest to lowest, that would hesitate if they were confronted with an indictment written like these articles, to throw it out," Ruff said.

Claims of vagueness are often made by criminal defense lawyers, who cite the Sixth Amendment's guarantee that defendants "be informed of the nature and cause of the accusation."

Ruff also raised the related claim of "duplicity," a little-known principle of criminal law that frowns on prosecutors who bundle together multiple charges or alleged criminal acts in a single indictment.

The problem with such indictments is that different jurors might find guilt on some incidents mentioned in the count but not others. That would cast doubt on whether their ultimate verdicts are truly unanimous.

The first article of impeachment against Clinton cites four separate incidents, and the second article alleges seven separate acts, which Ruff said "creates a risk that a verdict may be based, not on a unanimous finding of guilt as to any particular charge, but instead, may be composed with multiple individual judgments."

Ruff added, "That risk is in direct violation of the requirement of the Constitution that this body agree by a two-thirds majority before the president may be removed."

Criminal defense lawyer William Moffitt said the duplicity assertion is "a dusty old legal argument, but it's a viable argument."

In the Walter Nixon impeachment in 1989, the judge was convicted on two articles but the Senate rejected a third count that had 14 subsections, according to Stewart. "The Senate is not interested in this kind of compound, omnibus article. You can't get a true verdict," he said.

But Rep. Charles Canaday, R-Fla., one of the impeachment managers, dismissed Ruff's argument as "legal hairsplitting."

"The legalistic challenge to the articles and the form in which they are cast, I think, is an unfortunate instance of the president and his lawyers seeking to turn away from the actual facts of this case and to find refuge in some technicalities which don't stand up to analysis," Canady said.

USA TODAY · WEDNESDAY, JANUARY 20, 1999

Cities: Increase in services largest since '91

By Richard Wolf
USA TODAY

Strong local economies are enabling the nation's cities to expand services, but poverty, drugs and unchecked development loom as their biggest problems entering 1999.

A survey out today of 393 city officials by the National League of Cities shows that 42% increased services last year, and 40% plan to do so this year. That's the biggest expansion of municipal services since 1991.

By contrast, only 4% of those surveyed report a decline in city services last year. The remaining 54% maintained levels of service. This year, only 3% of those surveyed say they expect to cut services; 57% predict no changes.

SURVEY FINDINGS

A survey of 393 municipal officials finds some conditions improving while others are deteriorating. Here are the reported ups and downs:

Most Improved City Conditions:
- Police-community relations
- Fiscal/economic conditions
- Vitality of downtown
- Level of employment
- Recreation services

Most Deteriorating City Conditions:
- Cable television rates
- Youth violence/crime
- Infrastructure needs
- Drug/alcohol abuse
- Affordable housing

Source: National League of Cities

The economy, employment, downtown development and recreation are rated among the most improved city conditions. In each area, more than half those polled say there have been improvements.

But at the same time, officials say there continues to be a gap between the haves and the have-nots in their communities. Nearly half also say development has been poorly planned, which resulted in sprawl.

One of every three municipal officials says the need for food, shelter, clothing and health care has risen in the past year; only 11% say the need has declined. In addition, 14% say poverty and homelessness have worsened.

"As America is prospering, we're concerned about the issues of continuing poverty and homelessness," says Clarence Anthony, mayor of South Bay, Fla., and president of the group of more than 1,400 cities.

Thirty percent cite a growing problem with crime by youths, and 29% say drug and alcohol abuse is getting worse.

Although applauding the impact of welfare reform in moving people into work, 59% say cities need to provide more well-paying jobs.

Officials say the same development that has helped them economically is strangling them physically. About 40% face a problem with overdevelopment that is straining traffic, schools and other services.

"The infrastructure is not keeping up with the growth," Anthony says. When asked to rate 35 issues, officials cite infrastructure needs as the top priority for the next two years.

The issue is a problem in small cities and new suburbs, says urban policy consultant David Rusk, former mayor of Albuquerque. "There's more and more focus on the need to control growth, not simply capture it."

Contributing: Haya El Nasser.

Sidestep of embryo-research ban possible

By Elizabeth Neus
Gannett News Service

WASHINGTON — Researchers might be able to sidestep a federal ban on human embryo research under a policy announced Tuesday.

Such research, expected to lead to treatments one day for such killers as heart disease and diabetes, has been controversial because cells have come from aborted fetuses, embryos left over from efforts to create test-tube babies or embryos grown using cloning.

At issue are embryonic stem cells, the basic cells from which all of a body's tissues and organs develop. With private funding, these cells have recently been derived from embryonic tissue and then grown in laboratories.

Congress has banned federal money for research that involves human embryos. But Harold Varmus, director of the National Institutes of Health (NIH), said a legal team's review of that ban concluded that the laboratory-grown cells could not grow into a human being and therefore do not qualify as an embryo.

"We have reached a conclusion based on the law that it is appropriate for NIH to support such research, and we intend to do so," Varmus told a meeting of the National Bioethics Advisory Commission.

Despite the potential for medical breakthroughs, not everyone is pleased. The NIH is breaking the spirit of the embryo research ban, said one group that has opposed federal funds for stem-cell research. "The NIH is going to support everything about the destruction of embryos except the act of destruction itself," said Richard Doerflinger of the National Conference of Catholic Bishops.

The panel met at President Clinton's request to discuss research into human stem cells, and commission Chairman Harold Shapiro, president of Princeton University, said a report could be complete by June.

Embryonic stem cells appear early in the developmental process, and are the cells that eventually take on assigned roles such as muscle or blood cells. In a naturally developing embryo, cells begin to take on new roles within days, and eventually die.

Stem cells grown in the lab have been kept alive and not taken assigned roles for months. They can grow only into other cells, not a full embryo.

Scientists doing the research were pleased by the news. "This is terrific," said John Gearhart, a professor at Johns Hopkins University in Baltimore who developed stem cells from fetal tissue. "The perception is that by not having public funding, you're doing something wrong."

The funds might be available in a few months, Varmus said.

Contributing: Wire reports

The New York Times
THURSDAY, DECEMBER 3, 1998

Gates Testifies He Knew Little of Microsoft-Sun Legal Battle Over Java

By JOEL BRINKLEY

WASHINGTON, Dec. 2 — In excerpts from a videotaped deposition played in Federal court today, William H. Gates, chairman of the **Microsoft** Corporation, professed general ignorance of his company's legal battles with **Sun Microsystems** Inc. over Sun's Java programming language.

Asked under oath on Aug. 29 if he was familiar with a civil lawsuit that Sun had recently filed accusing Microsoft of violating its contract to use Java, Mr. Gates paused for nearly 30 seconds before replying, "Not really." Later he said with a shrug, "I read something about it on our Web site four days ago."

The questioning in August was in the form of a sworn deposition taken by the Justice Department for the Government's lawsuit accusing Microsoft of predatory business practices that violated antitrust laws.

The trial turned today to the company's difficult relationship with Sun, which created and owns Java, a programming language that could in theory threaten the domination by Microsoft's Windows of the market for personal computer operating systems. Microsoft licensed Java from Sun three years ago but then wrote its own version of the language, which is in some ways incompatible with Sun's original.

Sun sued, contending that Microsoft's changes violated its licensing agreement. Two weeks ago, a Federal judge in California ordered Microsoft to make its version of Java compatible with Sun's version within 90 days.

In the antitrust case, the Government is trying to show that Microsoft's battles with Sun are part of a broad pattern of illegal, predatory behavior intended to protect its Windows operating system monopoly.

Through a long day of testimony, live and videotaped, Microsoft presented two faces. On videotape, Mr. Gates seemed largely unconcerned by Sun, though at one point he said that Java "might be evolved in the future" into a competitive threat. But in live questioning, a Microsoft lawyer, Tom Burt, tried to force James A. Gosling, the Sun executive who created Java, into saying that Sun intended to mount a deadly threat against Microsoft.

In taped deposition, few concerns over a potential rival.

Mr. Burt displayed memos and E-mail from Sun executives describing ambitions to challenge Microsoft using Java.

"Charge! Kill Hewlett-Packard, I.B.M., Microsoft and Apple all at once" using Java, Sun's chief executive, Scott G. McNealy, wrote in one E-mail message, according to a newsletter entered into evidence.

Bill Joy, another Sun executive, wrote in 1995 that "Java gives Sun a chance to break away from the Microsoft monopoly."

But Dr. Gosling seemed amused by that and other exuberant statements by Sun executives over the years. And when Mr. Burt asked him if Sun wanted to take over "100 percent of the computer market," Dr. Gosling chuckled before responding, "I think we would be happy if we achieved two orders of magnitude less than that," or 1 percent.

Microsoft's goal in court was to suggest that it could not be considered an enduring monopoly if it was threatened by aggressive competitors like Sun. The Government can make few of its charges stick if Judge Thomas Penfield Jackson does not conclude that Microsoft is a monopoly as defined by Federal law.

While it is not illegal to have a monopoly, a company with a recognized monopoly is barred from employing predatory practices to maintain its domination of a market.

In contrast to Mr. Burt's strategy, however, Mr. Gates seemed wholly unconcerned by Sun and Java.

At one point in the Aug. 28 deposition, David Boies, the Government's lead lawyer, asked Mr. Gates, "Did you ever try to find out what Microsoft is charged with, what they're alleged to have done wrong?"

In a casual tone, Mr. Gates responded that he had asked Paul Maritz, a senior Microsoft executive: " 'Do I need to learn about this lawsuit? Do I need to spend a lot of time on it?' He said, no, he's focused on it, and I can focus on other things."

But then Mr. Boies presented E-mail to Mr. Gates from others in his company last year showing that they were quite concerned with Sun and Java — particularly since Java was a significant component of the World Wide Web browser made by the Netscape Communications Corporation, Microsoft's chief competitor in Internet software. And in an E-mail entered into evidence earlier in the trial, Mr. Gates once remarked that Java "scares the hell out of me."

In one E-mail introduced today, Mr. Maritz wrote to Mr. Gates: "If we looked further at Java being our major threat, then Netscape is the major distribution vehicle."

Mr. Gates said he could not recall that E-mail, adding that "Maritz may or may not have agreed" with the notions he was describing.

In another message to Mr. Gates last year, a Micrsoft executive, Todd Nielson, wrote, "We are proactively trying to put obstacles in Sun's path and get anyone that wants to write in Java to use J/Direct," Microsoft's version of the language for Windows.

Mr. Gates said he did not recall the message, adding, "I don't know what it means."

Microsoft issued a statement today defending Mr. Gates's responses and criticizing the Government for playing the video of the deposition.

"Mr. Gates's performance reflects his adherence to the instructions lawyers routinely give their clients who are being deposed," it said.

Justin Lane for The New York Times

James A. Gosling of Sun Microsystems played down its ambitions to take over the computer market.

Panel Told of Vast Benefits of Embryo Cells

By NICHOLAS WADE

WASHINGTON, Dec. 2 — In unusually emphatic and optimistic terms, scientists told a Senate hearing today that research with human embryonic stem cells was likely to yield important medical benefits and should be supported by the Federal Government.

"It is not too unrealistic to say that this research has the potential to revolutionize the practice of medicine and improve the quality and length of life," said Dr. Harold Varmus, director of the National Institutes of Health.

The scientists who announced last month that they had isolated and cultured the cells told the hearing of the cells' potential to be grown into any desired tissue of the body and used to treat almost any disease, particularly those, like Parkinson's disease and juvenile diabetes, that are caused by deficiency of a specific type of cell.

Dr. Varmus agreed with that assessment. "There is almost no realm of medicine," he said, "that might not be touched by this innovation."

But use of the human embryonic stem cells also raises ethical issues, because they are widely regarded as meriting a special moral status: they are close cousins of the fertilized egg, although they cannot by themselves develop into an infant.

Among a panel of ethicists who followed the scientists as witnesses today, some said the practical benefits of treatments using the cells should outweigh moral qualms about their use. But one witness, Richard M. Doerflinger of the National Conference of Catholic Bishops, said that "scientific progress must not come at the expense of human dignity" and warned against use of the cells unless they were derived from spontaneously aborted fetuses.

The purpose of the hearing — held by the Senate Appropriations Subcommittee on Labor, Health and Human Services, and Education, a panel that approves Federal financing for biomedical research — was to explore the implications of the recent innovation in light of the current ban on using Federal money for research on embryos. That ban, originating in the House, has been attached to Congressional appropriations for the last three years.

The human embryonic stem cells described last month were developed by academic scientists who were supported by a California biotechnology company, the Geron Corporation, and received no Federal financing. But other university scientists, who receive most of their support from the National Institutes of Health, would like to work with the cells and will most likely be unable to do so unless the Federal ban on embryo research financing is lifted.

Evidently hoping that the ban will not be introduced for a fourth year, Dr. Varmus and other scientist witnesses were unusually eloquent in describing the expected benefits of embryonic stem cell research.

The importance of embryonic stem cells is that they are the all-purpose clay from which all the body's tissues are molded. In the womb, the embryonic cells develop naturally into the highly organized set of tissues that constitute a living infant. Now that the cells can for the first time be cultured in the laboratory, scientists hope to channel them into any desired type of cell, replacing or lessening the need for transplantable donor organs and providing novel treatments for many kinds of disease.

Dr. Thomas Okarma, Geron's vice president for research, said embryonic stem cells were a potential source of the following:

¶Heart muscle cells to treat congestive heart failure.

¶Blood-forming cells to help cancer patients whose own bone marrow cells have been damaged by chemotherapy.

¶Cells to line the inside of blood vessels, as treatment for atherosclerosis.

¶Insulin-producing cells to cure those with insulin-dependent diabetes.

¶Nerve and brain cells to treat victims of stroke, Parkinson's disease and Alzheimer's disease.

The two scientists whose embryonic stem cell work was financed by Geron, Dr. James A. Thomson of the University of Wisconsin and Dr. John Gearhart of Johns Hopkins University, offered similarly optimistic testimony. And, although Geron has a strong commercial interest in advertising the value of the cells, on whose use it holds an exclusive license, the company's general position on their wide applicability was supported by Dr. Varmus, an eminent biologist.

When the subcommittee's chairman, Senator Arlen Specter of Pennsylvania, pressed the scientists to say how soon treatments using the cells might be available, Dr. Thomson said therapy for Parkinson's disease could be expected in 5 to 10 years, and Dr. Gearhart predicted 7 to 12 years. Scientists usually decline to predict a date for prospective treatments, because many results that seem promising in the laboratory stumble before reaching the marketplace and because regulatory delays are equally unpredictable.

But even this enthusiastic panel of researchers became resolutely noncommittal when Senator Specter asked, "Do we have a realistic fountain of youth with this technique?"

At least two major obstacles remain to be overcome before any possible stem cell treatments emerge.

One is that biologists have not yet identified the natural signals that are assumed to govern the differentiation of embryonic cells in the body.

Another is that the developed cells produced from the embryonic stem cells will be rejected unless they can somehow be genetically manipulated so as to avoid provoking the patient's immune defenses.

Dr. Varmus said that "these technical challenges, though significant, are not insurmountable."

Both the derivation and the use of human embryonic stem cells raise unaccustomed ethical questions, which President Clinton last month asked the National Bioethics Advisory Commission to address.

Dr. Thomson derived his cells from pre-implantation embryos that had been created in fertility clinics. The embryos, at that stage a small blob of cells known as a blastocyst, had been frozen for several years and would otherwise have been discarded.

Dr. Gearhart's cells came from aborted fetuses, from an anatomical region destined to form the egg or sperm cells.

Mr. Doerflinger, representing the position of the Roman Catholic bishops, objected to any method that involved the creation or destruction of an embryo for research purposes, which in his view included the work with Dr. Thomson's cells and, in practice, Dr. Gearhart's. But he said Dr. Gearhart's method might be acceptable if the cells were to be taken from spontaneously aborted fetuses, provided that a human embryo was not created in the process.

"I think the answer is no," Mr. Doerflinger said of the likelihood of such a prospect, "but I don't know, and I don't think anyone knows."

Dr. Varmus said that he believed that Dr. Gearhart's research, performed with aborted fetuses rather than viable embryos, probably could have been financed by the National Institutes of Health despite the Congressional ban, but that he was awaiting a ruling from the general counsel of the Department of Health and Human Services.

The New York Times
THURSDAY, DECEMBER 3, 1998

Court Declines Shoplifter's '3 Strikes' Appeal

By Joan Biskupic
Washington Post Staff Writer

Touching on the controversial "three strikes, you're out" laws that have swept the nation, the Supreme Court yesterday let California impose a 25-year prison sentence on a man who stole a bottle of vitamins from a supermarket.

Michael Wayne Riggs was caught taking the pills from a store display rack and putting them in his jacket pocket. If this had been his first offense, he would have gotten a fine or, under the most harsh circumstances, six months in jail. But because Riggs had a record of drug crimes, robbery and other felonies, California law required that he spend at least 25 years behind bars.

Riggs appealed through state courts, and although the California Court of Appeal described his crime as "a petty theft motivated by homelessness and hunger," it upheld the stiff sentence. Last year the California Supreme Court refused to hear the case, leaving Riggs to petition the U.S. Supreme Court for a hearing.

Had he gotten four justices to agree to hear the dispute, Riggs would have had another chance to make his case. But yesterday the court turned him down. Only one justice, Stephen G. Breyer, said the appeal should have been heard, questioning how the state could possibly apply such a penalty "to what is in essence a petty offense." In an unusual move, three other justices also noted concern that such tough mandatory sentences can so disproportionately punish a repeat criminal that they violate the Eighth Amendment's ban on cruel and unusual punishment.

"While this court has traditionally accorded to state legislatures considerable (but not unlimited) deference to determine the length of sentences for crimes . . . classifiable as felonies," Justice John Paul Stevens wrote, "petty theft does not appear to fall into that category."

But as much as Stevens, joined in his statement by Justices David H. Souter and Ruth Bader Ginsburg, voiced constitutional worries about California's three-strikes law, the three justices did not vote to take up Riggs's case. Rather than joining Breyer, they said that the particulars of Riggs's criminal record were not clear and that they would rather wait until lower courts had established a more definitive record on California's three-strikes law.

But in declining to accept the case, the three justices also may have wondered whether they could have gotten the requisite fifth vote from any of the rest of the more conservative justices to build a majority opinion against a tough three-strikes law.

In a climate of rigid law enforcement and longer sentences, the justices have never taken up the question of whether a three-strikes law can be cruel and unusual punishment, particularly when the third offense is relatively minor. In past cases, the high court has said states may punish a repeat offender more severely than a first-time offender, but it also has said a sentence cannot be "grossly disproportionate" to the crime.

Over the past decade, more than two dozen states and the federal government have enacted laws that require lengthy prison sentences after a third felony. California's 1994 law, mandating at least 25 years for the third offense, is among the toughest in the nation. Stevens said the state is the only one that allows a misdemeanor offense to qualify for such a severe sentence.

In his roughly typed pauper petition to the Supreme Court, Riggs quoted from past court cases and said, "The state, even as it punishes, must treat its members with respect for their intrinsic worth as human beings. Punishment which is so excessive as to transgress those limits and deny that worth cannot be tolerated."

But California officials, urging the justices to reject the case of *Riggs v. California*, asserted that the state court had based its ruling on past Supreme Court decisions and its general rule of declining to second-guess state sentencing laws. The California attorney general's office emphasized Riggs's criminal history: convictions for car theft, two counts of possession of a controlled substance, two counts of forgery, two counts of receiving stolen property, attempted burglary, passing a check with intent to defraud and four counts of robbery.

The state appeals court said Riggs had spent most of the past 15 years behind bars and has had a recurring drug problem. When he was arrested a syringe was found hidden in his sock.

Separately yesterday, the justices also spurned an effort by Operation Rescue to revive a defamation lawsuit against Sen. Edward M. Kennedy (D-Mass.), who described the antiabortion group as engaging in firebombing and murder. Lower courts had ruled that Kennedy, as an employee of the government, is protected from such a lawsuit.

SUPREME COURT CALENDAR

The Supreme Court will hear arguments from 10 a.m. until noon today in the following cases:

No. 98-84. *National Collegiate Athletic Association v. Smith.* Whether the NCAA is bound by the prohibition in Title IX of the 1972 Education Amendments against sex discrimination because its member institutions receive Title IX funds. (One hour.)

No. 98-85. *Hunt v. Cromartie.* Whether, in a gerrymandering case, shape and demographic evidence are enough to prove that race was a predominant motive in the creation of a majority-black voting district. (One hour.)

The Washington Post
Wednesday, January 20, 1999

NIH to Fund Controversial Research on Human Stem Cells

By Rick Weiss
Washington Post Staff Writer

The National Institutes of Health has decided to fund research on human embryonic stem cells—recently discovered cells that appear to have great therapeutic potential but have also stirred controversy because they are derived from intentionally destroyed human embryos.

The decision, announced yesterday by NIH Director Harold Varmus at a Washington meeting of the National Bioethics Advisory Commission, makes the $14 billion federal agency a reluctant participant in the nation's long-running battle over abortion rights and embryo research just a month before Congress starts considering appropriations for the 2000 fiscal year.

Varmus told the presidentially appointed commission that the general counsel of the Department of Health and Human Services had determined that research on the embryo-like cells does not constitute research on human embryos. Under that interpretation, he said, the research is not subject to a four-year-old congressional ban on federal funding of human embryo research.

"We have made a determination of law that it is appropriate for NIH to support this research, and we intend to do so" as soon as clarifying rules are drawn up, Varmus told the commission, which is preparing a report on the science and ethics of human embryonic stem-cell research at President Clinton's request.

Scientists and patient advocates, many of whom believe that embryonic stem cells will someday be coaxed to grow into replacement tissues for people with Alzheimer's disease, Parkinson's disease, heart disease, diabetes and a host of other ailments, cheered the decision, saying the research will pay off much more quickly with its expansion beyond the handful of privately funded laboratories now pursuing the work. They encouraged Congress not to argue with HHS's interpretation of the ban.

FILE PHOTO/BY RAY LUSTIG—THE WASHINGTON POST

Harold Varmus, director of the National Institutes of Health, said that "it is appropriate for NIH to support [stem-cell] research, and we intend to do so."

"It is vitally important that the view expressed by Dr. Varmus today should prevail in federal policy," said Daniel Perry, executive director of the Alliance for Aging Research.

Praise also came from Sen. Tom Harkin (D-Iowa), ranking minority member of the appropriations subcommittee that funds NIH. Harkin had lobbied HHS Secretary Donna Shalala in support of stem-cell research.

"I look forward to working with NIH to ensure that the federal government does everything possible to advance this type of research," said Harkin, who has argued that the regulatory oversight that comes with federal support helps ensure that ethical standards of research will prevail.

But the announcement was criticized by antiabortion activists and others who believe embryo cells should have special moral status. They argued it amounted to an end run around the congressional ban on human embryo research. Although federal researchers would still be precluded from destroying human embryos to retrieve stem cells, critics said, their ability to conduct studies on such cells retrieved by others would create a market for—and lend credibility to—the mass destruction of human embryos.

"The Clinton administration now seeks to do indirectly what Congress has forbidden it to do directly: Provide federal support for research in which human embryos are created and destroyed," said Richard M. Doerflinger of the Washington-based National Conference of Catholic Bishops.

Congress has banned the use of federal funds for human embryo research since 1996. But the wording of that ban—known as the Dickey-Wicker Amendment, for coauthors Jay Dickey (R-Ark.) and Roger Wicker (R-Miss.)—did not anticipate last year's discovery of human embryonic stem cells.

The ban precludes the use of federal funds for research in which human embryos are "destroyed, discarded or knowingly subjected to risk of injury or death. . . ." That wording raised the question of whether federal funds could be used for research on human embryonic stem cells.

Those cells were first isolated last year by privately funded researchers from surplus human embryos that were about to be discarded by a fertility clinic. They have many of the properties of embryos, including the capacity to grow into virtually any kind of human tissue when cultured under the right conditions. But they do not have the potential to grow into an entire person.

After examining the issue for two months, HHS lawyers told Varmus last week that human embryonic stem cells "are not a human embryo within the statutory definition." In a five-page letter to Varmus dated Jan. 15, NIH General Counsel Harriet S. Rabb wrote that the cells "do not have the capacity to develop into a human being, even if transferred to the uterus." Thus, Rabb said, their destruction in the course of research would not constitute the destruction of an embryo.

The letter does not address a point raised by some ethicists and others: that the NIH may be held "complicit" in the destruction of embryos by making use of the products of their demise. That question has been raised before in the context of whether doctors today should make use of medical information gleaned from horrific Nazi experiments on unconsenting people.

"It's a debated question within the ethics community whether you have to take into account how you got the stem cells," said LeRoy Walters, director of Georgetown University's Kennedy Institute of Ethics.

Varmus denied that federal support of stem-cell research would create a market for the destruction of embryos or fetuses, which are also a source of stem cells. "The supply of these cells is far in excess of demand," Varmus said in an interview. "This would not drive or increase the use of either in vitro fertilization or abortion for research purposes."

Varmus said he hoped to have guidelines ready within the next several months describing conditions under which human embryonic stem cells could be studied with federal funds. If those rules parallel those now in force for federal research on human fetal cells, they will require that researchers be certain that the cells were gathered in an ethically appropriate manner.

Under current rules, for example, a woman's decision to have an abortion must be made prior to and independent from any solicitation by scientists for her to donate fetal tissues for research. That is designed to ensure that the research does not affect her decision to abort or the "timing or manner" of the abortion.

CORRECTION

An article Monday on President Clinton's defense strategy incorrectly identified the program on which Rep. Asa Hutchinson (R-Ark.) had appeared the previous day. The program was ABC News's "This Week."

The Washington Post

W[illegible] JANUARY 20, 1999

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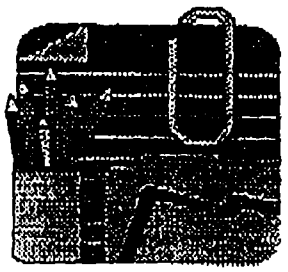

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COMMITTEES:
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United States Senate

WASHINGTON, DC 20510-1502

December 18, 1998

The Honorable Donna Shalala
Secretary
Department of Health and Human Services
200 Independence Avenue, SW
Washington, DC 20201

Dear Secretary Shalala,

I am writing to urge you and your General Counsel to make a timely decision on the issue of whether stem cell research can be supported by the National Institutes of Health (NIH). I know the NIH has requested a legal review of the statute on this, and I know that your General Counsel has been considering it for the past several weeks. However, from my reading of the law, it is very clear that research on stem cells does not fall within the federal ban on human embryo research, and should be allowed to go forward with federal support.

As you know, the Labor, Health and Human Services and Education Appropriations Subcommittee held a hearing on December 2, 1998 to discuss the ethical and scientific issues arising from recent breakthroughs in stem cell research. This research holds tremendous promise for the development of therapies that can treat a wide range of chronic and catastrophic diseases, from Alzheimer's to heart disease, from diabetes to Parkinson's.

It is critical that federally-funded scientists be able to conduct research using the stem cell lines isolated by Dr. Thomson of the University of Wisconsin and Dr. Gearhart of Johns Hopkins University. Therefore, I would like to know who at the Department will be making this decision, and when you expect that decision to be made. Thank you in advance for your attention to this matter.

Sincerely,

Tom Harkin

Senator Tom Harkin

cc: Dr. Harold Varmus

TH/sc

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12-21-98-00402

THE SECRETARY OF HEALTH AND HUMAN SERVICES
WASHINGTON, D.C. 20201

JAN 19 1999

The Honorable Tom Harkin
United States Senate
Washington, D.C. 20510-1502

Dear Senator Harkin:

Thank you for your recent letter urging me and the General Counsel of the Department of Health and Human Services to make a timely decision on the issue of whether stem cell research can be supported by the National Institutes of Health. I am pleased to enclose a copy of that decision which Dr. Harold Varmus discussed today at the meeting of the National Bioethics Advisory Commission.

I understand that your staff was briefed on this decision last week. I appreciate your interest in this issue.

Sincerely,

Donna E. Shalala

Enclosure

DEPARTMENT OF HEALTH & HUMAN SERVICES
Office of the Secretary

The General Counsel
Washington, D.C. 20201

January 15, 1999

TO: Harold Varmus, M.D.
Director, NIH

FROM: Harriet S. Rabb

SUBJECT: Federal Funding for Research Involving Human Pluripotent Stem Cells

The Office of the General Counsel of the U.S. Department of Health and Human Services (HHS) has prepared the following in response to your request for a legal opinion on whether federal funds may be used for research conducted with human pluripotent stem cells derived from embryos created by *in vitro* fertilization or from primordial germ cells isolated from the tissue of non-living fetuses. This inquiry arises from the recently reported research of: (1) Dr. James A. Thomson of the University of Wisconsin-Madison, who isolated pluripotent stem cells from embryos donated for research by persons undergoing fertility treatment[1]; and (2) Dr. Michael Shamblott of the Johns Hopkins University School of Medicine, who derived pluripotent stem cells from primordial germ cells from non-living fetuses.[2] The research described in these two published reports was not funded by HHS.

Summary Answer

The statutory prohibition on the use of funds appropriated to HHS for human embryo research would not apply to research utilizing human pluripotent stem cells because such cells are not a human embryo within the statutory definition. To the extent human pluripotent stem cells are considered human fetal tissue by law, they are subject to the statutory prohibition on sale for valuable consideration, the restrictions on fetal tissue transplantation research that is conducted or funded by HHS, as well as to the federal criminal prohibition on the directed donation of fetal

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[1] James A. Thomson et al., Embryonic Stem Cell Lines Derived from Human Blastocysts, Science, vol. 282, November 6, 1998, pp. 1145-1147.

[2] Michael J. Shamblott et al., Derivation of Pluripotent Stem Cells from Cultured Human Primordial Germ Cells, 95 Proc. Nat'l. Acad. Sci. USA 13726 (Nov. 1998).

tissue. Research involving human pluripotent stem cells excised from a non-living fetus may be conducted only in accordance with any applicable state or local law. Finally, the Presidential Directive banning federal funding of human cloning would apply to pluripotent stem cells, only if they were to be used for that purpose.

Analysis

I. Prohibition on Federal Funding for Human Embryo Research

In the appropriations provision for the Departments of Labor, Health and Human Services, and Education, and Related Agencies in the Omnibus Consolidated and Emergency Supplemental Appropriations Act, Fiscal Year 1999, Public Law 105-277, section 511 provides that none of the funds made available in that appropriation may be used for:

> (1) the creation of a human embryo or embryos for research purposes; or
> (2) research in which a human embryo or embryos are destroyed, discarded or knowingly subjected to risk of injury or death greater than that allowed for research on fetuses in utero under 45 CFR 46.208(a)(2) and section 498(b) of the Public Health Service Act (42 U.S.C. 289g (b)).

The term "human embryo or embryos" is defined in the statute to include "any organism, not protected as a human subject under 45 CFR 46 as of the date of the enactment of this Act, that is derived by fertilization, parthenogenesis, cloning, or any other means from one or more human gametes or human diploid cells."

Pluripotent stem cells are not a human "organism" as that term is used in the definition of human embryo provided by statute. The term "organism" is not itself defined by law, and the question of what is an organism calls for a science-based answer. According to the McGraw-Hill Dictionary of Scientific and Technical Terms (hereinafter McGraw-Hill), an organism is "[a]n individual constituted to carry out all life functions."[3] Pluripotent stem cells are not organisms

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[3] McGraw-Hill Dictionary of Scientific and Technical Terms 1408 (5th edition 1994). See also N. Campbell, Biology, (4th edition 1996) pp. 8-9, which defines organism as follows:

> While cells are the units of organisms, it is organisms that are the units of life. It's an important distinction. Except for unicellular life, 'cell' does not equal 'organism.' A single-celled organism such as an amoeba is analogous not to one of your cells, but to your whole body. What the amoeba accomplishes with a single cell -- the uptake and processing of nutrients, excretion of wastes, response to environmental stimuli, reproduction, and other functions -- a human or other multicellular organism accomplishes with a division of labor among specialized tissues, organs, and organ systems. Unlike the amoeba, none of your cells could live for long on its own. The organism we recognize as an animal or plant is not a

and do not have the capacity to develop into an organism that could perform all the life functions of a human being – in this sense they are not even precursors to human organisms.[4] They are, rather, human cells that have the potential to evolve into different types of cells such as blood cells or insulin producing cells.

Moreover, a human embryo, as that term is virtually universally understood, has the potential to develop in the normal course of events into a living human being. The scientific definition of embryo, as described in McGraw-Hill, is "[t]he product of conception up to the third month of human pregnancy."[5] Pluripotent stem cells do not have the capacity to develop into a human being, even if transferred to a uterus.[6] Therefore, in addition to falling outside of the legal definition provided by statute, pluripotent stem cells cannot be considered human embryos consistent with the commonly accepted or scientific understanding of that term. Thus, based on

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collection of unicells, but a multicellular cooperative with the emergent properties of 'whole organism.'

[4] At a December 2, 1998, stem cell research hearing before the Subcommittee on Labor, Health and Human Services, Education and Related Agencies of the Senate Appropriations Committee, Senator Tom Harkin asked five scientists, two bioethicists, and a theologian testifying before the committee if, in their view, stem cells were organisms. All of the experts who responded concluded that human pluripotent stem cells are not organisms. Use of Fetal Tissue in Brain Stem Cell Research: Hearing Before the Subcomm. on Labor, Health and Human Services, and Education of the Senate Appropriations Comm., 105th Cong. (December 2, 1998) available in LEGI-SLATE, Transcript No. 983360015 [hereinafter Stem Cell Hearing] (statement of Dr. Harold Varmus, Director, National Institutes of Health; Dr. John Gearhart, Johns Hopkins University School of Medicine; Dr. James Thomson, Wisconsin Primate Research Center, University of Wisconsin; Dr. Michael West, Advanced Cell Technology; Dr. Thomas Okarma, Geron Corporation; Dr. Arthur Caplan, Center for Bioethics, University of Pennsylvania Health System; and Mr. Richard Doerflinger, Associate Director for Policy Development, Secretariat of Pro-Life Activities, National Conference of Catholic Bishops). One expert, Dr. Eric Meslin, Executive Director of the National Bioethics Advisory Commission, stated that he could not speak on behalf of the Commission because it had not considered the question. Stem Cell Hearing, supra, (statement of Dr. Eric Meslin).

[5] McGraw-Hill Dictionary, supra note 3, at 673.

[6] See Letter from the Chair of the National Bioethics Advisory Commission, to the President of the United States, response to question no. 2, November 20, 1998; National Institutes of Health, Report of the Human Embryo Research Panel, Sept. 1994, p. 26. See also Stem Cell Hearing, supra note 4, (statements of Dr. Michael West, Advanced Cell Technology; Dr. Thomas Okarma, Geron Corporation; and Dr. Arthur Caplan, Center for Bioethics, University of Pennsylvania Health System).

an analysis of the relevant law and scientific facts, federally funded research that utilizes human pluripotent stem cells would not be prohibited by the HHS appropriations law prohibiting human embryo research, because such stem cells are not human embryos.

II. Restrictions on the Use of Human Fetal Tissue

There are a number of potential sources of human pluripotent stem cells; some of these stem cells may fall within the legal definition of human fetal tissue and would, therefore, be subject to federal regulations. Section 498A of the Public Health Service Act specifies that fetal tissue "means tissue or cells obtained from a dead human embryo or fetus after a spontaneous or induced abortion, or after a stillbirth." 42 U.S.C. 289g-1(g). Some stem cells, for example those derived from the primordial germ cells of non-living fetuses, would be considered human fetal tissue for purposes of Section 498A.

The Public Health Service Act (hereinafter "The Act") contains three relevant provisions governing the use and transfer of human fetal tissue: (1) a criminal prohibition against the sale of human fetal tissue for valuable consideration; (2) restrictions on fetal tissue transplantation research supported by federal funds; and (3) a prohibition on the directed donation of fetal tissue for transplantation. We explore each of these restrictions in turn.

Section 498B(a) of the Act states that it is unlawful for any person to knowingly acquire, receive, or otherwise transfer any human fetal tissue for valuable consideration,[7] if the transfer affects interstate commerce.[8] 42 U.S.C. 289g-2(a). It is common practice for scientists throughout the United States to share research materials through transactions that result in such materials crossing state boundaries. Such exchanges, as well as transactions within the District of Columbia, or exchanges within a state that "affect interstate commerce" would meet the statutory criterion of affecting interstate commerce, but would not fall within the scope of the criminal

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[7] The term "valuable consideration" encompasses both monetary and non-monetary payments. Section 498B (d)(3) provides that the term does not include "reasonable payments associated with the transportation, implantation, processing, preservation, quality control, or storage of human fetal tissue."

[8] The statute adopts the definition of interstate commerce in section 201(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 321(b): ". . . commerce between any State or Territory and any place outside thereof, and . . . commerce within the District of Columbia or within any other Territory not organized with a legislative body." The statute does not define what "affects" interstate commerce, but, in interpreting similar language in another criminal statute the Supreme Court found that "affecting interstate commerce" is an expression of Congress' intent to broadly exercise its Commerce Clause power under the Constitution. Scarborough v. United States, 431 U.S. 563, 571-72 (1977).

prohibition unless the scientist providing the materials sought payment in excess of the expenses included in the statutory definition of "valuable consideration."

In addition, the law places some restrictions on federal support for research on the transplantation of fetal tissue. Section 498A of the Act provides that the Secretary may conduct or support research on the "transplantation of fetal tissue for therapeutic purposes," only if certain statutory requirements are met. 42 U.S.C. 289g-1. These requirements include obtaining: (1) the informed consent of the woman donating the tissue; (2) a statement by the attending physician regarding the woman's consent and the method of obtaining the tissue; (3) a statement by the researcher regarding his or her understanding of the source of the tissue, that such information has been conveyed to the donee, and that the researcher has not participated in any decision regarding termination of the pregnancy.

Finally, section 498B(b) of the Act provides that it shall be unlawful for any person to solicit or knowingly acquire, receive, or accept a donation of human fetal tissue for the purpose of transplantation into another person if the tissue will be or is obtained pursuant to an induced abortion, and there is a promise to the donor: (1) to transplant the tissue into a person specified by the donor; (2) the tissue will be transplanted into a relative of the donor; or (3) the donee of the tissue has provided valuable consideration for the costs associated with the abortion. 42 U.S.C. 289g-2(b). The Act provides criminal penalties for violation of the prohibition on directed donations.

III. Federal Restrictions on Fetal Research

Federal regulation provides that activities involving cells, tissues, or organs excised from a non-living fetus shall be conducted only in accordance with any applicable state or local law. 45 CFR 46.210, Subpart B. This regulation would apply to certain human pluripotent stem cells, including those derived from the primordial germ cells of non-living fetuses.

IV. Prohibition on Federal Funding for Cloning of Human Beings

In a March 4, 1997, memorandum to the heads of executive departments and agencies, the President directed that no federal funds will be used for the cloning of human beings and that federal funds shall not be allocated for that purpose.[9] There are myriad uses for human pluripotent stem cells that are completely unrelated to cloning. However, to the extent such stem cells were to be used for human cloning, the prohibition on the use of federal funds for that purpose would apply.

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[9] Memorandum from the President of the United States to Heads of Executive Departments and Agencies (March 4, 1997).

Date: 02/17/99 Time: 12:07
SSeventy in Congress send letter opposing human stem-cell research

WASHINGTON (AP) Seventy members of Congress say that National Institute of Health plans to sponsor human stem cell research would violate a law banning federal support of studies in which human embryos are destroyed.

In a letter sent last week to Donna E. Shalala, the secretary of health and human services, the lawmakers objected to the announced plans of NIH to fund research using stem cells that had been obtained from human embryos or fetuses.

Stem cells are basic biological building blocks. The cells have the ability to create any organ or any tissue. Scientists say that by guiding the growth of these cells it might be possible to culture new organs to replace ailing hearts, or neurons for the treatment of brain disease or injury, or insulin-producing cells to cure diabetes. Stem cells usually are obtained from an embryo or fetus.

No government-backed research has been conducted on stem cells because a 1996 law specifically forbids spending federal dollars for medical research that involves creation of a human embryo for research purposes, or conducting research in which a human embryo has been destroyed.

However, privately funded researchers not covered by the ban last year grew colonies of stem cells from tissue taken from human fetuses and embryos.

Last month, NIH Director Harold Varmus announced that the agency had decided these laboratory-grown cells were not covered by the federal ban because they are not human embryos capable of creating a new person. Varmus based his announcement on a memo from HHS general counsel Harriet Rabb.

In their letter, the Congress members said federal funding of such research ''would violate both the letter and the spirit'' of the law.

The group's letter said that Rabb's memo to Varmus ''appears to be a carefully worded effort to justify transgressing that law.''

The letter said Rabb's memo claims the law only prohibits research involving the specific act of destroying an embryo, but not the cells that were later grown from embryonic tissue.

But the lawmakers said the federal law also forbids funding of research ''which follows or depends upon the destruction of or injury to a human embryo.''

''This area of the law has provided a bulwark against government's misuse and exploitation of human beings in the name of medical progress,'' the letter says. ''It would be a travesty for the administration to attempt to unravel this accepted ethical standard.''

Laurie Boeder, an HHS spokeswoman, said Shalala received the letter Tuesday, but has not yet responded. Boeder said the NIH has not funded any stem-cell research and is only analyzing what studies might be sponsored by the agency.

''NIH and the department are very aware of the serious legal, ethical and moral issues raised by this research,'' said Boeder.

Rep. Christopher Smith, R-N.J., initiated the letter. Among the 70 signers were Rep. Tom DeLay, R-Texas, the majority whip; Rep. J.C. Watts Jr. of Oklahoma, the Republican conference chairman; and Rep. Henry Hyde, R-Ill., chairman of the House Judiciary committee.
APNP-02-17-99 1225EST

Rich
Harold
Harriet
Kevin

} HHS internal mtg.

January 19, 1999

Disputed Stem Cell Research Financed

A.P. INDEXES: TOP STORIES | NEWS | SPORTS | BUSINESS | TECHNOLOGY | ENTERTAINMENT

Filed at 5:14 p.m. EST

By The Associated Press

WASHINGTON (AP) -- Despite ethical questions, the Clinton administration is about to finance research using the body's own ``master cells'' -- the building blocks of tissue that scientists have culled from human embryos.

Studying how to harness these embryonic stem cells and turn them into therapies for Alzheimer's disease or diabetes, as well as ways to prevent birth defects and rebuild damaged organs, is considered one of the most promising new frontiers of science.

It's also controversial because these ``master cells'' are present only in early-stage human embryos. Some anti-abortion groups in particular call stem cell research morally unacceptable, because to get the cells, embryos would have to be destroyed.

Until now the research has largely been taboo, because federal law prohibits using taxpayers' money for research using human embryos.

But scientists working last year with scarce private funding succeeded in isolating some embryonic stem cells -- both from aborted fetuses and from unused embryos from infertility treatments -- and succeeded in multiplying the stem cells in laboratories to grow a supply for research.

Now the National Institutes of Health, the main provider of money for U.S. medical research, says that because these lab-grown stem cells do not constitute an embryo, it thus is legal for NIH to fund experiments using them -- and it will do so within months.

``We know this is ethically sensitive territory,'' NIH Director Harold Varmus said Tuesday after announcing the decision before President Clinton's National Bioethics Advisory Commission. But ``the prospects of benefit to living human beings ... are dramatic.''

Stem cells are the basic or primordial cells from which all of a human's tissues and organs develop. By themselves, the cells can't grow into a person.

But if scientists could control how the cells switch on to form different bodily tissues, they might produce lifesaving therapies: Growing heart cells to rebuild disease-ravaged hearts, or insulin-producing cells for diabetics, or new brain cells for victims of Parkinson's or Alzheimer's disease.

The NIH's decision ``is terrific'' because it will speed that research ``absolutely by years,'' said Dr. John Gearhart of Johns Hopkins University, who grew one of the stem cell supplies from aborted fetuses.

In addition, NIH involvement will ensure the science is done with the public scrutiny not possible when private companies control the purse strings, Gearhart added.

Abortion opponents immediately decried the decision.

``Today's announcement ... is the latest step by the Clinton administration to treat human beings as property to be manipulated and destroyed,'' said Rep. Chris Smith, R-N.J.

NIH money will allow researchers to ``experiment with cells obtained from human beings ruthlessly killed in the first weeks of life,'' said Smith.

The congressman didn't say whether he would challenge NIH's plans.

Because of Congress' ban, NIH ``will not fund the act of destruction itself, but will reward those who destroy embryos by paying them to develop the cells and tissues they have obtained by destructive means,'' said Richard Doerflinger of the National Conference of Catholic Bishops.

The bioethics commission will wrestle with other questions: How appropriate is it to derive stem cells from live human embryos? After all, University of Wisconsin scientists successfully used spare embryos with the full consent of couples treated at infertility clinics, who donated the embryos they didn't end up using to attempt a pregnancy.

And what if doctors one day decide they want to create an embryo solely for the purpose of deriving stem cells -- which means growing the embryo to destroy it?

It also may be possible to use cloning techniques to derive human stem cells by, for instance, placing human genes into an animal's egg to grow a hybrid embryo.

Varmus says he does not expect Congress to stop his funding plans. Indeed, Sen. Arlen Specter, R-Penn., who heads the subcommittee that controls NIH's budget, has been investigating stem cell research and praised the decision.

``We've got the potential for enormous advances in medical science and we should utilize them,'' Specter said. Even where stem cells did come from live embryos, they were embryos destined to be discarded ``that could not be used to produce human life.''

Within months, NIH will draw up guidelines that set just what kind of research the agency will fund.

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DATE: 1/19/99

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
200 INDEPENDENCE AVE., SW
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REMARKS:

HHS FACT SHEET

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

January 19, 1999

Contact: HHS Press Office
(202) 690-6343

STEM CELL RESEARCH

The Department of Health and Human Services has concluded that current law permits federal funds to be used for research utilizing human pluripotent stem cells. This decision is consistent with existing congressional restrictions on human embryo research and with federal law and regulations governing human fetal tissue research. The National Institutes of Health (NIH) plans to move forward in a careful and deliberate fashion to develop rigorous guidelines that address the special ethical, legal, and moral issues surrounding this research. The NIH will not be funding any research using pluripotent stem cells until guidelines are developed and widely disseminated to the research community and an oversight process is in place.

The Promise of Stem Cell Research

Scientists at the University of Wisconsin and another group of scientists at Johns Hopkins University recently have isolated and successfully cultured human pluripotent stem cells and have grown these cells for prolonged periods in culture dishes. Human pluripotent stem cells have an unlimited capacity to divide, and the ability to turn into most of the cells or tissues in the body.

This exciting advance represents a huge step forward in human biology and has generated tremendous enthusiasm among scientists and the public, particularly patients and their families. Because these cells can give rise to many different types of cells, such as muscle cells, nerve cells, heart cells, blood cells, and others, they are enormously important to science and hold great promise for advances in health care. For example, further research using pluripotent stem cells can help us:

- Generate cells and tissue that could be used for transplantation. Pluripotent stem cells can be stimulated to develop into specialized cells, which can be used as replacement cells and tissue to treat many diseases and conditions including Parkinson's disease, spinal cord injury, stroke, burns, heart disease, diabetes, osteoarthritis and rheumatoid arthritis.

- Improve our understanding of the complex events that occur during normal human development and also help us understand what goes wrong to cause birth defects and cancer.

- Change the way we develop drugs and test them for safety. Rather than evaluating the safety of candidate drugs in an animal model, the drugs could be initially tested against a human cell line; only the safest candidate drugs would be likely to graduate to animal and then human testing.

Legal Issues

The stem cells produced by the scientists in Wisconsin and Maryland were developed by different methods. The Wisconsin scientists derived the pluripotent stem cells from early-stage embryos donated by people who were undergoing fertility treatment in an in vitro fertilization (IVF) clinic; all of the

individuals gave informed consent for the embryos to be used in research. The scientists at Johns Hopkins University isolated the pluripotent stem cells from non-living fetuses obtained from pregnancies that had been terminated. Neither research project utilized federal funds. Because of the regenerative capacity of pluripotent stem cells, these cells alone could supply numerous other researchers without the need to generate a new line of cells.

Federal law currently prohibits the NIH from funding human embryo research. In light of this legislative ban, the Director of the NIH sought a legal opinion from the DHHS Office of the General Counsel on whether federal funds may be used for research utilizing human pluripotent stem cells.

After a thorough analysis of the law, DHHS concluded that the congressional prohibition on the use of DHHS funds for certain types of embryo research does not apply to research utilizing human pluripotent stem cells because such cells are not an embryo as defined by statute. Moreover, because pluripotent stem cells do not have the capacity to develop into a human being, they cannot be considered human embryos consistent with the commonly accepted or scientific understanding of that term. The legal opinion also clarified that pluripotent stem cells derived from non-living fetuses would fall within the legal definition of human fetal tissue and are, therefore, subject to certain Federal restrictions on the use of such tissue.

Thus, research using pluripotent stem cells derived from human embryos can be funded by DHHS. Research that generates and uses pluripotent stem cells from non-living fetuses can also be supported by DHHS, subject to existing law and regulation.

NIH Support

In view of the tremendous scientific and medical benefits that may result from research using pluripotent stem cells, the NIH plans to fund research using these cells. It is essential that the Federal government play a role in funding and overseeing the conduct of this research so that all scientists-- both privately and federally funded--have the opportunity to pursue this important line of research. Federal funding will provide oversight and direction that would be lacking if this research were the sole province of industry and academe.

The NIH understands and respects the compelling ethical, legal, and moral issues surrounding pluripotent stem cell research and is sensitive to the need for stringent oversight of this research that goes beyond the traditional rigorous NIH scientific peer review process. In light of these issues, the NIH plans to move forward in a careful way prior to funding any research utilizing pluripotent stem cells. The NIH will develop and issue guidelines regarding special considerations that must be met in conducting such research, including an assurance that the research is consistent with current federal law governing embryo research. Also, the NIH will convene a special oversight group to review all research grant applications in this area, in addition to the rigorous scientific and programmatic reviews that all NIH-funded research currently undergoes. The NIH has asked the National Bioethics Advisory Board (NBAC) for additional guidance, and those views will be factored into the process of approving research proposals. The NIH will not be funding any research using pluripotent stem cells until guidelines are developed and widely disseminated to the research community and an oversight process is in place.

# # #

DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary

The General Counsel
Washington, D.C. 20201

January 15, 1999

TO: Harold Varmus, M.D.
Director, NIH

FROM: Harriet S. Rabb

SUBJECT: Federal Funding for Research Involving Human Pluripotent Stem Cells

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Summary Answer

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> While cells are the units of organisms, it is organisms that are the units of life. It's an important distinction. Except for unicellular life, 'cell' does not equal 'organism.' A single-celled organism such as an amoeba is analogous not to one of your cells, but to your whole body. What the amoeba accomplishes with a single cell -- the uptake and processing of nutrients, excretion of wastes, response to environmental stimuli, reproduction, and other functions -- a human or other multicellular organism accomplishes with a division of labor among specialized tissues, organs, and organ systems. Unlike the amoeba, none of your cells could live for long on its own. The organism we recognize as an animal or plant is not a

and do not have the capacity to develop into an organism that could perform all the life functions of a human being -- in this sense they are not even precursors to human organisms.[4] They are, rather, human cells that have the potential to evolve into different types of cells such as blood cells or insulin producing cells.

Moreover, a human embryo, as that term is virtually universally understood, has the potential to develop in the normal course of events into a living human being. The scientific definition of embryo, as described in McGraw-Hill, is "[t]he product of conception up to the third month of human pregnancy."[5] Pluripotent stem cells do not have the capacity to develop into a human being, even if transferred to a uterus.[6] Therefore, in addition to falling outside of the legal definition provided by statute, pluripotent stem cells cannot be considered human embryos consistent with the commonly accepted or scientific understanding of that term. Thus, based on

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collection of unicells, but a multicellular cooperative with the emergent properties of 'whole organism.'

[4] At a December 2, 1998, stem cell research hearing before the Subcommittee on Labor, Health and Human Services, Education and Related Agencies of the Senate Appropriations Committee, Senator Tom Harkin asked five scientists, two bioethicists, and a theologian testifying before the committee if, in their view, stem cells were organisms. All of the experts who responded concluded that human pluripotent stem cells are not organisms. Use of Fetal Tissue in Brain Stem Cell Research: Hearing Before the Subcomm. on Labor, Health and Human Services, and Education of the Senate Appropriations Comm., 105th Cong. (December 2, 1998) available in LEGI-SLATE, Transcript No. 983360015 [hereinafter Stem Cell Hearing] (statement of Dr. Harold Varmus, Director, National Institutes of Health; Dr. John Gearhart, Johns Hopkins University School of Medicine; Dr. James Thomson, Wisconsin Primate Research Center, University of Wisconsin; Dr. Michael West, Advanced Cell Technology; Dr. Thomas Okarma, Geron Corporation; Dr. Arthur Caplan, Center for Bioethics, University of Pennsylvania Health System; and Mr. Richard Doerflinger, Associate Director for Policy Development, Secretariat of Pro-Life Activities, National Conference of Catholic Bishops). One expert, Dr. Eric Meslin, Executive Director of the National Bioethics Advisory Commission, stated that he could not speak on behalf of the Commission because it had not considered the question. Stem Cell Hearing, supra, (statement of Dr. Eric Meslin).

[5] McGraw-Hill Dictionary, supra note 3, at 673.

[6] See Letter from the Chair of the National Bioethics Advisory Commission, to the President of the United States, response to question no. 2, November 20, 1998; National Institutes of Health, Report of the Human Embryo Research Panel, Sept. 1994, p. 26. See also Stem Cell Hearing, supra note 4, (statements of Dr. Michael West, Advanced Cell Technology; Dr. Thomas Okarma, Geron Corporation; and Dr. Arthur Caplan, Center for Bioethics, University of Pennsylvania Health System).

an analysis of the relevant law and scientific facts, federally funded research that utilizes human pluripotent stem cells would not be prohibited by the HHS appropriations law prohibiting human embryo research, because such stem cells are not human embryos.

II. Restrictions on the Use of Human Fetal Tissue

There are a number of potential sources of human pluripotent stem cells; some of these stem cells may fall within the legal definition of human fetal tissue and would, therefore, be subject to federal regulations. Section 498A of the Public Health Service Act specifies that fetal tissue "means tissue or cells obtained from a dead human embryo or fetus after a spontaneous or induced abortion, or after a stillbirth." 42 U.S.C. 289g-1(g). Some stem cells, for example those derived from the primordial germ cells of non-living fetuses, would be considered human fetal tissue for purposes of Section 498A.

The Public Health Service Act (hereinafter "The Act") contains three relevant provisions governing the use and transfer of human fetal tissue: (1) a criminal prohibition against the sale of human fetal tissue for valuable consideration; (2) restrictions on fetal tissue transplantation research supported by federal funds; and (3) a prohibition on the directed donation of fetal tissue for transplantation. We explore each of these restrictions in turn.

Section 498B(a) of the Act states that it is unlawful for any person to knowingly acquire, receive, or otherwise transfer any human fetal tissue for valuable consideration,[7] if the transfer affects interstate commerce.[8] 42 U.S.C. 289g-2(a). It is common practice for scientists throughout the United States to share research materials through transactions that result in such materials crossing state boundaries. Such exchanges, as well as transactions within the District of Columbia, or exchanges within a state that "affect interstate commerce" would meet the statutory criterion of affecting interstate commerce, but would not fall within the scope of the criminal

[7] The term "valuable consideration" encompasses both monetary and non-monetary payments. Section 498B (d)(3) provides that the term does not include "reasonable payments associated with the transportation, implantation, processing, preservation, quality control, or storage of human fetal tissue."

[8] The statute adopts the definition of interstate commerce in section 201(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 321(b): ". . . commerce between any State or Territory and any place outside thereof, and . . . commerce within the District of Columbia or within any other Territory not organized with a legislative body." The statute does not define what "affects" interstate commerce, but, in interpreting similar language in another criminal statute the Supreme Court found that "affecting interstate commerce" is an expression of Congress' intent to broadly exercise its Commerce Clause power under the Constitution. Scarborough v. United States, 431 U.S. 563, 571-72 (1977).

prohibition unless the scientist providing the materials sought payment in excess of the expenses included in the statutory definition of "valuable consideration."

In addition, the law places some restrictions on federal support for research on the transplantation of fetal tissue. Section 498A of the Act provides that the Secretary may conduct or support research on the "transplantation of fetal tissue for therapeutic purposes," only if certain statutory requirements are met. 42 U.S.C. 289g-1. These requirements include obtaining: (1) the informed consent of the woman donating the tissue; (2) a statement by the attending physician regarding the woman's consent and the method of obtaining the tissue; (3) a statement by the researcher regarding his or her understanding of the source of the tissue, that such information has been conveyed to the donee, and that the researcher has not participated in any decision regarding termination of the pregnancy.

Finally, section 498B(b) of the Act provides that it shall be unlawful for any person to solicit or knowingly acquire, receive, or accept a donation of human fetal tissue for the purpose of transplantation into another person if the tissue will be or is obtained pursuant to an induced abortion, and there is a promise to the donor: (1) to transplant the tissue into a person specified by the donor; (2) the tissue will be transplanted into a relative of the donor; or (3) the donee of the tissue has provided valuable consideration for the costs associated with the abortion. 42 U.S.C. 289g-2(b). The Act provides criminal penalties for violation of the prohibition on directed donations.

III. Federal Restrictions on Fetal Research

Federal regulation provides that activities involving cells, tissues, or organs excised from a non-living fetus shall be conducted only in accordance with any applicable state or local law. 45 CFR 46.210, Subpart B. This regulation would apply to certain human pluripotent stem cells, including those derived from the primordial germ cells of non-living fetuses.

IV. Prohibition on Federal Funding for Cloning of Human Beings

In a March 4, 1997, memorandum to the heads of executive departments and agencies, the President directed that no federal funds will be used for the cloning of human beings and that federal funds shall not be allocated for that purpose.[9] There are myriad uses for human pluripotent stem cells that are completely unrelated to cloning. However, to the extent such stem cells were to be used for human cloning, the prohibition on the use of federal funds for that purpose would apply.

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[9] Memorandum from the President of the United States to Heads of Executive Departments and Agencies (March 4, 1997).

STEM CELL RESEARCH - TALKING POINTS

- The recent announcements by scientists at universities in Wisconsin and Maryland that they have isolated "pluripotent" human stem cells are among the most exciting scientific advances for human biology and medical research in years. This research has the potential to lead to profound advances in our understanding of human development and disease, our ability to develop and test new drugs, and our ability to treat some of the most debilitating, painful and deadly diseases of mankind.

- Because of the regenerative capacity of pluripotent stem cells, these cells alone could supply numerous other researchers without the need to generate a new line of cells.

- Pluripotent stem cells cannot develop into a human being, but they have the potential to grow into most of the tissues and cells of the human body, such as heart cells, nerve cells, muscle cells, and blood cells. Their versatility provides an incredible range of targets for promising research. They may allow us to more safely test new drugs and therapies. They may help us prevent or repair the ravages of birth defects. And perhaps most importantly, they may help us generate cells and tissue vitally needed for transplantation -- including possible treatments for Parkinson's disease, stroke, spinal cord injury, burns, heart disease, diabetes, osteoarthritis and rheumatoid arthritis, and a range of diseases from the commonplace to the rare.

- While the private sector has already invested resources in such research, the rich promise of stem cell research makes it imperative that the Federal government play a role in funding and overseeing the conduct of that research. Federal funding will help provide oversight and direction that would be lacking if this research were the sole province of industry and academe.

- The decision to fund stem cell research at NIH is the right decision. As one of the premier medical research entities in the world, the NIH can foster world-class research on stem cells, and bring together the finest minds and facilities to further that research.

- While stem cell research is richly promising, it does raise real moral and ethical concerns. While the stem cells produced by the scientists in Wisconsin and Maryland could never develop into human beings, they were derived through two separate processes. In Wisconsin, the cells were derived from embryos donated by couples undergoing in vitro fertilization procedures. In Maryland, the cells were derived from terminated pregnancies.

- The NIH appreciates the compelling moral, ethical and legal issues surrounding these issues, and will proceed with great caution to ensure that the highest standards are set before research proposals are funded, and that extraordinary measures are taken to insure strict internal and external oversight. The NIH also understands and respects the deep convictions of people in the research, academic and religious communities, and in Congress, and intends to seek the advice and comment of those communities as this research continues.

- Before making the decision to fund stem cell research, the NIH asked for a legal opinion to ensure that any research undertaken was consistent with federal laws and regulations governing fetal tissue research, and consistent with the ban on human embryo research. That carefully considered opinion states that these stem cell lines cannot be considered human embryos under the law, and therefore research using them is legal and appropriate. However, research that *generates* pluripotent stem cells **from embryos** cannot be funded by DHHS. **But, research in which the pluripotent stem cells are derived from non-living human fetuses is allowable, subject to certain restrictions in law and regulation.**

- The NIH has long experience in overseeing ethical standards in medical research, and will of course apply its traditional stringent standards to stem cell research. Over and above those traditional standards, the NIH plans to set out guidelines for research proposals. The NIH will also establish a separate oversight board to review stem cell research. And of course, the NIH has sought the advice of the President's National Bioethics Advisory Commission, and will continue to consult with that commission and other outside experts as questions regarding stem cell research arise. NIH will not be funding any research using pluripotent stem cells until guidelines are **developed and** widely disseminated to the research community and **an oversight** process is in place.

TELEFAX TRANSMITTAL

Harold Varmus, M.D.
Director, National Institutes of Health
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Confirmation Phone No. (301) 496-2433

DATE: December 1, 1998

TO: Chris Jennings
Deputy Assistant to the President
for Health Policy Development

FAX NUMBER: 202-456-5557

PHONE NUMBER: 202-456-5560

NUMBER OF PAGES (INCLUDING COVER PAGE): 9

[ ] **PLEASE CALL TO CONFIRM RECEIPT. THANK YOU.**

REMARKS: Per your discussion with Dr. Varmus.
A copy of Dr. Varmus' statement has
also been faxed to Elena Kagan.

FOR RELEASE UPON DELIVERY

STATEMENT OF

HAROLD VARMUS, M. D.

DIRECTOR

DECEMBER 2, 1998

Mr. Chairman and Members of the Subcommittee, I am Harold Varmus, Director of the National Institutes of Health. I am pleased to appear before you to discuss recent published reports on the isolation and propagation of the first human pluripotent stem cell lines. These findings, reported by Drs. John Gearhart from Johns Hopkins University and James Thomson from the University of Wisconsin, bring medical research to the edge of a new frontier that is extraordinarily promising. The development of human pluripotent stem cell lines deserves close scientific examination, further evaluation of the promise of the research, and careful consideration and open discussion of the ethical and legal issues. I want to thank you for the opportunity to discuss this important issue with you and the Members of this Subcommittee.

Why the excitement? For the first time, scientists have obtained human stem cells that can give rise to many types of cells in our body. Let me briefly describe these experiments. Dr. Thomson and coworkers derived stem cell lines from embryos donated by couples undergoing in vitro fertilization (IVF) as part of treatment for infertility. These cells were grown in culture and found to divide indefinitely and have the ability to form cells of the three major tissue types–endoderm (which goes on to form the lining of the gut), mesoderm (which gives rise to muscle, bone and blood) and ectoderm (which gives rise to epidermal tissues and the nervous system). The ability of the cells to specialize into the three major tissues types is an important indicator that these cells are pluripotent. Dr. Gearhart and his coworkers derived pluripotent stem cells from fetal gonadal tissue destined to form germ cells. When grown in culture, these cells resemble other types of pluripotent stem cells in that they, like the cells from Dr. Thomson's work, also can develop into cells of the three major tissue types.

What Are Stem Cells?

As policy makers proceed to consider the scientific, ethical and societal issues raised by this research, it is absolutely essential to clarify terms and definitions. There are many types of stem cells. In general, they all have the ability to divide (and self renew) and to commit to a more specialized function. There is a hierarchy of stem cell types. Some stem cells are more

committed than others. Some stems cells - the pluripotent stem cell we are discussing today - have the ability to become many, but not all, of the cells types in the human body.

Through processes we are only beginning to understand, primitive stem cells can be stimulated to become specialized, so that they are precursors to any one of many different cell types such as muscle cells, skin cells, nerve cells, liver cells. Unlike the stem cells from which they are derived, these specialized cells are "committed" to a particular function.

All stem cells have the capability of self-renewal, i.e., they can continually reproduce themselves. Cells from the very earliest embryo (up to about the 16 cell stage) are totipotent stem cells. They are "totally potent" or totally capable of forming all cells of the body, including the cells required to support embryonic and fetal development. Each cell of this early embryo has the potential to develop into a human being.

After a few days of development, the early embryo forms a hollow ball of cells, called a blastocyst. This is the next stage of embryonic development. The clustered cells within this ball are called the inner cell mass. The cells in the inner cell mass are not totipotent. Rather, they are pluripotent. Pluripotent stem cells are more "committed" than totipotent stem cells. Unlike the fertilized egg, or the early embryo, or the intact blastocyst, neither the disaggregated inner cell mass nor the pluripotent stem cells derived from it (nor the pluripotent stem cells derived from fetal germ cells) will produce a human being even if returned to a woman's uterus. These cells do not have the potential to form a human being, because they do not have the capacity to give rise to the cells of the placenta or other extraembryonic tissues necessary for implantation, nor can they support fetal development in the uterus.

During fetal development, pluripotent stem cells become even more committed, i.e, they have the capacity to form only one or a few different kinds of cells. For example, hematopoietic stem cells

can form all the blood cells, but no other tissue types. The adult human being continues to harbor many types of stem cells responsible for the body's ability to repair some but not all tissues. Stem cells that permit new skin growth and renewal of blood cells are two examples.

Potential Applications of Pluripotent Stem Cells

There are several important reasons why the isolation of human pluripotent stem cells is, indeed, important science and for the future of public health. At the most fundamental level, pluripotent stem cells could help us to understand the complex events that occur during human development. A primary goal of this work would be the most basic kind of research -- the identification of the factors involved in the cellular decision-making process that determines cell specialization. We know that turning genes on and off is central to this process, but we do not know much about these "decision-making" genes or what turns them on or off. Some of our most serious diseases, like cancer, are due to abnormal cell differentiation and growth. A deeper understanding of normal cell processes will allow us to further delineate the fundamental errors that cause these deadly illnesses.

Human pluripotent stem cell research could also dramatically change the way we develop drugs and test them for safety and efficacy. Rather than evaluating safety and efficacy of a candidate drug in an animal model of a human disease, these drugs could be tested against a human cell line that had been developed to mimic the disease processes. This would not replace whole animal and human testing, but it would streamline the road to discovery. Only the most effective and safest candidate would be likely to graduate to whole animal and then human testing.

Perhaps the most far-reaching potential application of human pluripotent stem cells is the generation of cells and tissue that could be used for transplantation, so-called cell therapies. Many diseases and disorders result from disruption of cellular function or destruction of tissues of the body. Today, donated organs and tissues are often used to replace the function of ailing or destroyed tissue. Unfortunately, the number of people suffering from these disorders far outstrips

the number of organs available for transplantation. Pluripotent stem cells stimulated to develop into specialized cells offer the possibility of a renewable source of replacement cells and tissue to treat a myriad of diseases, conditions and disabilities including Parkinson's and Alzheimer's disease, spinal cord injury, stroke, burns, heart disease, diabetes, osteoarthritis and rheumatoid arthritis. There is almost no realm of medicine that might not be touched by this innovation. Let me expand on two of these examples.

- Transplant of healthy heart muscle cells could provide new hope for heart attack victims. The hope is to develop heart muscle cells from human pluripotent stem cells and transplant them into the failing heart muscle in order to augment the function of the heart. Preliminary work in mice and other animals has demonstrated that healthy heart muscle cells transplanted into the heart successfully repopulate the heart tissue and integrate with the host cells. These experiments show that this type of transplantation is feasible.

- In the many individuals who suffer from Type I diabetes, the production of insulin by the pancreas by specialized cells called islet cells is disrupted. There is evidence that transplantation of either the entire pancreas or isolated islet cells could mitigate the need for insulin injections. Islet cell lines derived from human pluripotent stem cells could be used for this critical research and, ultimately, for transplantation.

While I have taken this opportunity to outline the promise of this research, there is much to be done before we can realize these innovations. First, we must do the basic research to understand the cellular events that lead to cell specialization in the human, so that we can direct these pluripotent stem cells to become the type(s) of tissue needed for transplantation in great numbers. And before we can use these cells for transplantation, we must overcome the well-known problem of immune rejection. Because human pluripotent stem cells derived from embryos or fetal tissue would likely be genetically different from the recipient, future research would need to focus on

modifying human pluripotent stem cells to minimize tissue incompatibility. Technological challenges remain before these discoveries can be incorporated into clinical practice. These challenges, though significant, are not insurmountable.

How Are Pluripotent Stem Cells Produced?

There are several ways to produce human pluripotent stem cells. These methods have been developed over the past 17 years by researchers working with animals. The work you will hear about today builds on this important basic animal research.

As I mentioned earlier, one method of creating these pluripotent stem cells was described by Dr. Thomson and his coworkers. The techniques they used were initially developed using mice. Dr. Thomson first made stem cells from non-human primates. In the most recent work, they used inner cell mass cells from blastocyst stage human embryos that were created in the course of infertility treatment and donated by couples for research to derive stem cells. The researchers allowed cell division to continue in culture to the blastocyst stage and then removed the inner cell mass, which was cultured to derive pluripotent stem cells.

Pluripotent stem cells can also be derived from fetal tissue, as was first done using primordial germ cells from mouse fetal tissue. Dr. Gearhart and coworkers isolated human primordial germ cells, the cells that will go on to become eggs and sperm, from 5-9 week old fetal tissue obtained after pregnancy termination. When grown in culture, these stem cells appear to be pluripotent.

It may also be possible to make human pluripotent stem cells by using somatic cell nuclear transfer -- the technology that received so much attention with the announcement of the birth of the sheep, Dolly. Although there has been no scientific publication of this to date, presumably any cell from the human body (except the egg or sperm cell) could be fused with an enucleated egg cell and stimulated to return to highly immature, pluripotent and possibly totipotent state.

The Role of the Federal Government

Federal funds were not used in either of the experiments that you will hear about today. First, let me first address Dr. Thomson's work in which cells were derived from embryos created by in vitro fertilization but not used for infertility treatment. This work falls clearly within the Congressional ban on human embryo research. NIH could not, and did not, support Dr. Thomson's recent work developing this cell line.

The same restrictions do not apply to Dr. Gearhart's work, although it may be governed by other laws and regulations. Dr. Gearhart derived his pluripotent stem cells from fetal tissue from terminated pregnancies. The Public Health Service Act authorizes Federal funding of human fetal tissue research and provides safeguards for its conduct. The department may conduct or support research on the transplantation of human fetal tissue for therapeutic purposes if a number of statutory requirements are met. Thus, if Dr. Gearhart's research falls within these boundaries, NIH could have supported his recent work deriving pluripotent stem cells from fetal tissue, as long as he followed these Federal statutes and regulations. For the record, NIH did not, however, support any of this research.

Ethical issues

I have just described the science and the medical promise of research on the pluripotent stem cell. But the realization of this promise is also dependent on a full and open examination of the social and ethical implications of this work. The fact that these stem cells have been created from embryos and from fetal tissue raises a number of ethical concerns -- concerns that require an increase in public awareness and understanding as well as public fora for discussion and review.

The 1994 NIH Human Embryo Research Panel recommended that Guidelines be developed for the conduct of human embryo research prior to the initiation and funding of such research. Because Federally funded embryo research is banned and embryo research is done only in the private sector, a mechanism to provide this oversight has never existed.

If research on the pluripotent stem cell could receive Federally funding, it would be important for the NIH to first review the 1994 Human Embryo Panel Report to determine if the recommendations of the Panel needed to be updated in light of these recent scientific advances. At the President's request, the National Bioethics Advisory Commission has already begun this review. Ultimately, guidelines would need to be developed that ensure that investigators are aware of the Federal laws and regulations as well as those Presidential Directives related to human embryo, fetal tissue and cloning research. Guidelines should also consider the sources of embryonic stem cells to ensure that this research does not encourage the creation of embryos or the termination of pregnancies for research purposes. As always, research protocols would be peer reviewed for quality and merit.

Summary

The development of cell lines that may produce almost every tissue of the human body is an unprecedented scientific breakthrough. It is not too unrealistic to say that this research has the potential to revolutionize the practice of medicine and improve the quality and length of life.

Mr. Chairman, I am grateful to you for providing a forum to present information about this promising arena of science and medicine. I would be pleased to answer any questions you might have.

FAX TRANSMITTAL SHEET

DATE: November 19, 1998

TO: Chirs Jennings

ORGANIZATION:

TELEPHONE:

FAX: 65557

FROM: RACHEL E. LEVINSON

TELEPHONE: (202) 456-6137

FAX: (202) 456-6027

NUMBER OF PAGES, INCLUDING COVER PAGE: 3

SPECIAL INSTRUCTIONS: **URGENT – Time sensitive**

November 19, 1998

The President
The White House
Washington, DC 20500

Dear Mr. President:

The Commission clearly shares your views that combining a human cell with a cow egg raises important ethical issues that need to be considered. In particular, we believe that any attempt to create a child by combining a human cell and a non-human egg would raise profound ethical concerns and should not be permitted.

As you know, the design and results of the human cell-cow egg experiment are not yet publicly available and, as a consequence, we are unable to evaluate fully its implications. Nonetheless, if this recent research does result in the production of embryos, it raises many potentially controversial issues, including those associated with cloning as well as those associated with crossing human/non-human species boundaries, which need further careful examination.

We reached these conclusions after consultation with Dr. Ralph Brinster, a recognized expert in the field of embryology, from the University of Pennsylvania and Dr. Michael West, of Advanced Cell Technology, Inc., the company that reported having fused a human cell with a cow egg.

The common understanding of a human "embryo" includes, at least, the concept of an organism at its earliest stage of development, which has the potential, if transferred to a uterus, to develop in the normal course of events into a child. The little evidence that exists from previous experimentation involving combining early developmental cells from more than one species suggest that the hybrid cells that result do not have this potential, hence are not embryos. At this time, however, there is insufficient scientific evidence to be able to say whether combining of a human cell and an animal egg results in an embryo in this sense. In our opinion, if this is an embryo, important ethical concerns arise, as is the case with all research involving human embryos. These concerns will be made more complex and controversial by the fact that these hybrid cells will contain both human and non-human genetic material.

It is worth noting that these hybrid cells should not be confused with human embryonic stem cells. Embryonic stem cells, while derived from embryos, are not themselves capable of developing into children. The use of embryonic stem cells, for example to generate cells for transplantation, does not directly raise the same type of moral concerns.

If this line of research does not give rise to embryos, and therefore cannot be used to produce a child, we do not believe that totally new issues arise. We note that scientists routinely conduct non-controversial research that involves combining material from human and other species. This research has led to such useful therapies as: blood clotting factor for hemophilia, insulin for diabetes, erythropoietin for anemia, and heart valves for transplants. Combining human cells with non-human eggs might possibly lead some day

to methods to overcome transplant rejections without the need to create human embryos, or to subject women to invasive, risky medical procedures to obtain human eggs.

We recognize that some of the issues raised by this type of research may also be pertinent to stem cell research in general. We intend to address these and other issues in the report that you requested regarding human stem cell research.

Sincerely,

Harold T. Shapiro
Chair

urgent!

FAX to 65557

FAX TO CHRIS JENNINGS FYI

NATIONAL BIOETHICS ADVISORY COMMISSION

Nov. 18, 1998

12:30 pm Miami, FL.

Jeff Smith 6-6047

6100 Executive Blvd
Suite 5B01
Rockville, MD
I-7508

Telephone
301-402-4242
Facsimile
301-480-6900
Website
www.bioethics.gov

Dear Dr. Lane

Attached please find a draft letter prepared by Dr. Shapiro. Please comment on this draft and send your comments by fax to Dr. Shapiro tomorrow [FAX: 609-258-1615]

Many thanks.

Eric Meslin

~~CONFIDENTIAL~~ DRAFT

November 18, 1998

The President
The White House
Washington, DC 20500

Dear Mr. President:

I am responding to your letter of November 14, 1998 requesting that the National Bioethics Advisory Commission discuss at its meeting in Miami this week the ethical, medical, and legal concerns arising from the fusion of a human cell with a cow egg. I would also note however, that since the design and results of this experiment are not yet publicly available, we are unable to evaluate fully its implications. Nevertheless, the Commission clearly shares your view that this development raises important ethical issues that need to be considered. In particular, we believe that any attempt to create a child through the fusion of a human cell and a non-human egg would raise profound ethical concerns and should not be permitted.

Moreover, this newly reported research raises many new and potentially controversial issues, including concerns about crossing species boundaries and exercising excessive control over nature, which need further careful discussion. This is especially the case if the product resulting from the fusion of a human cell and the egg from a non-human animal is transferred into a woman's uterus and, in a different manner, if the fusion products are embryos even if no attempt is made to bring them to term.

We devoted time at our meeting to discuss this issue in public, benefiting in particular from consultation (via telephone) with Dr. Ralph Brinster, a recognized expert in the field of embryology, from the University of Pennsylvania. Also in attendance at our meeting was Dr. Michael West, of Advanced Cell Technology, who was given an opportunity to answer questions from Commission members.

We found it helpful to consider three questions:

1. *Can the product of fusing a human cell with the egg of a non-human animal, if transferred into a woman's uterus, develop into a child?*

At this time there is insufficient scientific evidence to answer this question. However, if it *were* possible, the Commission believes that any attempt to create a child in this manner would raise profound ethical concerns, and should not be permitted. This objection is consistent with our views expressed in *Cloning Human Beings*, in which we concluded that:

> "...at this time it is morally unacceptable for anyone in the public or private sector, whether in a research or clinical setting, to attempt to create a child using somatic cell nuclear transfer cloning"

2. *Does the fusion of a human cell and an egg from a non-human animal result in a human embryo?*

The common understanding of an "embryo" includes, at least, the concept of an organism at its earliest stage of development, which has the potential, if transferred to a uterus, to develop in the normal course of events into a living being. The little evidence that exists from previous experimentation involving combining early developmental cells from more than one species suggests that the products of such fusions do not have this potential, hence are not embryos. At this time, however, there is insufficient scientific

evidence to be able to say whether the fusion of a human cell and an animal egg results in an embryo in this sense. In our opinion, if this fusion does result in an embryo, important ethical concerns arise, as is the case with all research involving human embryos. These concerns will be made more complex and controversial by the fact that these fusion products will contain both human and non-human genetic material.

It is worth noting that these fusion products should not be confused with human embryonic stem cells. Embryonic stem cells, while derived from embryos, are not themselves capable of developing into organisms. The use of embryonic stem cells, for example to generate cells for transplantation, does not directly raise the same type of moral concerns.

3. *If the fusion of a human cell and an animal egg does not result in an embryo with the potential to develop into a child, what ethical, medical or scientific issues remain?*

If there is no attempt to create children or an embryo, we do not believe that totally new issues arise. We note that scientists routinely conduct non-controversial research that involves combining material from human and other species. This research has led to such useful therapies as: blood clotting factor for hemophilia, insulin for diabetes, erythropoietin for anemia, and heart valves for transplants. Combining human cells with non-human eggs might possibly lead some day to methods to overcome transplant rejections without the need to create human embryos, or to subject women to invasive, risky medical procedures to obtain human eggs.

We recognize that some of the issues raised by this type of research may also be pertinent to stem cell research in general. We intend to address these and other issues in the report that you requested regarding human stem cell research.

Sincerely,

Harold T. Shapiro
Chair

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P5 Release would disclose confidential advice between the President and his advisors, or between such advisors [a)(5) of the PRA]
P6 Release would constitute a clearly unwarranted invasion of personal privacy [(a)(6) of the PRA]

C. Closed in accordance with restrictions contained in donor's deed of gift.
PRM. Personal record misfile defined in accordance with 44 U.S.C. 2201(3).
RR. Document will be reviewed upon request.

Freedom of Information Act - [5 U.S.C. 552(b)]

b(1) National security classified information [(b)(1) of the FOIA]
b(2) Release would disclose internal personnel rules and practices of an agency [(b)(2) of the FOIA]
b(3) Release would violate a Federal statute [(b)(3) of the FOIA]
b(4) Release would disclose trade secrets or confidential or financial information [(b)(4) of the FOIA]
b(6) Release would constitute a clearly unwarranted invasion of personal privacy [(b)(6) of the FOIA]
b(7) Release would disclose information compiled for law enforcement purposes [(b)(7) of the FOIA]
b(8) Release would disclose information concerning the regulation of financial institutions [(b)(8) of the FOIA]
b(9) Release would disclose geological or geophysical information concerning wells [(b)(9) of the FOIA]

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

Dr. Richard G. Seed
P6/(b)(6)
[001]

Dear Dr. Seed:

The purpose of this letter is to advise you that the Food and Drug Administration (FDA) has jurisdiction over clinical research using cloning technology to create a human being, and to inform you of the FDA regulatory process that is required before you or any other investigator can proceed with such a clinical investigation. You are receiving this letter because in a number of reports in the media, you are quoted as saying that you are actively pursuing the use of cloning technology to create human beings. As described more fully below, the appropriate mechanism to pursue such clinical investigation using cloning technology is the submission of an investigational new drug application (IND) to FDA.

Clinical research using cloning technology to create a human being is subject to FDA regulation under the Public Health Service Act and the Federal Food, Drug, and Cosmetic Act. Under these statutes and FDA's implementing regulations, before such research may begin, you as the sponsor of the research are required to submit to FDA an IND describing the proposed research plan; to obtain authorization from a properly constituted institutional review board (IRB); and to obtain a commitment from the investigators to obtain informed consent from all human subjects of the research. Such research may proceed only when an IND is in effect. Since we believe that there are major unresolved safety questions pertaining to the use of cloning technology to create a human being, until those questions are appropriately addressed in the IND, FDA would not permit any such investigation to proceed.

FDA may prohibit a sponsor from conducting a study proposed in an IND application (often referred to as placing the study on "clinical hold") for a variety of reasons. If the Agency finds that "human subjects are or would be exposed to an unreasonable and significant risk of illness or injury," that would be sufficient reason to put a study on clinical hold. Other reasons listed in the regulations include "the IND does not contain sufficient information required . . . to assess the risks to subjects of the proposed studies," or "the clinical investigators . . . are not qualified by reason of their scientific training and experience to conduct the investigation."

The procedures and requirements governing the use of investigational new drugs, including those for the submission and review of INDs, are set forth in Title 21 of the Code of Federal Regulations (CFR), Part 312. Additional responsibilities of the sponsor of an IND include: selecting qualified investigators and overseeing the conduct of the investigators; ensuring that the investigations are performed in accordance with the protocols of the IND; submitting adverse experience reports and annual reports; and other duties as outlined in the regulations. The responsibilities of an investigator include: ensuring that the study is conducted in accordance

with the protocols; obtaining informed consent from study participants; and ensuring that an IRB that complies with the requirements of 21 CFR Part 56 reviews and approves the proposed clinical study and the informed consent form and procedures for obtaining informed consent, among other requirements specified in the regulations. Clinical investigators are encouraged to obtain a copy of the current "Information Sheets for IRBs and Clinical Investigators" (which contain useful information regarding clinical investigations) from FDA's Office of Health Affairs (301-827-1685) or FDA's home page on the world wide web (http://www.fda.gov/OHA/IRB/TOC.HTML).

Enclosed is information on submitting an IND to FDA, along with relevant sections of 21 CFR, including Parts 50 (Protection of Human Subjects), 56 (Institutional Review Boards), and 312 (Investigational New Drug Application). We encourage you to meet with the Agency prior to submitting any IND application. Please contact Wendy Aaronson at 301-827-5101 at FDA's Center for Biologics Evaluation and Research within 14 days of receipt of this letter, to notify us of your intentions regarding the requirements outlined in this letter.

Sincerely,

Jay Siegel, M.D.
Director
Office of Therapeutics Research and Review
Center for Biologics Evaluation
and Research

Enclosures

Fax to Ethics Secretary 6-5557

November 20, 1998

The President
The White House
Washington, DC 20500

Dear Mr. President:

I am responding to your letter of November 14, 1998 requesting that the National Bioethics Advisory Commission discuss at its meeting in Miami this week the ethical, medical, and legal concerns arising from the fusion of a human cell with a cow egg.

The Commission shares your view that this development raises important ethical and potentially controversial issues that need to be considered, including concerns about crossing species boundaries and exercising excessive control over nature, which need further careful discussion. This is especially the case if the product resulting from the fusion of a human cell and the egg from a non-human animal is transferred into a woman's uterus and, in a different manner, if the fusion products are embryos even if no attempt is made to bring them to term. In particular, we believe that any attempt to create a child through the fusion of a human cell and a non-human egg would raise profound ethical concerns and should not be permitted.

We devoted time at our meeting to discussing various aspects of this issue, benefiting not only from the expertise of the Commissioners, but from our consultation (via telephone) with Dr. Ralph Brinster, a recognized expert in the field of embryology, from the University of Pennsylvania. Also in attendance at our meeting was Dr. Michael West, of Advanced Cell Technology, who was given an opportunity to answer questions from Commission members. As you know, however, the design and results of this experiment are not yet publicly available, and as a consequence the Commission was unable to evaluate fully its implications.

As a framework for our initial discussion, we found it helpful to consider three questions:

1. ***Can the product of fusing a human cell with the egg of a non-human animal, if transferred into a woman's uterus, develop into a child?***

At this time, there is insufficient scientific evidence to answer this question. What little evidence exists, based on other fusions of non-human eggs with non-human cells from a different species, suggests that a pregnancy cannot be maintained. If it were possible, however, for a child to develop from these fused cells, then profound ethical issues would be raised. An attempt to develop a child from these fused cells should not be permitted. This objection is consistent with our views expressed in *Cloning Human Beings*, in which we concluded that:

> "...at this time it is morally unacceptable for anyone in the public or private sector, whether in a research or clinical setting, to attempt to create a child using somatic cell nuclear transfer cloning."

2. ***Does the fusion of a human cell and an egg from a non-human animal result in a human embryo?***

The common understanding of a human embryo includes, at least, the concept of an organism at its earliest stage of development, which has the potential, if transferred to a uterus, to develop in the normal course of events into a living human being. At this time, however, there is insufficient scientific evidence to be able to say whether the combining of a human cell and the egg of a non-human animal results in an embryo in this sense. In our opinion, if this combination does result in an embryo, important ethical concerns arise, as is the case with all research involving human embryos. These concerns will be made more complex and controversial by the fact that these hybrid cells will contain both human and non-human biological material.

It is worth noting that these hybrid cells should not be confused with human embryonic stem cells. Human embryonic stem cells, while derived from embryos, are not themselves capable of developing into children. The use of human embryonic stem cells, for example to generate cells for transplantation, does not directly raise the same type of moral concerns.

3. ***If the fusion of a human cell and the egg of a non-human animal does not result in an embryo with the potential to develop into a child, what ethical issues remain?***

If this line of research does not give rise to human embryos, we do not believe that totally new ethical issues arise. We note that scientists routinely conduct non-controversial and highly beneficial research that involves combining material from human and other species. This research has led to such useful therapies as: blood clotting factor for hemophilia, insulin for diabetes, erythropoietin for anemia, and heart valves for transplants. Combining human cells with non-human eggs might possibly lead some day to methods to overcome transplant rejections without the need to create human embryos, or to subject women to invasive, risky medical procedures to obtain human eggs.

We recognize that some of the issues raised by this type of research may also be pertinent to stem cell research in general. We intend to address these and other issues in the report that you requested regarding human stem cell research.

Sincerely,

Harold T. Shapiro
Chair

Human-Cow Hybrid Cells Are Topic of Ethics Panel

By NICHOLAS WADE

At the request of President Clinton, the ethical implications of creating hybrid human-cow cells were discussed by the National Bioethics Advisory Commission at its meeting yesterday in Miami, but at least in the public portion of their discussion, none of the commissioners voiced concern about the creation of the hybrid cells.

Mr. Clinton requested the discussion last week in a letter to the commission's chairman, Dr. Harold Shapiro of Princeton University. Mr. Clinton said he was "deeply troubled" by news that Advanced Cell Technology, a small biotechnology company in Worcester, Mass., had created the hybrid cells. The company proposes to use the technique to take any body cell from a patient, return it to its embryonic form and use it to grow any of a variety of body tissues for possible transplant back into the patient.

One advantage of the technique is that the patient would receive tissues made from his own cells. Another is that no cells would be taken from human embryos or fetuses.

Noting that scientists had been fusing together cells of different origin for years, Dr. David R. Cox of Stanford University, a member of the commission, said, "We should tell the President there is nothing new in cells fused from different eggs."

The hybrid cow-human cells consist of the nucleus of a human cell inserted into a cow egg whose own nucleus has been removed. Factors in the cow egg are thought to make the human cell nucleus revert to its embryonic form. Because the proteins of a cell turn over rapidly, the cow proteins are expected to be rapidly replaced by human proteins. The mitochondria of the cell, however, are likely to remain cowlike, giving rise at least initially to cells that are not wholly human.

> 'Nothing new in cells fused from different eggs.'

An outside expert who spoke to the commission by telephone, Ralph Brinster, a physiologist at the University of Pennsylvania, said of the cow-human hybrid cell, "Most scientists would not regard it as a chimera." Chimeras are animals made from the cells of two different individuals by injecting the embryonic cells of one into the embryo of another.

Making human chimeras is widely regarded as unethical.

Dr. Michael West, the president of Advanced Cell Technology, attended the commission's meeting and was invited speak. In response to questions, he said he did not believe the cells formed in his procedure, called embryonic stem cells, were capable of forming a fetus if transferred to a uterus, something he said he had no intention of doing.

Asked how he would prevent the technique from being misused, such as in cloning a person, he suggested that the cloning of humans should be made a crime.

The commission members said they would draft a reply to Mr. Clinton.

Stm Cell Eth

THE WHITE HOUSE

Office of the Press Secretary

For Immediate Release **November 20, 1998**

Ethics Panel Echoes President's Views on Part Human/Part Cow Hybrid Cells

Today the National Bioethics Advisory Commission (NBAC) advised the President in a letter that they share his view that the recently reported creation of a part human and part cow embryonic stem cell "raises important ethical and potentially controversial issues that need to be considered..."

In a letter to NBAC last week, the President said that he was "deeply troubled by this news of experiments involving the mingling of human and non-human species" and requested that the Commission consider the ethical implications at their meeting in Miami this week.

The Commission further concluded that any attempt to develop a child from such hybrid cells raises the most profound ethical issues and should not be permitted.

The Commission will also address ethical, medical, and legal issues associated with human stem cell research in a later report.

The full text of the National Bioethics Advisory Commission's letter follows:

National Bioethics Advisory Commission

6100 Executive Blvd
Suite 5B01
Rockville, MD
20892-7508

Telephone
301-402-4242
Facsimile
301-480-6900
Website
www.bioethics.gov

November 20, 1998

The President
The White House
Washington, DC 20500

Dear Mr. President:

I am responding to your letter of November 14, 1998 requesting that the National Bioethics Advisory Commission discuss at its meeting in Miami this week the ethical, medical, and legal concerns arising from the fusion of a human cell with a cow egg.

The Commission shares your view that this development raises important ethical and potentially controversial issues that need to be considered, including concerns about crossing species boundaries and exercising excessive control over nature, which need further careful discussion. This is especially the case if the product resulting from the fusion of a human cell and the egg from a non-human animal is transferred into a woman's uterus and, in a different manner, if the fusion products are embryos even if no attempt is made to bring them to term. In particular, we believe that any attempt to create a child through the fusion of a human cell and a non-human egg would raise profound ethical concerns and should not be permitted.

We devoted time at our meeting to discussing various aspects of this issue, benefiting not only from the expertise of the Commissioners, but from our consultation (via telephone) with Dr. Ralph Brinster, a recognized expert in the field of embryology, from the University of Pennsylvania. Also in attendance at our meeting was Dr. Michael West, of Advanced Cell Technology, who was given an opportunity to answer questions from Commission members. As you know, however, the design and results of this experiment are not yet publicly available, and as a consequence the Commission was unable to evaluate fully its implications.

As a framework for our initial discussion, we found it helpful to consider three questions:

1. ***Can the product of fusing a human cell with the egg of a non-human animal, if transferred into a woman's uterus, develop into a child?***

At this time, there is insufficient scientific evidence to answer this question. What little evidence exists, based on other fusions of non-human eggs with non-human cells from a different species, suggests that a pregnancy cannot be maintained. If it were possible, however, for a child to develop from these fused cells, then profound ethical issues would be raised. An attempt to develop a child from these fused cells should not be permitted.

This objection is consistent with our views expressed in *Cloning Human Beings*, in which we concluded that:

> "...at this time it is morally unacceptable for anyone in the public or private sector, whether in a research or clinical setting, to attempt to create a child using somatic cell nuclear transfer cloning."

2. ***Does the fusion of a human cell and an egg from a non-human animal result in a human embryo?***

The common understanding of a human embryo includes, at least, the concept of an organism at its earliest stage of development, which has the potential, if transferred to a uterus, to develop in the normal course of events into a living human being. At this time, however, there is insufficient scientific evidence to be able to say whether the combining of a human cell and the egg of a non-human animal results in an embryo in this sense. In our opinion, if this combination does result in an embryo, important ethical concerns arise, as is the case with all research involving human embryos. Those concerns will be made more complex and controversial by the fact that these hybrid cells will contain both human and non-human biological material.

It is worth noting that these hybrid cells should not be confused with human embryonic stem cells. Human embryonic stem cells, while derived from embryos, are not themselves capable of developing into children. The use of human embryonic stem cells, for example to generate cells for transplantation, does not directly raise the same type of moral concerns.

3. ***If the fusion of a human cell and the egg of a non-human animal does not result in an embryo with the potential to develop into a child, what ethical issues remain?***

If this line of research does not give rise to human embryos, we do not believe that totally new ethical issues arise. We note that scientists routinely conduct non-controversial and highly beneficial research that involves combining material from human and other species. This research has led to such useful therapies as: blood clotting factor for hemophilia, insulin for diabetes, erythropoietin for anemia, and heart valves for transplants. Combining human cells with non-human eggs might possibly lead some day to methods to overcome transplant rejections without the need to create human embryos, or to subject women to invasive, risky medical procedures to obtain human eggs.

We recognize that some of the issues raised by this type of research may also be pertinent to stem cell research in general. We intend to address these and other issues in the report that you requested regarding human stem cell research.

Sincerely,

Harold T. Shapiro

Harold T. Shapiro
Chair

Cloning

Now that genetically modified and copied mammals are a reality, biomedical researchers are starting to develop imaginative ways to use this technology

JOHN CHADWICK PHOTOGRAPHIC AND PPL THERAPEUTICS

RODDY FIELD *Roslin Institute*

In the summer of 1995 the birth of two lambs at my institution, the Roslin Institute near Edinburgh in Midlothian, Scotland, heralded what many scientists believe will be a period of revolutionary opportunities in biology and medicine. Megan and Morag, both carried to term by a surrogate mother, were not produced from the union of a sperm and an egg. Rather their genetic material came from cultured cells originally derived from a nine-day-old embryo. That made Megan and Morag genetic copies, or clones, of the embryo.

Before the arrival of the lambs, researchers had already learned how to produce sheep, cattle and other animals by genetically copying cells painstakingly isolated from early-stage embryos. Our work promised to make cloning vastly more practical, because cultured cells are relatively easy to work with. Megan and Morag proved that even though such cells are partially specialized, or differentiated, they can be genetically reprogrammed to function like those in an early embryo. Most biologists had believed that this would be impossible.

We went on to clone animals from cultured cells taken from a 26-day-old fetus and from a mature ewe. The ewe's cells gave rise to Dolly, the first mammal to be cloned from an adult. Our announcement of Dolly's birth in February 1997 attracted enormous press interest, perhaps because Dolly drew attention to the theoretical possibility of cloning humans. This is an outcome I hope never comes to pass. But the ability to make clones from cultured cells derived from easily obtained tissue should bring numerous practical benefits in animal husbandry and medical science, as well as answer critical biological questions.

How to Clone

Cloning is based on nuclear transfer, the same technique scientists have used for some years to copy animals from embryonic cells. Nuclear transfer involves the use of two cells. The recipient cell is normally an unfertilized egg taken from an animal soon after ovulation. Such eggs are poised to begin developing once they are appropriately stimulated. The donor cell is the one to be copied. A researcher working under a high-power microscope holds the recipient egg cell by suction on the end of a fine pipette and uses an extremely fine micropipette to suck out the chromosomes, sausage-shaped bodies that incorporate the cell's DNA. (At this stage, chromosomes are not enclosed in a distinct nucleus.) Then, typically, the donor cell, complete with its nucleus, is fused with the recipient egg. Some fused cells start to develop like a normal embryo and produce offspring if implanted into the uterus of a surrogate mother.

In our experiments with cultured cells, we took special measures to make the donor and recipient cells compatible. In particular, we tried to coordinate the cycles of duplication of DNA and those of the production of messenger RNA, a molecule that is copied from DNA and guides the manufacture of proteins. We chose to use donor cells whose DNA was not being duplicated at the time of the transfer [*see box on page 60*]. To arrange this, we worked with cells that we forced to become quiescent by reducing the concentration of nutrients in their culture medium. In addition, we delivered pulses of electric current to the egg after the transfer, to encourage the cells to fuse and to mimic the stimulation normally provided by a sperm.

After the birth of Megan and Morag demonstrated that we could produce viable offspring from embryo-derived cultures, we filed for patents and started experiments to see whether offspring could be produced from more completely differentiated cultured cells. Working in collaboration with

for Medicine

by Ian Wilmut

MEGAN AND MORAG (*above*) were the first mammals cloned from cultured cells. That basic technique has allowed the creation of cloned sheep carrying human genes. Such animals produce milk that can be collected and processed (*left*) to yield therapeutic human proteins.

PPL Therapeutics, also near Edinburgh, we tested fetal fibroblasts (common cells found in connective tissue) and cells taken from the udder of a ewe that was three and a half months pregnant. We selected a pregnant adult because mammary cells grow vigorously at this stage of pregnancy, indicating that they might do well in culture. Moreover, they have stable chromosomes, suggesting that they retain all their genetic information. The successful cloning of Dolly from the mammary-derived culture and of other lambs from the cultured fibroblasts showed that the Roslin protocol was robust and repeatable.

All the cloned offspring in our experiments looked, as expected, like the breed of sheep that donated the originating nucleus, rather than like their surrogate mothers or the egg donors. Genetic tests prove beyond doubt that Dolly is indeed a clone of an adult. It is most likely that she was derived from a fully differentiated mammary cell, although it is impossible to be certain because the culture also contained some less differentiated cells found in small numbers in the mammary gland. Other laboratories have since used an essentially similar technique to create healthy clones of cattle and mice from cultured cells, including ones from nonpregnant animals.

Although cloning by nuclear transfer is repeatable, it has

Is Quiescence the Key to Cloning?

All the cells that we used as donors for our nuclear-transfer experiments were quiescent—that is, they were not making messenger RNA. Most cells spend much of their life cycle copying DNA sequences into messenger RNA, which guides the production of proteins. We chose to experiment with quiescent cells because they are easy to maintain for days in a uniform state. But Keith H. S. Campbell of our team recognized that they might be particularly suitable for cloning.

He conjectured that for a nuclear transfer to be successful, the natural production of RNA in the donor nucleus must first be inhibited. The reason is that cells in a very early stage embryo are controlled by proteins and RNA made in the precursor of the parent egg cell. Only about three days after fertilization does the embryo start making its own RNA. Because an egg cell's own chromosomes would normally not be making RNA, nuclei from quiescent cells may have a better chance of developing after transfer.

A related possibility is that the chromosomes in quiescent nuclei may be in an especially favorable physical state. We think regulatory molecules in the recipient egg act on the transferred nucleus to reprogram it. Although we do not know what these molecules are, the chromosomes of a quiescent cell may be more accessible to them. —*I.W.*

limitations. Some cloned cattle and sheep are unusually large, but this effect has also been seen when embryos are simply cultured before gestation. Perhaps more important, nuclear transfer is not yet efficient. John B. Gurdon, now at the University of Cambridge, found in nuclear-transfer experiments with frogs almost 30 years ago that the number of embryos surviving to become tadpoles was smaller when donor cells were taken from animals at a more advanced developmental stage. Our first results with mammals showed a similar pattern. All the cloning studies described so far show a consistent pattern of deaths during embryonic and fetal development, with laboratories reporting only 1 to 2 percent of embryos surviving to become live offspring. Sadly, even some clones that survive through birth die shortly afterward.

Clones with a Difference

The cause of these losses remains unknown, but it may reflect the complexity of the genetic reprogramming needed if a healthy offspring is to be born. If even one gene inappropriately expresses or fails to express a crucial protein at a sensitive point, the result might be fatal. Yet reprogramming might involve regulating thousands of genes in a process that could involve some randomness. Technical improvements, such as the use of different donor cells, might reduce the toll.

The ability to produce offspring from cultured cells opens up relatively easy ways to make genetically modified, or transgenic, animals. Such animals are important for research and can produce medically valuable human proteins.

The standard technique for making transgenic animals is painfully slow and inefficient. It entails microinjecting a genetic construct—a DNA sequence incorporating a desired gene—into a large number of fertilized eggs. A few of them take up the introduced DNA so that the resulting offspring express it. These animals are then bred to pass on the construct [see "Transgenic Livestock as Drug Factories," by William H. Velander, Henryk Lubon and William N. Drohan; SCIENTIFIC AMERICAN, January 1997].

In contrast, a simple chemical treatment can persuade cultured cells to take up a DNA construct. If these cells are then used as donors for nuclear transfer, the resulting cloned offspring will all carry the construct. The Roslin Institute and PPL Therapeutics have already used this approach to produce transgenic animals more efficiently than is possible with microinjection.

We have incorporated into sheep the gene for human fac-

How Megan and Morag Were Made

Cultured cells were combined with egg cells to yield embryos that developed into cloned offspring.

KEITH KASNOT

tor IX, a blood-clotting protein used to treat hemophilia B. In this experiment we transferred an antibiotic-resistance gene to the donor cells along with the factor IX gene, so that by adding a toxic dose of the antibiotic neomycin to the culture, we could kill cells that had failed to take up the added DNA. Yet despite this genetic disruption, the proportion of embryos that developed to term after nuclear transfer was in line with our previous results.

The first transgenic sheep produced this way, Polly, was born in the summer of 1997. Polly and other transgenic clones secrete the human protein in their milk. These observations suggest that once techniques for the retrieval of egg cells in different species have been perfected, cloning will make it possible to introduce precise genetic changes into any mammal and to create multiple individuals bearing the alteration.

RODDY FIELD Roslin Institute

DOLLY (*right*) shot to worldwide fame in 1997 as the first mammal cloned from an adult's cells. Now mature, Dolly has given birth to a healthy lamb, Bonnie (*left*), the product of a normal mating and gestation.

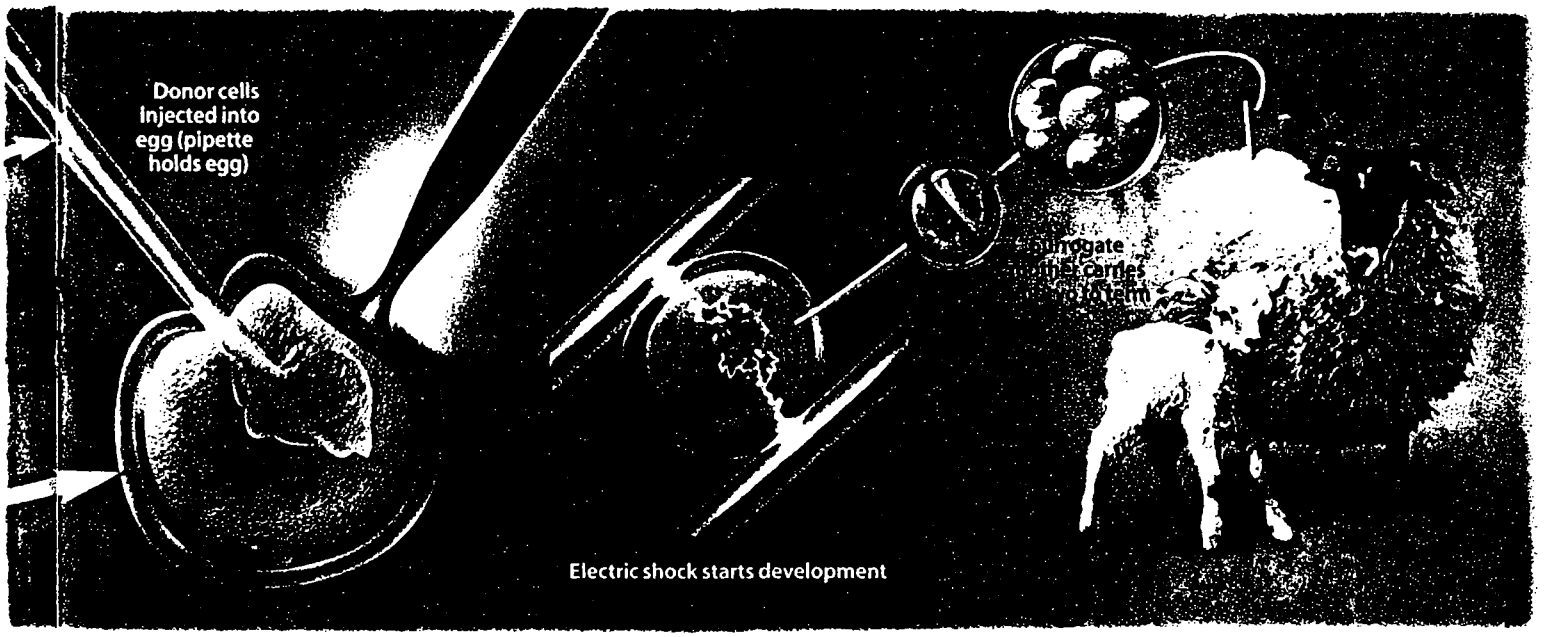
Cultures of mammary gland cells might have a particular advantage as donor material. Until recently, the only practical way to assess whether a DNA construct would cause a protein to be secreted in milk was to transfer it into female mice, then test their milk. It should be possible, however, to test mammary cells in culture directly. That will speed up the process of finding good constructs and cells that have incorporated them so as to give efficient secretion of the protein.

Cloning offers many other possibilities. One is the generation of genetically modified animal organs that are suitable for transplantation into humans. At present, thousands of patients die every year before a replacement heart, liver or kidney becomes available. A normal pig organ would be rapidly destroyed by a "hyperacute" immune reaction if transplanted into a human. This reaction is triggered by proteins on the pig cells that have been modified by an enzyme called alpha-galactosyl transferase. It stands to reason, then, that an organ from a pig that has been genetically altered so that it lacks this enzyme might be well tolerated if doctors gave the recipient drugs to suppress other, less extreme immune reactions.

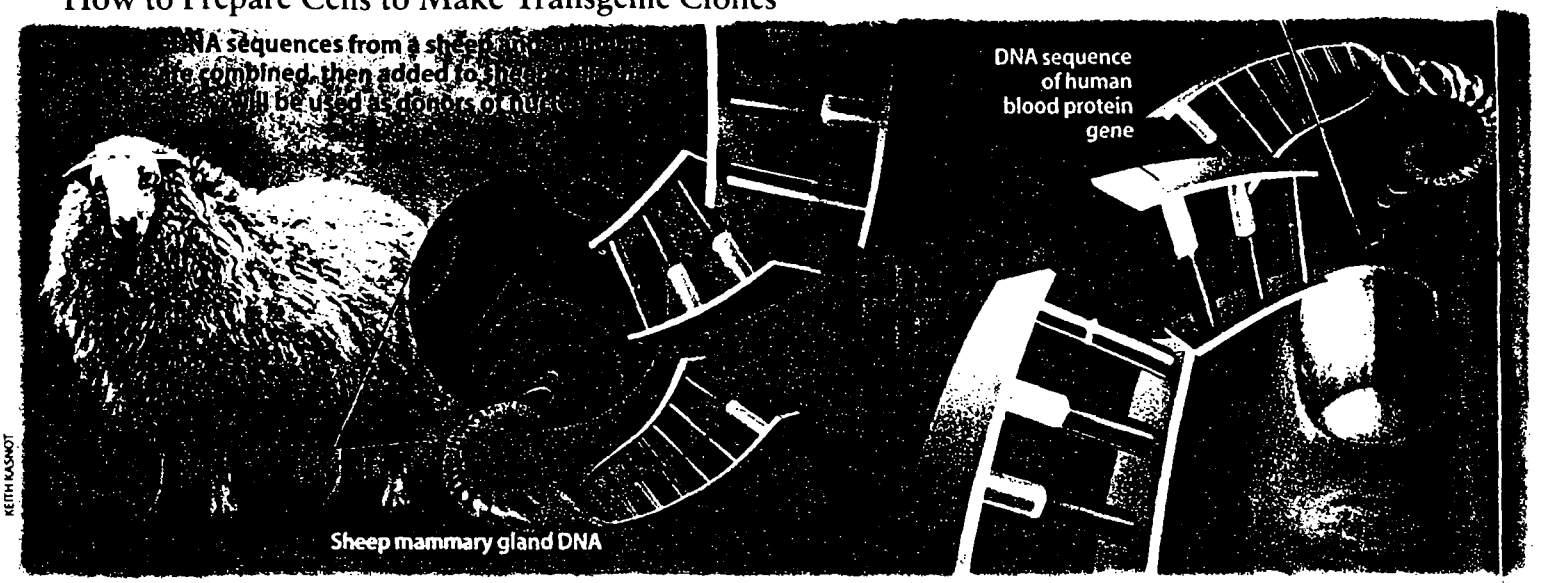
Another promising area is the rapid production of large animals carrying genetic defects that mimic human illnesses, such as cystic fibrosis. Although mice have provided some information, mice and humans have very different genes for cystic fibrosis. Sheep are expected to be more valuable for research into this condition, because their lungs resemble those of humans. Moreover, because sheep live for years, scientists can evaluate their long-term responses to treatments.

Creating animals with genetic defects raises challenging ethical questions. But it seems clear that society does in the main support research on animals, provided that the illnesses being studied are serious ones and that efforts are made to avoid unnecessary suffering.

The power to make animals with a precisely engineered genetic constitution could also be employed more directly in cell-based therapies for important illnesses, including Parkinson's disease, diabetes and muscular dystrophy. None of these conditions currently has any fully effective treatment. In each, some pathological process damages specific cell populations, which are unable to repair or replace themselves. Several novel approaches are now being explored that would provide



How to Prepare Cells to Make Transgenic Clones



KEITH KASNOT

new cells—ones taken from the patient and cultured, donated by other humans or taken from animals.

To be useful, transferred cells must be incapable of transmitting new disease and must match the patient's physiological need closely. Any immune response they produce must be manageable. Cloned animals with precise genetic modifications that minimize the human immune response might constitute a plentiful supply of suitable cells. Animals might even produce cells with special properties, although any modifications would risk a stronger immune reaction.

Cloning could also be a way to produce herds of cattle that lack the prion protein gene. This gene makes cattle susceptible to infection with prions, agents that cause bovine spongiform encephalitis (BSE), or mad cow disease. Because many medicines contain gelatin or other products derived from cattle, health officials are concerned that prions from infected animals could infect patients. Cloning could create herds that, lacking the prion protein gene, would be a source of ingredients for certifiable prion-free medicines.

The technique might in addition curtail the transmission of genetic disease. Many scientists are now working on therapies that would supplement or replace defective genes in cells, but even successfully treated patients will still pass on defective genes to their offspring. If a couple was willing to produce an embryo that could be treated by advanced forms of gene therapy, nuclei from modified embryonic cells could be transferred to eggs to create children who would be entirely free of a given disease.

Some of the most ambitious medical projects now being considered envision the production of universal human donor cells. Scientists know how to isolate from very early mouse embryos undifferentiated stem cells, which can contribute to all the different tissues of the adult. Equivalent cells can be obtained for some other species, and humans are probably no exception. Scientists are learning how to differentiate stem cells in culture, so it may be possible to manufacture cells to repair or replace tissue damaged by illness.

Making Human Stem Cells

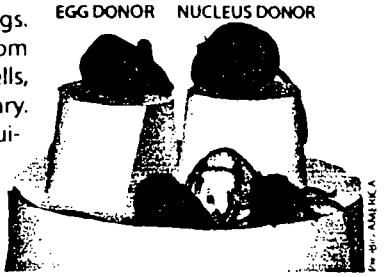
Stem cells matched to an individual patient could be made by creating an embryo by nuclear transfer just for that purpose, using one of the patient's cells as the donor and a human egg as the recipient. The embryo would be allowed to develop only to the stage needed to separate and culture stem cells from it. At that point, an embryo has only a few hundred cells, and they have not started to differentiate. In particular, the nervous system has not begun to develop, so the embryo has no means of feeling pain or sensing the environment. Embryo-derived cells might be used to treat a variety of serious diseases caused by damage to cells, perhaps including AIDS as well as Parkinson's, muscular dystrophy and diabetes.

Scenarios that involve growing human embryos for their cells are deeply disturbing to some people, because embryos have the potential to become people. The views of those who consider life sacred from conception should be respected, but I suggest a contrasting view. The embryo is a cluster of cells that does not become a sentient being until much later in development, so it is not yet a person. In the U.K., the Human Genetics Advisory Commission has initiated a major public consultation to assess attitudes toward this use of cloning.

Creating an embryo to treat a specific patient is likely to be an expensive proposition, so it might be more practical to establish permanent, stable human embryonic stem-cell lines from cloned embryos. Cells could then be differentiated as needed. Implanted cells derived this way would not be genetically perfect matches, but the immune reaction would prob-

Now, Cloned Mice

Recently Ryuzo Yanagimachi of the University of Hawaii at Honolulu and his colleagues successfully cloned mice by transferring donor nuclei—not whole cells—into eggs. The group took nuclei from cells called cumulus cells, which surround the ovary. These cells are naturally quiescent. So far we believe that no one has shown that offspring can be produced from differentiated cells that are not quiescent. —*I.W.*



Surrogate mother (*center*) is flanked by cloned offspring of nucleus donor.

ably be controllable. In the longer term, scientists might be able to develop methods for manufacturing genetically matched stem cells for a patient by "dedifferentiating" them directly, without having to utilize an embryo to do it.

Several commentators and scientists have suggested that it might in some cases be ethically acceptable to clone existing people. One scenario envisages generating a replacement for a dying relative. All such possibilities, however, raise the concern that the clone would be treated as less than a complete individual, because he or she would likely be subjected to limitations and expectations based on the family's knowledge of the genetic "twin." Those expectations might be false, because human personality is only partly determined by genes. The clone of an extrovert could have a quite different demeanor. Clones of athletes, movie stars, entrepreneurs or scientists might well choose different careers because of chance events in early life.

Some pontificators have also put forward the notion that couples in which one member is infertile might choose to make a copy of one or the other partner. But society ought to be concerned that a couple might not treat naturally a child who is a copy of just one of them. Because other methods are available for the treatment of all known types of infertility, conventional therapeutic avenues seem more appropriate. None of the suggested uses of cloning for making copies of existing people is ethically acceptable to my way of thinking, because they are not in the interests of the resulting child. It should go without saying that I strongly oppose allowing cloned human embryos to develop so that they can be tissue donors.

It nonetheless seems clear that cloning from cultured cells will offer important medical opportunities. Predictions about new technologies are often wrong: societal attitudes change; unexpected developments occur. Time will tell. But biomedical researchers probing the potential of cloning now have a full agenda.

JOHN CHADWICK PHOTOGRAPHIC AND PPL THERAPEUTICS

POLLY

(*left*) is a transgenic clone of a poll Dorset sheep. A gene for a human protein, factor IX, was added to the cell that provided the lamb's genetic heritage, so Polly has the human gene. The ewe that carried Polly (*right*) is a Scottish blackface.

The Author

IAN WILMUT pursues research on the genetic engineering of livestock at the Roslin Institute near Edinburgh in Midlothian, Scotland. After obtaining a Ph.D. from the University of Cambridge for research on methods of freezing boar semen, he did postdoctoral work at Cambridge on techniques for freezing animal embryos. Later Wilmut identified developmental and physiological causes of prenatal death in sheep and pigs, before turning to studies of ways to improve economically important animals.

Further Reading

CELL CYCLE CO-ORDINATION IN EMBRYO CLONING BY NUCLEAR TRANSFER. K.H.S. Campbell, P. Loi, P. J. Otaegui and I. Wilmut in *Reviews of Reproduction*, Vol. 1, No. 1, pages 40–46; January 1996.

GENOMIC POTENTIAL OF DIFFERENTIATED CELLS. Marie A. Di Berardino. Columbia University Press, 1997.

SHEEP CLONED BY NUCLEAR TRANSFER FROM A CULTURED CELL LINE. K.H.S. Campbell, J. McWhir, W. A. Ritchie and I. Wilmut in *Nature*, Vol. 385, pages 810–813; February 27, 1997.

HUMAN FACTOR IX TRANSGENIC SHEEP PRODUCED BY TRANSFER OF NUCLEI FROM TRANSFECTED FETAL FIBROBLASTS. E. Schnieke et al. in *Science*, Vol. 278, pages 2130–2133; December 19, 1997.

DATE: 12/1

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REMARKS:

Questions and Answers

1. What are human embryonic stem cells and are they related to human embryo research?

Because the term "embryonic stem cell" can be so easily confused with the embryo itself, it is preferable to refer to these cells as "pluripotent stem cells." The term "embryonic stem cell" was borrowed from mouse research, which derived stem cells from mouse embryos. Human pluripotent stem cells are cells of a human organism which have an unlimited capacity to divide, and the ability to turn into most of the cells or tissues in the body. They are related to human embryo research in that one of the ways pluripotent stem cells can be derived is from the human embryo. These stem cells are not themselves embryos and would not develop into a fetus or result in a live birth if implanted into a woman's uterus. Embryonic stem cells can also be derived from human fetal tissue. It is believed that pluripotent stem cells can also be derived from cells created by somatic cell nuclear transfer.

2. What is human embryo research?

Human embryo research involves studies of human fertilization (entry of sperm into a mature egg) and the subsequent several cell divisions that occur in a laboratory dish. This research is also called human in vitro fertilization research. The research is only conducted at these very early stages of development. At these stages, the embryo is also referred to as a preimplantation embryo because it is not yet to the point at which it would have finished implanting into the wall of the uterus. Human embryo research does not involve human embryos (or fetuses) developing in the uterus. It does not involve abortion or aborted human fetal tissue.

Unfortunately, the widely used term "embryo research" has caused a misperception about the nature of this work. In fact, the research is conducted with the one-cell product of fertilization and the subsequent few cell divisions that follow fertilization.

3. What are pluripotent stem cells?

Pluripotent stem cells are cells from an organism that have an unlimited capacity to divide and the ability to turn into many different types of cells or tissues in the body. These stem cells are not themselves embryos and would not develop into a fetus or result in a live birth if implanted into a woman's uterus. They can be derived from embryos, from fetal tissue germ cell tissue, and by using somatic cell nuclear transfer technology.

4. **Are pluripotent stem cells embryos? Do they have the potential to become embryos?**

Pluripotent stem cells are not embryos because they do not have the capacity to develop into a fetus if implanted into a woman's uterus. On their own, pluripotent stem cells do not have the potential to become embryos.

5. **Do the regulations that govern human subjects research cover embryo research? Do they cover fetal tissue research? Would they cover embryonic stem cell research?**

Human embryo research is covered by DHHS regulations, 45 CFR 46 Subpart B entitled, "Additional DHHS Protections Pertaining to Research, Development, and Related Activities Involving Fetuses, Pregnant Women, and Human In Vitro Fertilization." The regulations require that, before being initiated, federally funded research involving human in vitro fertilization must be reviewed and approved by an institutional review board. In addition, research involving human embryos or fetuses developing in the uterus is regulated by 45 CFR 46.201-46.211. Human embryos, however, are not considered human subjects under the HHS human subjects regulations. Although NIH is currently prohibited from supporting IVF and preimplantation embryo research due to a Presidential directive and Congressional ban, this research would be permitted under the human subject regulations. The 1994 Presidential directive prohibits the use of Federal resources to support the creation of human embryos for research purposes. In addition, in FY 1996 appropriations law (P.L. 104-99), DHHS was prohibited, for the first time, from conducting or supporting human embryo research. This annual prohibition in appropriations law has been repeated in every subsequent year since. The current appropriations law is P.L. 105-277. The language prohibits DHHS from supporting research in which a human embryo or embryos–organisms derived by fertilization, parthenogenesis, cloning, or any other means from one or more human gametes or human diploid cells–are destroyed, discarded or knowingly subjected to risk of injury or death greater than that allowed for research on fetuses in utero under 45 CFR 46.208(a)(2) and section 498(b) of the Public Health Service Act (42 U.S.C. 289g(b)).

These regulations would not cover research on the pluripotent stem cells derived from either embryos or fetal tissue, since the stem cells themselves are not embryos.

Human fetal tissue research–the study of tissues and cells from *nonliving* fetuses–is also addressed in Subpart B of the HHS human subject regulations (45 CFR 46.210), requiring that such research be conducted only in accordance with any applicable State or local laws regarding such activities. Furthermore, the regulations require that individuals engaged in research involving fetuses, pregnant women, and human IVF will have no part in any decisions as to the timing, method, and procedures used to terminate the pregnancy

(45 CFR 46.206(a)(3)(I)). Nonliving fetuses are not considered human subjects under the regulations. In addition to these regulations governing human fetal tissue research, section 498A of the Public Health Service Act (42 U.S.C. 289g-1) permits HHS to conduct or support research on the transplantation of human fetal tissue for therapeutic purposes, but such tissue may be used for research only if a number of statutory requirements are met.

6. **Has NIH ever funded human embryo research? Has NIH ever considered funding human embryo research?**

The NIH has never funded human embryo research. From 1980 to 1993, Federal funding of human embryo research was subject to a de facto administrative moratorium. In 1993, Congress passed legislation (P.L. 103-43) that effectively nullified this moratorium, making it possible for NIH to consider funding human embryo research. The NIH did not proceed, however, without first broadly considering the moral and ethical questions raised by such research and developing guidelines for its review and conduct.

During 1994, therefore, the NIH organized a multi-disciplinary panel of experts--composed of 19 people from outside government with diverse background in science, ethics, law, sociology, theology, public health, and public policy--to study the ethical, scientific, medical, and public policy implications of Federal funding of this research. The work of this panel was carried out in open forums, involved substantial public input, and led to the formulation of recommendations for stringent guidelines that would govern the review and conduct of any future research that might be considered for funding by the NIH. Though never implemented, the panel also recommended areas of research that would have been acceptable for Federal funding, would not have been acceptable for Federal funding, and areas that would have required further consideration. Beginning in FY 1996, and continuing to the present day, Congress bars NIH from conducting or supporting human embryo research through language in the HHS appropriations law.

7. **Has NIH ever funded research on human pluripotent stem cells?**

The NIH has not funded research involving human pluripotent stem cells derived from either sources of these cells, human embryos or fetal tissue. However, NIH does fund research on human stem cells that are derived from sources such as adult blood cells and newborn cord cells. These stem cells can go on to differentiate into several different kinds of blood cells. Although they are also considered pluripotent, they have limited capacity to turn into other cells of the body.

8. **If Federal funding of human embryo research were allowable, would NIH institute any limits to that funding and what standards would be applied to decide which research to fund?**

When this matter was initially under consideration in 1994, the NIH carefully considered the ethical, legal, scientific, and medical issues before moving forward and, with the help of a group of diverse outside experts, defined areas that should and should not be supported with Federal funding. The panel recommended that special guidelines be applied that would go beyond what is required of other areas of research and that an ad hoc review body be established at the Federal level to provide further oversight of the research. Subsequent funding bans were instituted, so the NIH did not establish the review body or proceed with the development of guidelines.

9. **If Federal funding of pluripotent stem cell research were allowed, would NIH institute any limits to that funding and what standards would be applied to decide which research to fund?**

Given the ethical and legal considerations as well as the need for clarification about Federal funding restrictions in closely related areas, the NIH would develop guidelines for the conduct of this research. As always, research proposals would be peer reviewed and funded on the basis of merit.

10. **What are the arguments for the Federal investment in this research?**

Federal involvement in this research would provide important scientific and ethical oversight. The NIH formally addressed the issue of human embryo research with the 1994 NIH Panel on Human Embryo Research. This multi-disciplinary panel of experts--composed of 19 people from outside government with diverse backgrounds in science, ethics, law, sociology, theology, public health, and public policy--evaluated the ethical, scientific, medical, and public policy implications of Federal funding of human embryo research. The work of this panel was carried out in open forums, involved substantial public input, and led to the formulation of recommendations for stringent guidelines that would govern the review and conduct of any future research that might be considered for funding by the NIH. The panel also recommended areas of research that were acceptable for Federal funding, areas that were not acceptable for Federal funding, and areas that required further consideration. After the Panel released its report, the President directed that no Federal funds be used to create embryos for research purposes. At present there is a legislative ban on the use of Federal funds for the support of human embryo research, hence the recommendations of the Panel were never implemented. If the Federal government were able to fund human embryo research in the future, the recommendations of the 1994 NIH would need to be reviewed and possibly updated to reflect the changes that have occurred since 1994.

11. Is Federal funding of human fetal tissue research allowed?

Federal funding of human fetal tissue research is permitted within certain regulatory parameters, and the NIH is funding studies that involve both basic and clinical investigations. Between 1988 and 1993, an administrative moratorium was in place that prohibited research involving clinical or therapeutic transplantation of human fetal tissue. Congress overturned the moratorium and added provisions to the Public Health Service Act that spelled out stringent rules that would have to be followed by Federally funded investigators. These rules include detailed informed consent procedures and a prohibition on commercialization of fetal tissue that must be followed for research that is Federally funded.

12. How does current law apply to research on the derivation of pluripotent stem cells?

The stem cells isolated in Dr. Thomson's research were derived from embryos donated by couples who had undergone infertility treatment. Public Law 105-277 prohibits Federal funding of research involving spare embryos, therefore this work clearly falls within the Congressional ban on human embryo research.

Dr. Gearhart derived his pluripotent stem cells from fetal tissue. The Public Health Services Act permits the Secretary of Health and Human Services to conduct or support research on the transplantation of human fetal tissue for therapeutic purposes if a number of statutory requirements are met. Thus, if Dr. Gearhart's research falls within these boundaries, it would be supportable with Federal funds as long as Federal statutes and regulations are followed. This research was, however, supported from non-Federal sources.

13. Would current law prohibit NIH from funding research on pluripotent stem cells derived from human embryos or fetal tissue?

14. Were NIH funds used to support Dr. Thomson's research? Dr. Gearhart's? Dr. West's?

NIH did not support the research of these investigators to derive pluripotent stem cells.

15. Has NIH ever supported the work of these investigators and, if so, what was the substance of that work?

NIH supports the work of Dr. Gearhart on Down's syndrome using a mouse model and Dr. Thomson's work on non-human primate pluripotent stem cells.

16. Since Dr. Thomson's work is prohibited and Dr. Gearhart's is not, why not just encourage scientists to work with Dr. Gearhart's cell line?

It is not known at this time whether or not the cells derived by these two investigators have identical capacities. Therefore, both lines of inquiry should be pursued.

17. Are there examples of research that have not been legally restricted but for which NIH has established special review and oversight procedures? How has NIH provided the oversight to ensure the research moves forward, while the ethical, legal, and social implications of the research are given full and public consideration?

In the 1970s, when it first became possible to use molecular cloning in bacteria, there was a great deal of public apprehension about possible risks of the research. The scientific community established a voluntary moratorium until guidelines could be developed to govern the research. Guidelines were written by the NIH in a public process to provide oversight of the research. The Recombinant DNA Advisory Committee was also established to ensure public review of the research and ongoing policy development to keep pace with scientific progress. With the advent of human gene therapy, the NIH Guidelines were extended to address specific concerns associated with human trials. For example, the NIH Guidelines state that protocols involving germline gene therapy will not be considered. NIH also has worked closely with FDA to coordinate the public reviews with FDA's regulatory oversight of the clinical trials using gene therapy products.

Xenotransplantation–which involves the transfer of living animal cells, tissues, and whole organs into humans–is another example. Xenotransplantation holds the promise of providing a means to treat a wide range of disorders, including diabetes, Parkinson's disease, and end-stage renal failure. However, it also presents a number of public health and ethical challenges, including the potential risk of transmission of infectious agents from animal donors to patients, their close contacts, and the general public; informed consent at individual and community levels; animal welfare issues; and social equity in access to novel biotechnologies. To this end, DHHS has issued draft Guidelines for the conduct of this research and is planning to establish a Secretarial Advisory Committee on Xenotransplantation. The Secretary's Advisory Committee on Xenotransplantation will provide an ongoing group to consider the full range of complex scientific, social, and

ethical issues and the public concerns raised by xenotransplantation, including ongoing and proposed protocols, and makes recommendations to the Secretary on policy and procedures. The Department also has a xenotransplant working group consisting of representatives from NIH, FDA, CDC and HRSA that will coordinate and implement as needed the recommendations of the Secretarial Advisory Committee.

18. **Are there any federal restrictions that reach pluripotent stem cell research in the private sector?**

With the exception of prohibitions on the commercialization of human fetal tissue, we are aware of no other restrictions in Federal statute affecting the conduct of this kind of research in the private sector. FDA would regulate any clinical use of human plenipotent stem cell research under the Public Health Service Act and the Food, Drug and Cosmetic Act.

19. **If the government supports research on these cell lines, wouldn't it create an incentive to create embryos for research purposes or encourage abortions?**

Couples undergo infertility treatment and in vitro fertilization procedures for personal reasons that likely have nothing to do with a desire to advance research. Likewise, the decision to terminate a pregnancy is also made for personal reasons.

Furthermore, steps can be taken to ensure that Federally funded research does not inadvertently create such incentives. For example, in part to allay such concerns, Federal law and regulations require a separation between fetal tissue research and decision-making regarding the termination of a pregnancy. Federal law prohibits the commercialization of fetal tissue.

20. **What aspects of pluripotent stem cell research are regulated by FDA? Do you know if FDA can regulate this research? Are they exploring such an option?**

As with other cellular therapies, FDA would regulate pluripotent stem cells under the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act. Individuals wishing to conduct clinical trials involving such products would need to have an investigational new drug application (IND) prior to using the products. In addition, FDA's informed consent and institutional review board regulations apply.

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Statement of

HAROLD VARMUS, M. D.

Director

National Institutes of Health

before

the Senate Appropriations Subcommittee on Labor, Health and Human Services, Education and Related Agencies

December 2, 1998

Mr. Chairman and Members of the Subcommittee, I am Harold Varmus, Director of the National Institutes of Health. I am pleased to appear before you to discuss recent published reports on the isolation and propagation of the first human pluripotent stem cell lines. These findings, reported by Drs. John Gearhart from Johns Hopkins University and James Thomson from the University of Wisconsin, bring medical research to the edge of a new frontier that is extraordinarily promising. The development of human pluripotent stem cell lines deserves close scientific examination, further evaluation of the promise of the research, and careful consideration and open discussion of the ethical and legal issues. I want to thank you for the opportunity to discuss this important issue with you and the Members of this Subcommittee.

Why the excitement? For the first time, scientists have obtained human stem cells that can give rise to many types of cells in our body. Let me briefly describe these experiments. Dr. Thomson and coworkers derived stem cell lines from embryos donated by couples undergoing in vitro fertilization (IVF) as part of treatment for infertility. These cells were grown in culture and found to divide indefinitely and have the ability to form cells of the three major tissue types--endoderm (which goes on to form the lining of the gut), mesoderm (which gives rise to muscle, bone and blood) and ectoderm (which gives rise to epidermal tissues and the nervous system). The ability of the cells to specialize into the three major tissues types is an important indicator that these cells are pluripotent. Dr. Gearhart and his coworkers derived pluripotent stem cells from fetal gonadal tissue destined to form germ cells. When grown in culture, these cells resemble other types of pluripotent stem cells in that they, like the cells from Dr. Thomson's work, also can develop into cells of the three major tissue types.

What Are Stem Cells?

As policy makers proceed to consider the scientific, ethical and societal issues raised by this research, it is absolutely essential to clarify terms and definitions. There are many types of stem cells. In general, they all have the ability to divide (and self renew) and to commit to a more

specialized function. There is a hierarchy of stem cell types. Some stem cells are more committed than others. Some stems cells - the pluripotent stem cell we are discussing today - have the ability to become many, but not all, of the cells types in the human body.

Through processes we are only beginning to understand, primitive stem cells can be stimulated to become specialized, so that they are precursors to any one of many different cell types such as muscle cells, skin cells, nerve cells, liver cells. Unlike the stem cells from which they are derived, these specialized cells are "committed" to a particular function.

All stem cells have the capability of self-renewal, i.e., they can continually reproduce themselves. Cells from the very earliest embryo (up to about the 16 cell stage) are totipotent stem cells. They are "totally potent" or totally capable of forming all cells of the body, including the cells required to support embryonic and fetal development. Each cell of this early embryo has the potential to develop into a human being.

After a few days of development, the early embryo forms a hollow ball of cells, called a blastocyst. This is the next stage of embryonic development. The clustered cells within this ball are called the inner cell mass. The cells in the inner cell mass are not totipotent. Rather, they are pluripotent. Pluripotent stem cells are more "committed" than totipotent stem cells. Unlike the fertilized egg, or the early embryo, or the intact blastocyst, neither the disaggregated inner cell mass nor the pluripotent stem cells derived from it (nor the pluripotent stem cells derived from fetal germ cells) will produce a human being even if returned to a woman's uterus. These cells do not have the potential to form a human being, because they do not have the capacity to give rise to the cells of the placenta or other extraembryonic tissues necessary for implantation, nor can they support fetal development in the uterus.

During fetal development, pluripotent stem cells become even more committed, i.e, they have the capacity to form only one or a few different kinds of cells. For example, hematopoietic stem cells can form all the blood cells, but no other tissue types. The adult human being continues to harbor

many types of stem cells responsible for the body's ability to repair some but not all tissues. Stem cells that permit new skin growth and renewal of blood cells are two examples.

Potential Applications of Pluripotent Stem Cells

There are several important reasons why the isolation of human pluripotent stem cells is, indeed, important to science and for the future of public health. At the most fundamental level, pluripotent stem cells could help us to understand the complex events that occur during human development. A primary goal of this work would be the most basic kind of research -- the identification of the factors involved in the cellular decision-making process that determines cell specialization. We know that turning genes on and off is central to this process, but we do not know much about these "decision-making" genes or what turns them on or off. Some of our most serious diseases, like cancer, are due to abnormal cell differentiation and growth. A deeper understanding of normal cell processes will allow us to further delineate the fundamental errors that cause these deadly illnesses

Human pluripotent stem cell research could also dramatically change the way we develop drugs and test them for safety and efficacy. Rather than evaluating safety and efficacy of a candidate drug in an animal model of a human disease, these drugs could be tested against a human cell line that had been developed to mimic the disease processes. This would not replace whole animal and human testing, but it would streamline the road to discovery. Only the most effective and safest candidate would be likely to graduate to whole animal and then human testing.

Perhaps the most far-reaching potential application of human pluripotent stem cells is the generation of cells and tissue that could be used for transplantation, so-called cell therapies. Many diseases and disorders result from disruption of cellular function or destruction of tissues of the body Today, donated organs and tissues are often used to replace the function of ailing or destroyed tissue. Unfortunately, the number of people suffering from these disorders far outstrips

the number of organs available for transplantation. Pluripotent stem cells stimulated to develop into specialized cells offer the possibility of a renewable source of replacement cells and tissue to treat a myriad of diseases, conditions and disabilities including Parkinson's and Alzheimer's disease, spinal cord injury, stroke, burns, heart disease, diabetes, osteoarthritis and rheumatoid arthritis. There is almost no realm of medicine that might not be touched by this innovation. Let me expand on two of these examples.

- Transplant of healthy heart muscle cells could provide new hope for heart attack victims. The hope is to develop heart muscle cells from human pluripotent stem cells and transplant them into the failing heart muscle in order to augment the function of the heart. Preliminary work in mice and other animals has demonstrated that healthy heart muscle cells transplanted into the heart successfully repopulate the heart tissue and integrate with the host cells. These experiments show that this type of transplantation is feasible.

- In the many individuals who suffer from Type I diabetes, the production of insulin by the pancreas by specialized cells called islet cells is disrupted. There is evidence that transplantation of either the entire pancreas or isolated islet cells could mitigate the need for insulin injections. Islet cell lines derived from human pluripotent stem cells could be used for this critical research and, ultimately, for transplantation.

While I have taken this opportunity to outline the promise of this research, there is much to be done before we can realize these innovations. First, we must do the basic research to understand the cellular events that lead to cell specialization in the human, so that we can direct these pluripotent stem cells to become the type(s) of tissue needed for transplantation in great numbers. And before we can use these cells for transplantation, we must overcome the well-known problem of immune rejection. Because human pluripotent stem cells derived from embryos or fetal tissue would likely be genetically different from the recipient, future research would need to focus on modifying human pluripotent stem cells to minimize tissue incompatibility. Technological

challenges remain before these discoveries can be incorporated into clinical practice. These challenges, though significant, are not insurmountable.

How Are Pluripotent Stem Cells Produced?

There are several ways to produce human pluripotent stem cells. These methods have been developed over the past 17 years by researchers working with animals. The work you will hear about today builds on this important basic animal research.

As I mentioned earlier, one method of creating these pluripotent stem cells was described by Dr. Thomson and his coworkers. The techniques they used were initially developed using mice. Dr. Thomson first made stem cells from non-human primates. In the most recent work, they used inner cell mass cells from blastocyst stage human embryos that were created in the course of infertility treatment and donated by couples for research to derive stem cells. The researchers allowed cell division to continue in culture to the blastocyst stage and then removed the inner cell mass, which was cultured to derive pluripotent stem cells.

Pluripotent stem cells can also be derived from fetal tissue, as was first done using primordial germ cells from mouse fetal tissue. Dr. Gearhart and coworkers isolated human primordial germ cells, the cells that will go on to become eggs and sperm, from 5-9 week old fetal tissue obtained after pregnancy termination. When grown in culture, these stem cells appear to be pluripotent.

It may also be possible to make human pluripotent stem cells by using somatic cell nuclear transfer -- the technology that received so much attention with the announcement of the birth of the sheep, Dolly. Although there has been no scientific publication of this to date, presumably any cell from the human body (except the egg or sperm cell) could be fused with an enucleated egg cell and stimulated to return to highly immature, pluripotent and possibly totipotent state.

The Role of the Federal Government

Federal funds were not used in either of the experiments that you will hear about today. First, let me first address Dr. Thomson's work in which cells were derived from embryos created by in vitro fertilization but not used for infertility treatment. This work falls clearly within the Congressional ban on human embryo research. NIH could not, and did not, support Dr. Thomson's recent work developing this cell line.

The same restrictions do not apply to Dr. Gearhart's work, although it may be governed by other laws and regulations. Dr. Gearhart derived his pluripotent stem cells from fetal tissue from terminated pregnancies. The Public Health Service Act authorizes Federal funding of human fetal tissue research and provides safeguards for its conduct. The department may conduct or support research on the transplantation of human fetal tissue for therapeutic purposes if a number of statutory requirements are met. Thus, if Dr. Gearhart's research falls within these boundaries, NIH could have supported his recent work deriving pluripotent stem cells from fetal tissue, as long as he followed these Federal statutes and regulations. For the record, NIH did not, however, support any of this research.

Ethical Issues

I have just described the science and the medical promise of research on the pluripotent stem cell. But the realization of this promise is also dependent on a full and open examination of the social and ethical implications of this work. The fact that these stem cells were produced from embryos and fetal tissue raises a number of ethical concerns including, for example, the need to ensure that stem cell research not encourage the creation of embryos or the termination of pregnancies for research purposes. In strict accordance with the President's 1994 directive, no NIH funds will be used for the creation of human embryos for research purposes. We also will continue to abide by relevant statutes.

The ethical and social issues associated with stem cell research are complex and controversial and require thoughtful discourse in public fora to reach resolution. To this end, the President has asked the National Bioethics Advisory Commission to undertake a thorough review of the issues associated with human stem cell research, balancing all ethical and medical considerations.

Summary

The development of cell lines that may produce almost every tissue of the human body is an unprecedented scientific breakthrough. It is not too unrealistic to say that this research has the potential to revolutionize the practice of medicine and improve the quality and length of life.

Mr. Chairman, I am grateful to you for providing a forum to present information about this promising arena of science and medicine. I would be pleased to answer any questions you might have.

Total Pages: 15

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URGENT

Monday, January 11, 1999

LEGISLATIVE REFERRAL MEMORANDUM

TO: Legislative Liaison Officer - See Distribution below

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OMB CONTACT: Robert J. Pellicci
PHONE: (202)395-4871 FAX: (202)395-6148
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LRM ID: RJP351 **SUBJECT:** COMMERCE Oversight Testimony on stem cell research

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Statement

of

Q. Todd Dickinson

Acting Assistant Secretary of Commerce

and Acting Commissioner of Patents and Trademarks

before the

Subcommittee on Labor, Health and Human Services,

Education and Related Agencies

of the

Senate Appropriations Committee

January 12, 1999

Mr. Chairman and Members of the Subcommittee:

I am Q. Todd Dickinson, Acting Assistant Secretary of Commerce and Acting Commissioner of Patents and Trademarks. I want to thank you for providing me with this opportunity to discuss the patent system, more specifically the patenting of stem cells, and the licensing of technology. It is my understanding that you have recently been considering the scientific implications of research into these cells and are now interested in investigating the patent and technology transfer implications.

Background

The history of the U.S Patent System is a long and distinguished one. Grounded in Article 1, Section 8 of the Constitution, the Patent Act of 1790 was one of the first statutes passed by the First Congress sitting in Philadelphia. The first patent was granted that same year to Samuel Hopkins, also of Philadelphia, for a method of making potash, a chemical useful for fertilizer and gunpowder – critical technologies for a new, agriculturally based nation. The application was examined by the first patent examining board: Secretary of State Thomas Jefferson, Attorney General Edmund Randolph and Secretary of the Treasury Alexander Hamilton. The patent itself was personally signed by the President of the United States, George Washington.

The system has evolved in many ways since that auspicious beginning, and continues to serve the primary function it was intended to serve by the Founding Fathers: as an incentive to technological innovation and economic growth. From the cotton gin to the computer, America has been a model for technological development throughout its history, and patents have provided protection for the fledgling enterprises that were based on that innovation. For example, Thomas Edison still holds the record as the individual inventor holding the most patents, and his efforts led to the General Electric Co., one of the United States most successful and valuable corporations.

The premise on which the system is based is a simple one: in exchange for a full and complete disclosure of an invention, the government grants a limited right in that invention to the inventor or his or her assignee. It is not a monopoly right to own an invention, as is sometimes suggested, but rather the right to exclude others from making using or selling it. Moreover, this right may or may not be exercised at the patent owner's discretion.

The public benefits from this arrangement since full disclosure permits others to improve that technology by developing alternative solutions, or to find a better, unexpected species invention within the broad genus of the patent claim, thereby expanding mankind's technological base. Additional benefits include preventing wasteful duplication of research and development; a comprehensive teaching of the technology, permitting it to be used efficiently after the patent term expires; and the creation of indexed databases of technology in the form of the patent classification system which permit easier and more comprehensive searching.

Studies have consistently shown that many important industries rely on a strong and effective patent system. University of Pennsylvania economist Edwin Mansfield surveyed 100 U.S. corporations chosen randomly in six industries.[1] In each case, he asked senior management if strong intellectual property laws were a significant consideration for different kinds of investment the corporation would make in a particular country. The survey found that approximately 60% of companies investing in final product manufacturing facilities said that intellectual property rights had a "strong effect" on whether direct investment would be made. In chemical, pharmaceutical, or electrical equipment manufacturing, the percentages were even higher, between 74 and 87%. Even more telling, when executives were asked if they would invest in research and development facilities (the top end of wealth creation in an economy), 80% said that the

[1] E. Mansfield; "Intellectual Property Protection, Foreign Direct Investment and Technology Transfer"; International Finance Corporation, Discussion Paper Number 19, The World Bank, 1994.

strength or weakness of intellectual property rights in a country would have a strong effect on whether the company invests there.

Non-profit research institutions also benefit financially from strong intellectual property protection. The largest public university system in the United States is the University of California with over 7,000 faculty members among its 9 campuses. In 1997, the University had 2,943 active inventions. Revenues on those patent and technology licenses produced $74.7 million for the University in 1997. Carnegie Mellon University in Pittsburgh recently assigned a patent claiming spidering technology used to search the World Wide Web to Lycos for a reported $500,000 in cash, 20% equity in the start-up and an unspecified percentage of royalties.

In the biotechnology field, this effect is even more apparent. I recently participated in a conference hosted by members of the European Parliament who were finally successful in passing a new biotechnology patent law for Europe after more than ten years of effort. (It is reputed to be the most extended debate ever about a piece of legislation before the European Parliament.). Speaker after speaker bemoaned the fact that the absence of such legislation in Europe, and the presence of strong biotechnological patent protection in the U.S., had caused significant research and development funds, manufacturing investment, and large numbers of research scientists to relocate to the United States.

U.S Patent Law

The current patent statute, 35 United States Code, dates from 1952, and specifies that to obtain a patent the applicant must meet four basic statutory requirements: that the claimed invention be statutory subject matter (35 U.S.C. §101); that it be novel, i.e. that it was not invented before, (35 U.S.C. §102); that it be not obvious to a person having ordinary skill in the art to which it pertains (35 U.S.C. §103); and that it be fully and unambiguously disclosed in the text of the patent itself, sufficient to enable the skilled

practitioner to practice the claimed invention (35 U.S.C. §112). If the patent application and its claims do not meet these requirements, it is rejected. These requirements are not easy hurdles to overcome. Section 103 non-obviousness, in particular, requires a careful review of the state of the art and often very skillful crafting of claims to avoid it. In the biotechnology field, the §112 enablement requirement is often a major stumbling block.

It should also be noted that the claims are the only legally operative portion of the patent itself. Readers of patents often incorrectly assume that the teaching of the detailed description or background of the invention found in the body of the patent in some way defines the metes and bounds of the protected invention, or that the "concept" of the invention taught in the claims is what is covered. This is incorrect. Furthermore, while the applicant may be his or her own lexicographer and define terms, undisclosed meanings not apparent in the text cannot be read into a claim and inferences cannot be drawn; the plain language of the claim alone defines the parameters of the invention. This means that claim interpretation is a difficult and often semantic art.

It is also important to remember that the patent grant is a limited right in time. The patent term runs for twenty years from the date that the application is filed. After it expires, anyone is free to use it. Furthermore, owners of patents do not necessarily have to enforce their rights: they can and do dedicate them to the public. Since a patent may not be granted on an invention known to the public for more than a year, inventors may also dedicate their inventions to the public through public disclosure without filing applications, as NIH has generously chosen to do with its cell line inventions. See, United States Public Health Service, Technology Transfer Manual; Chapter No. 200; "PHS Patent Policy".

Biotechnology and Stem Cell Research

Biotechnology generally encompasses any technique that uses living organisms or their components to make or modify products, to improve plants and animals, or to use

microorganisms for specific uses. Biotechnology has begun to affect our daily lives in ever-increasing ways. It is opening new pathways in the treatment of incurable diseases and is showing promising alternatives to less effective traditional treatments. In the field of nutrition, biotechnology makes ever-greater headway to improve food production and plant breeding in a manner that one could only dream about a decade ago. In the field of genetics, the use of new techniques is beginning to open substantial and wide-ranging benefits for human and animal health, the protection of the environment and the potential for productivity gains in food, agricultural and pharmaceutical industries.

One downside of this near-miracle is that research and development in the biotechnology area is voraciously expensive and often requires substantial time periods for commercial development. Moreover, many lines of research eventually prove to have been fruitless. Yet, the successful results, once known, are often not difficult to replicate by others. Other factors, including public perception regarding anything new and different, also keep many biotechnology inventions from reaching their full market potential. Consequently, very few biotechnology companies are profitable at this time. Many continue to require substantial additional investment to maintain operations. As a consequence, the biotechnology industry has a demonstrated need for patent protection to act as an effective incentive to innovation and to serve as a tangible asset for investment.

One exciting development in biotechnology research has been the isolation and purification of particular types of undifferentiated cells that can give rise to a succession of mature functional cells. These are known as stem cells, and are currently the subject of intensive research. Although most non-cancerous cells can divide only a limited number of times, the division of stem cells can be unlimited and may serve as a useful tool in solving many previously intractable medical conditions. Stem cells are known as "pluripotent" cell lines, meaning they can be made to develop into a variety of different mature cells.

One particular type of stem cell line is that which may be obtained at an early stage in the development in an embryo. By manipulating culture conditions, these embryonic stem (ES) cells can be induced to differentiate to specific cell types, such as blood cells, neuron cells, or muscle cells. They can also be grown into specific cell types for transplantation into an adult animal to treat specific diseases. These embryonic stem (ES) cells are derived from the embryo and are pluripotent--meaning they have the possibility under the correct conditions of developing into any organ or tissue type

Because ES cells can be grown in large quantities under tissue culture conditions, and researchers do not have to isolate large numbers of eggs or embryos, ES cells permit researchers to target their genetic manipulations better and avoid the use of whole embryos. In addition, because ES cells are all the same, genetically and functionally, they provide researchers with a uniform type of cell, thereby increasing the predictability and efficiency of experimentation and lowering cost.

Moreover, isolated and purified ES cells represents a potentially important invention that can be used in the study of developmental effects and mutations (e.g., birth defects), as well as in the introduction of new mutants or new genetic materials into embryos. They can also be used to generate more predictable disease models.

Patentability

Since stem cells are both living and found in nature, however, a question that may legitimately be raised is how they can constitute patentable subject matter under §101. Although the question of the subject matter patentability of living organisms was raised as long ago as [LISTER YEAST CASE], it was most firmly addressed by the Supreme Court almost twenty years ago in the famous case Diamond v. Chakrabarty[2]. In that case, Chief Justice Burger, writing for the Court, found that genetically engineered bacteria useful for cleaning up oil spills by ingesting hydrocarbons were themselves

[2] 447 U.S. 303, 65 L.Ed.2d 144, 100 S.Ct. 2207, 206 U.S.P.Q. 193 (1980)

patentable. As noted by the Court (citing the Congressional Report accompanying the 1952 Act[3]), "Congress intended statutory subject matter to 'include anything under the sun that is made by man". Many commentators believe that this case was a major factor in the phenomenal growth of the biotechnology industry. And it should also be noted that the PTO has long issued patents to living plants under the provisions of the Plant Patent Act of 1930.

Moreover, although stem cells do indeed occur in nature, they are always mixed with other cell types and do not occur in an isolated and purified form. Purified and isolated cell lines, as well as methods for their purification and isolation, represent important technological advances. They may also have novel or unexpected properties or uses. They may therefore result in a patent.[4] As stated by the Supreme Court, "To obtain a patent for a product made from raw material, it must possess a new or distinctive form, quality, or property."[5]

The patentability of biologically pure compositions has been the law for over twenty years. In In re Bergy (1977)[6], the Court of Customs and Patent Appeals (the predecessor court to the Court of Appeals for the Federal Circuit (CAFC), the appeals court to which PTO appeals are taken) ruled that a biologically pure bacterial culture was patentable, and not a "product of nature", since the culture did not exist in nature in its pure form and could only be produced in a laboratory under carefully controlled circumstances.[7] This has been extended since that time to "'purified and isolated' DNA sequences encoding human erythropoietin (EPO)",[8] and a preparation of Factor VIII: C, used for treating hemophilia. ("Although Factor VIII:C molecules occur in nature, a purified and concentrated preparation of Factor VIII:C as claimed in the patent constitutes

[3] S.Rep. No. 1979, 82nd Cong., 2d Sess., 5(1952); H.R.Rep. No. 1923, 82nd Cong., 2d Sess., 6 (1952).
[4] See generally Bozicevic, "Distinguishing 'Products of Nature' from Products Derived from Nature," 69 Journal of the Patent and Trademark Office Society 415 (1987).
[5] American Fruit Growers, Inc. v. Brodex Co., 283 U.S. 1, 11, 8 U.S.P.Q. 131, 133 (1931)
[6] 568 F.2d 1031, 195 U.S.P.Q. 344 (ccpa 1977)
[7] The Supreme Court granted certiorari, but summarily remanded to the CCPA in light of another related case. The CCPA later affirmed its earlier opinion.

a new form or combination not existing in nature, and hence is patentable under 35 U.S.C. §101.")[9]

Accordingly, it is the present position of the Patent and Trademark Office that purified and isolated stem cell lines are patentable subject matter under 35 U.S.C. §101.

One example of a stem cell which it may be useful to examine in this context is the hematopoietic stem cell, which can give rise to different types of mature blood cells. The hematopoietic stem cell has become very important in bone marrow transplantation therapy. While simple bone marrow transplants can provide a patient with new stem cells, this procedure carries risks. Notably, the presence of mature cells in transplanted bone marrow can give rise to Graft Verses Host Disease, a potentially fatal condition. Obtaining purified populations of hematopoietic stem cells isolated from mature myeloid and lymphoid cells that are normally found in the bone marrow can greatly decrease the danger of contracting this disease.

The technology to permit the isolation of such purified hematopoietic stem cells formed the basis for U.S. Patent Number 4,714,680, assigned to the Johns Hopkins University. That method was made with Government support under a grant from the Department of Health and Human Services. The intellectual property disclosed and claimed in the patent included: "A suspension of human cells comprising pluripotent lymphoi-hematopoietic stem cells substantially free of mature lymphoid and myeloid cells." An inspection of this claim reveals that the claimed subject matter is not something that has previously existed in nature: human hematopoietic stem cells are never found free of mature lymphoid and myeloid cells in humans. It was only through extensive and costly research that such an advance was possible. It is also appropriate to note that this patent has recently withstood a challenge to their validity in the Court of

[8] Amgen Inc. v. Chugai Pharmaceutical Co, Ltd., 13 USPQ2d 1737, *aff'd in part, rev'd in part, vacated in part*, 927 F.2d1200, 18 USPQ2d 1016 (Fed Cir. 1991), *cert.denied*, 112 S. Ct. 169 (1991).
[9] Scripps Clinic & Research Foundation v. Genentech Inc., 666 F.Supp. 1379, 1389 n.6, 3 USPQ2d 1481, 1487 n6. (N.D. Calif. 1897), *aff'd.in part, rev'd in part, vacted in part & remanded*,927 F.2d 1565, 18 USPQ2d 1001.

Appeals for the Federal Circuit and the infringer was penalized with significant damages for willful infringement.

Licensing

Concerns have also been raised regarding the licensing of technology in the biotechnology area, specifically in the context of the availability of research tools. While the Patent and Trademark Office does not normally concern itself with access issues, we do have responsibility for intellectual property policy generally, and, as such, have some experience in these matters.

A traditional way to exploit one's patent is to license it to others, under a wide variety of possible terms: exclusive or non-exclusive; royalty-free or royalty bearing. Patent owners may also choose not to license, for a variety of reasons, such as a desire to preserve exclusivity or maintain competitive advantage. This right is fundamental to the patent grant.

While some speculate that patent owners who refuse to license or exclusively license others may adversely effect access to biotechnological research tools, actual experiences lead to the conclusion that market realities almost always resolve this perceived problem. One famous example may prove illustrative.

A decade ago, Stanford University was granted a patent on a method covering basic recombinant DNA technology, the so-called Cohen-Boyer patent, U.S Patent Number 4,237,224. Because of the fundamental nature of the technology, great public concern was raised that biotechnology research would be blocked, or that Stanford would charge such exorbitant royalty rates that research would be priced out of reach. In reality, nothing of the sort occurred. Stanford quickly developed a reasonable and widely available licensing program and alternative technologies were developed to compete with it. Because the licenses were offered at reasonable rates to all who sought them,

technology was not stymied. Improvements to the technology also arose resulting in a moderating cross-licensing program.

Indeed, since this patent issued, others have applied this same approach with significant commercial application. Genentech, for example, has taken a similar approach with its Itakura/Riggs gene expression patents; and Columbia University with its Axel eukaryotic expression patents. These suggest that the biotechnology research community has developed effective strategies for negotiating and obtaining licenses to patented technology, facilitating additional downstream research and product development. Patents have not significantly impeded such activities.

Another question which has been raised concerns specific additional grants or limitations contained in certain licensing agreements. These include such provisions as a requirement that any improvements in the licensed technology be licensed back to the patent holder, commonly known as grant-backs. Provisions such as this are fairly common in commercial technology licenses, although they are also often the subject of significant negotiation.

It is also important to note that many of these aspects of intellectual property licenses may be subject to antitrust scrutiny. See, for example, the Antitrust Guidelines for the Licensing of Intellectual Property, recently promulgated by the Antitrust Division of the Justice Department and the Federal Trade Commission

In the context of these licensing considerations, it is also important to define specifically what "research tools" are being implicated in these concerns. Many of the instruments, chemicals and equipment used daily in research have patented technologies associated with them. A license to practice under those patents, and the related royalties, are often captured in the purchase price. Requiring that these tools be sold to the government at a royalty-free reduced price would likely be disruptive of the standard procurement regime.

Lastly, and significantly, it should be noted that restrictions on licensing or subject matter patentability may also adversely effect the United States international obligations. Through protracted negotiations, the U.S. has convinced our trading partners of the great value of intellectual property protection and has been able to reach agreement with them to provide strong intellectual property protection. In fact, we were able to incorporate our position on intellectual property protection into the Uruguay Round Trade Agreements of GATT. The Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) requires the United States and all other members of the World Trade Organization to provide similar patent protection for all patentable subject matter.

We have encouraged strong pharmaceutical patent protection by our trading partners and must continue to provide strong patent protection for biotechnological inventions, such as cell lines. That protection should not be diminished by inappropriate incursions into the rights of the patent owner. In fact, U.S. patent policy towards our trading partners strongly discourages compulsory licenses or any other such limitations on a patent holder's rights. Moreover, our international obligations under the TRIPS agreement require us to treat all types of patents equally and do not permit protection for biotechnology to be different from other technologies.

While we certainly share concerns about access to technology, and would highly recommend that oversight of potential abuses be maintained, the balance of interests in this area is currently a carefully calibrated one, and should not be upset absent strongly reasoned analysis and demonstration of actual harm.

Summary

The United States leads the world in biotechnology research and development. We also lead the world in intellectual property protection. It is imperative to the former that we maintain the latter. As stated long ago by President Abraham Lincoln, a patent

holder himself: the patent system has "added the fuel of interest to the fire of genius." Our continued success as the most technologically advanced nation in the history of the world demands that we honor that system and the benefits it brings.

Thank you.

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Washington Fax
December 4, 1998

Senate hearing focuses on whether the current embryo research ban extends to any or all stem cell research

Delving into such matters as what constitutes an organism and whether a funding ban on one type of research applies to its derivatives, a Senate panel Wednesday waded into the legal and ethical thicket surrounding the potential of primitive cells extracted from human embryos and fetuses to grow tissue for damaged hearts, treat Parkinson's disease and provide a range of other therapies and scientific insights.

The consensus from most of the scientists appearing before the Senate Appropriations Labor, Health and Human Services, Education and Related Agencies subcommittee (L/HHS) was that the scientific opportunities and ethical concerns surrounding research with stem cells demand federal support and oversight. Harold Varmus, the director of the National Institutes of Health (NIH), stopped short of joining his colleagues and calling for public funding, as the matter is still under review at his agency. But he spoke glowingly of the potential benefits of work with stem cells, which currently is being carried out in the private sector or by scientists who have other sources of funds.

"The development of cell lines that may produce almost every tissue of the human body is an unprecedented scientific breakthrough," he said. "It is not too unrealistic to say that this research has the potential to revolutionize the practice of medicine and improve the quality and length of life."

Varmus and the other scientists testifying--including the two investigators responsible for the recent breakthroughs in isolating stem cells--John Gearhart of Johns Hopkins and James Thomson of the University of Wisconsin--discussed the issue with two Senators who are particularly sympathetic to their concerns: Sen. Arlen Specter, R-PA, the chair of the panel, and Sen. Tom Harkin, D-IA, the subcommittee's highest ranking Democrat.

Specter said he is intrigued by the medical potential of stem cells, but wants to proceed cautiously on the issue of public funding, given the uncertainty about whether a federal ban on funding research with human embryos precludes supporting work with their derivatives, in this case stem cells.

"I think it's fuzzy, and I believe we have to do some work on it," he said in an interview. "This is a start on a very complex legal issue. I don't believe when the (embryo research ban) was enacted it was in the context of seeing the tremendous application. And now we need to take a much closer look at it and refine it to match the scientific research. I don't think you can rush to judgement on it. This is obviously on the cutting edge."

Harkin, however, concluded that because stem cells do not appear to have the potential to become human life, stem cell research is not covered by the embryo ban and should receive immediate federal support. "The research conducted by the distinguished scientists sitting before us today holds such hope, such potential for millions of Americans who are sick and in pain, that I believe it is morally wrong for us to prevent or delay our world-class scientists from building on this progress," he said in his opening statement. "As long as the research is conducted in an ethically validated manner, it should be allowed to go forward, and it should receive federal support."

Harkin made a point of quizzing the scientists about the distinction between an embryo or a fetus, which he said meet the legal definition of organism, and a stem cell, which he

said--quoting from a dictionary--does not. He contended that the federal ban on embryo research is intended solely to prevent research with organisms that could potentially become a human life.

All the scientists agreed that stem cells are not organisms, including Varmus. But Varmus said that despite his scientific opinion that stem cells are not organisms, he and other government officials are still "struggling" with the legal issues involved in making such a determination in order to "be sure that any actions we take are in compliance with existing law." He hopes that the administration--which has sought assistance on the matter from the National Bioethics Advisory Commission (NBAC)--will complete its review by the end of the year, he said.

The Clinton administration and Congress have variably sought to block federal support for research involving human embryos. In 1994 an NIH panel recommended that embryo research receive support as long it involves "spare" embryos; that is, embryos originally created through in vitro fertilization that have been deemed unsuitable for transplantation to the womb and donated to science.

President Clinton rejected the recommendation, and Congress has since included a "rider" to annual NIH appropriations bills forbidding expenditures in this area.

The question confronting Congress and NIH is whether the ban on embryo research precludes funding work with stem cells that have been cultured in a laboratory. Some scientists argue that even though their lineage may be ultimately traceable to the forbidden embryo, once isolated, stem cells appear to be capable of infinite propagation, and thus can end up being many generations removed from an embryo.

Richard Doerflinger, testifying on behalf of the National Conference of Catholic Bishops' Committee on Pro-Life Activities, said that one can't separate stem cells from their origins. He noted that stem cells extracted from embryos "clearly involve the creation and destruction of human embryos, which are organisms."

"One must refer here to the principles rather than to the exact letter of the law," he said. "Human embryos are destroyed precisely to obtain this tissue, and the timing and manner of destruction are tailored to obtaining this kind of tissue."

But further complicating the issue is the fact that some types of stem cells can be obtained from fetal tissue, as was the case in the stem cell isolation accomplished by Gearhart. And as long the investigator has no connection with the abortion that provides the tissue source, the work can be publicly funded (though Gearhart, while adhering to such guidelines, worked without public funds). Specter observed that there is a "curious dichotomy or inconsistency when federal funds may be used for fetal tissue research but not for human embryo research."

In other words, not only would research with stem cells obtained from aborted fetuses appear to qualify for public funding, so would the work with the fetuses themselves.

Varmus said in an interview that it is a "good question" when asked whether NIH should begin by supporting stem cell work where there is a clear legal path, i.e., funding research with cells extracted from aborted fetuses. But he said his agency would rather formulate a policy that would address all types of stem cell research--including work involving cells isolated from embryos or other means--rather than develop policy piecemeal.

For example, one of the scientists testifying Wednesday was Michael West, head of Advanced Cell Technology, which claims to have isolated human stem cells through a technique that involves fusing human tissue with portions of a cow's egg. While the work reportedly occurred several years ago, and has not been replicated or subjected to peer review, it has nonetheless complicated federal efforts to articulate a policy on stem cell

research.

Still, despite these dizzying details, what seemed to dominate Wednesday's discussions is the medical advances that stem cells could offer. While the cells have various stages of development that can narrow their potential uses, their largely "undifferentiated" state has made their isolation a prized biological achievement, given the evolving ability of medical scientists to direct such cells into becoming specific types of tissue that could perform an array of regenerative functions.

This potential has prompted a range of interests to come out this week in support of federal funding for stem cell research. For example, more than 50 disease advocates and scientific societies, representing such concerns as juvenile diabetes, blindness, Parkinson's, Down syndrome, cystic fibrosis, and cancer--sent a letter to members of Congress urging them to support federal funding for stem cell research. And the testimony at the hearing only served to re-enforce their enthusiasm for the curative powers of stem cells.

"Many diseases, such as juvenile onset diabetes mellitus and Parkinson's disease, result from the death or dysfunction of just one or a few cell types, and the replacement of those cells by transplantation could offer lifelong treatment," said Thomson, who has already grown heart tissue from stem cells he isolated from human embryos.

Thomson said heart tissue could be of immediate benefit. And Gearhart, who has coaxed stem cells into becoming neurons, predicted that within "several years," stem cells could be used to develop a treatment for Parkinson's.

Thomas Okarma, vice president for research at Geron Corporation, the company that has licensed Thomson and Gearhart's discoveries, said stem cells could also provide blood forming cells to aid cancer patients, insulin producing cells for people with diabetes and cells to line the inside of blood vessels for victims of atherosclerosis.

While there will be some applications likely to emerge absent federal support, Thomson asserted that the "number of discoveries will increase exponentially" if NIH begins funding stem cells research, particularly because NIH-funded investigators will look more closely at some of the basic science questions involved, while industry tends to focus more on immediate applications.

For Arthur Caplan, director of the Center of Biocthics at the University of Pennsylvania Health System, the moral concerns surrounding stem cell research versus its potential benefits are indicative of the kind of trade-offs that are increasingly common in a world of science, where new knowledge has made it difficult to resolve such moral issues as what constitutes life.

"I don't think we are in the realm of absolutes," he said. "I think we need judgement. I think we need virtue. That's why we need public funding, and public accountability to make the right trade-offs."

--Matthew Davis

Bush Blends Optimism and Challenge in Texas Inaugural

By RICK LYMAN

AUSTIN, Tex., Jan. 19 — Replaying the themes of unity, optimism and social responsibility that fueled his landslide re-election victory two months ago, George W. Bush was inaugurated as Governor of the nation's second-largest state today in a sun-warmed ceremony on the south promenade of Texas's red granite Capitol.

"The 21st century will be one of great opportunity," he told the crowd. "Our economy will be strong, so long as we pursue free markets, free trade, low taxes and limited government."

Governor's Bush's position as the presumptive front-runner for the Republican Presidential nomination in 2000 — a race he has not yet entered — was never mentioned during the daylong ceremonies. But there were moments — when he spoke of how the lessons learned in Texas might apply to the entire country — in which he seemed to be reaching for this larger audience.

"Texans can show America how to unite around issues that are larger than race or party," Mr. Bush said in his brief address.

The day began foggy and chill, and the dew still coated the Capitol's south lawn as the noon ceremony approached and the expectant crowd pushed against the white picket barricade around the base of the inaugural stage. As the Texas A&M band struck up "The Star Spangled Banner" and four F-16's roared overhead, the wind lost its chill and a bright sun began to push through the fracturing clouds.

Entering the platform beneath a canopy of raised swords, Governor Bush was joined by his wife, Laura, their twin daughters, Barbara and Jenna, and most of the rest of his family, including his parents, the former President and First Lady, and all of his four siblings save for Jeb, the new Governor of Florida, who was represented by his wife.

A private morning church service began the day's ceremonies. After the inaugural, a barbecue on the Capitol grounds perfumed the air with the mesquite smoke of 850 pieces of brisket and 5,000 pounds of sausage, turkey and ham. Midafternoon brought the traditional parade up Congress Avenue, and four inaugural balls ushered in the evening.

The Governor had that his inaugural speech would be short on legislative specifics and dwell, instead, on his vision for the state. The spine of his message was that the economy was doing very well, and was likely to continue to do so, but that this was not enough.

"I am optimistic our children's lives will continue to improve in material terms," he said. "The risk is that their moral and spiritual lives will not improve."

Mr. Bush urged families, communities and religious leaders to draw "a clear line between right and wrong," and said it was the responsibility of political leaders, public schools and public institutions to support this effort.

"Government can't solve all our problems," he said. "Economic growth can't solve all our problems. In fact, we're now putting too much hope in economics, just as we once put too much hope in government."

It was a difficult day for Democrats in Austin. For the first time since the Civil War, the party did not have a single statewide official to celebrate. Governor Bush's coattails led to a Republican sweep of the state offices in November.

Inaugurated as Lieutenant Governor today was Rick Perry, a social conservative and former agriculture commissioner.

Neither the impeachment proceedings in Washington nor the impending State of the Union speech by President Clinton were referred to during the inaugural ceremony, but there were plenty of references to the overriding importance of character and moral values.

"A healthy democracy depends upon the character of its citizens," Mr. Bush declared.

It was left to the Lieutenant Governor to underline the message. "George W. Bush is a man of character," Mr. Perry said. "The type of person we can point out to our children and say, We want you to grow up to be like him."

The Governor outlined three challenges that face Texas and said that each offered lessons for the rest of the country.

First, he said, Texas must assure equal opportunity.

"Texas must be an open society," Mr. Bush said. "We must not become two societies, one that believes in the American dream and one without such hope."

He recalled a visit last year with a group of "young tough criminals," one of whom asked him whether he saw any hope for them.

"His question reveals something crucial to the future of Texas, as well as this country," Mr. Bush said. The answer, he said, is to "rally the armies of compassion that are in every community of this great state."

Second, the Governor said, Texas must "become an educated society" that is "literate in the language of the 21st century" and ready to compete. This means not only ending social promotions and making sure all students learn to read, he said, but educating public school students in "the values of a civil society."

Finally, Mr. Bush said, Texas must embrace its ethnic and racial diversity.

"We should be proud of our various heritages," he said. "We should celebrate them in festivals, we should enjoy their traditions in our homes, we should share them with friends. This genuine appreciation of heritage stands in stark contrast to those who would divide people into groups for political purposes."

Essentially, the Governor said, he is optimistic about the new century. He recalled a favorite quotation by an El Paso writer who described himself as living on "the sunrise side" of the mountain.

"As we head into a new century, Texas lives on the sunrise side of the mountain," Governor Bush said. "And I see a very good day coming."

The New York Times

WEDNESDAY, JANUARY 20, 1999

Government Says Ban on Human Embryo Research Does Not Apply to Cells

By NICHOLAS WADE

Federally financed researchers will soon be able to work on human embryonic stem cells, the source cells from which the embryo develops, as a result of a ruling yesterday by the Department of Health and Human Services that a Congressional ban on human embryo research does not apply to those cells.

The decision was hailed as "an accurate interpretation of bad law" by the American Society for Reproductive Medicine and denounced by the National Conference of Catholic Bishops as a loophole that "violates the spirit of current law."

In its ruling, the Office of General Counsel at the health department said that because the cells by themselves did not have the capacity to develop into a human being, they could not be considered embryos.

Human embryonic stem cells, isolated for the first time last November, are capable of developing into any of the body's cell types and thus have great potential for repairing any damaged tissue, like failing heart muscles or the type of brain cells lost in Parkinson's disease.

Academic biomedical researchers, most of whom rely on Federal financing, have been unable to study human embryonic stem cells because of a Congressional ban, originating in the House of Representatives, that has been attached every year since 1995 to bills authorizing spending for the National Institutes of Health, the principal supporter of biomedical research.

The ban states that no Federal money may be used for "research in which a human embryo or embryos are destroyed, discarded or knowingly subjected to risk of injury or death greater than that allowed for research on fetuses in utero." In a statement issued last November Representative Jay Dickey, Republican of Arkansas, said human embryonic stem cells should not be excluded from the ban.

Congress could overturn the new ruling, but that prospect is uncertain, especially in light of recent Senate hearings that established the likelihood of a strong medical benefit from the cells.

The embryonic stem cells described in November by Dr. James Thomson of the University of Wisconsin were derived from human embryos created in surplus amounts in a fertility clinic. Deriving the cells is legal, provided it is not done with Federal money. Dr. Harold E. Varmus, director of the National Institutes of Health, said it would still be illegal for researchers to use Federal money to derive their own stem cells in this way. But they can now use Federal money to work on the cells Dr. Thomson has already obtained.

"The prospect of doing amazingly interesting science is really quite wonderful," Dr. Varmus said. But research cannot begin, he said, until the institutes have drawn up guidelines to insure that researchers do not do prohibited research, like generating new embryos

Senator Tom Harkin, an Iowa Democrat who last month called for speedy issuance of the ruling, said the decision would move researchers closer to finding cures for many diseases

"The Government should not issue blanket bans on medical research," Mr. Harkin said.

But the circumstance that federally supported scientists can now conduct research on cells that they cannot legally derive was seized upon by Richard M. Doerflinger, associate director for policy development at the National Conference of Catholic Bishops. "They will destroy the embryos with private funds and experiment on the tissue with public funds," Mr. Doerflinger said.

As to the medical benefits of stem cell research, Mr. Doerflinger suggested that the cells could be derived in ways that did not kill the embryo, like from spontaneously aborted fetuses.

One line of human embryonic stem cells was derived from fetuses obtained after induced abortions. A pocket of embryonic stem cells known as embryonic germline cells is preserved in the fetus. These germline cells are thought to be equivalent to embryonic stem cells. In a written statement Mr. Doerflinger said, "The Clinton Administration now seeks to do indirectly what Congress has forbidden it do to directly: provide Federal support for research in which human embryos are created and destroyed."

THE INDEPENDENT COUNSEL

Figure in a Starr Inquiry Pleads Not Guilty; Wants Trial Moved to Capital

By NEIL A. LEWIS

ALEXANDRIA, Va., Jan. 19 — As President Clinton's lawyers opened his defense before the Senate today, a peripheral figure in the impeachment pleaded not guilty in Federal court here to charges that she had interfered with the independent counsel's investigation of the President.

"Absolutely not guilty," declared Julie Hiatt Steele, whose lawyer charged that the independent counsel, Kenneth W. Starr, had brought the case in Virginia solely to avoid a decision in the District of Columbia, where a similar case brought by Mr. Starr was thrown out last summer.

Mr. Starr's office charged Ms. Steele earlier this month with three counts of obstructing justice and one count of making false statements when she cast doubt on accusations that the President once groped a friend of hers, Kathleen E. Willey.

Ms. Steele's lawyer, Nancy Luque, told Judge Claude M. Hilton of Federal District Court here that the case really belonged in the District of Columbia and that she would wage a legal battle to have it moved there.

In charging that Mr. Starr brought the indictment in Virginia to avoid the Federal District Court in Washington, Ms. Luque was apparently referring to the tax fraud case against Webster L. Hubbell, a longtime Arkansas friend of the Clintons.

Judge James Robertson of Federal District Court in Washington threw out that case last July, declaring in a stern ruling that the Hubbell tax investigation had far exceeded Mr. Starr's mandate. Mr. Starr is appealing that decision.

A prosecutor from the Office of the Independent Counsel, David Barger, did not respond in court to Ms. Luque's charge and declined to comment after the hearing.

The case against Ms. Steele involves an affidavit and statements she made about her knowledge of whether the President made an unwanted sexual advance to Ms. Willey in the Oval Office in 1993. Ms. Willey, who was a White House volunteer at the time, has said Mr. Clinton grabbed her intimately when they were alone briefly.

Ms. Steele initially told a reporter for Newsweek magazine that Ms. Willey told her of the incident just after she said it happened. But Ms. Steele then recanted that account and gave an affidavit in the Paula Jones sexual misconduct lawsuit denying that Ms. Willey had ever told her of the incident. Ms. Steele said later that she had claimed knowledge of the incident only as a favor to Ms. Willey, who had asked her to lie to confirm her account.

Mr. Clinton denied that he had ever made a sexual advance to Ms. Willey, both in his grand jury testimony and in his deposition in the Jones case.

Although Ms. Steele is a peripheral figure to the investigation of the President, her refusal to back up Ms. Willey's story was apparently a major factor in Mr. Starr's decision not to include information about Ms. Willey in his impeachment report to the House of Representatives.

To Mr. Starr's critics, his prosecution of Ms. Steele is a vivid demonstration of how far he is prepared to go to get anyone who gets in his way.

Besides having Ms. Steele testify before the grand jury on two occasions, Mr. Starr also had the grand jury take testimony from her daughter and brother. Ms. Steele, a 52-year-old single mother from Richmond, has said Mr. Starr's investigators raised questions about the legality of her adoption of an East European child in an effort to intimidate her. Mr. Starr has denied that any such activity took place.

Ms. Luque has said the timing of the case is designed to coincide with the impeachment trial. Charles G. Bakaly 3d, a spokesman for Mr. Starr, dismissed those claims. Judge Hilton set a trial date of March 30.

Jones's Attorneys Take On Prior Team

LITTLE ROCK, Ark., Jan. 19 (AP) — Paula Corbin Jones's lawyers said today that her first legal team, which won a crucial round before the Supreme Court in her sexual harassment case, is not entitled to any share of her $850,000 settlement with President Clinton.

The current team, from the Dallas law firm of Rader, Campbell, Fisher & Pyke, said in court papers that the work of the previous lawyers, Joseph Cammarata and Gilbert Davis, was "riddled with malpractice" and that they abandoned her case because they lacked "professional ability" and "personal resolve."

Mr. Cammarata and Mr. Davis said that they were offended by the claim and that they left the case after Mrs. Jones rejected their advice.

The New York Times

WEDNESDAY, JANUARY 20, 1999

GOP leaders oppose Social Security plan

By Donald Lambro
THE WASHINGTON TIMES

A1

Republican congressional leaders and business groups yesterday condemned President Clinton's plan to fix the Social Security system, warning that it would effectively lead to a government nationalization of Fortune 500 companies.

At issue is a key component of the president's plan to create a new government board to invest part of Social Security's funds in the stock market — raising the specter of the government for the first time in history becoming the majority owner of the nation's biggest corporations.

see PLAN, *page A9*

"If you thought a government takeover of health care was bad, just wait until the government becomes an owner of America's private-sector companies," said House Ways and Means Committee Chairman Bill Archer, whose committee has chief jurisdiction over the program.

The Texas Republican warned the White House plan would lead to "all kinds of mischief involving government dictates, favoritism and cronyism."

Martin Regalia, the chief economist for the U.S. Chamber of Commerce, agreed.

"It's basically nationalization. It goes in that direction," he said. "There is no reason for the government to be owning a part of the private sector."

The core of Mr. Clinton's plan would allocate more than 60 percent of future budget surpluses — estimated at $4.4 trillion over the next 15 years — into Social Security "cash reserves," putting most of the money into U.S. Treasury bonds that the system could redeem in years to come when funds are needed to pay future benefits.

An additional 11 percent of the budget surpluses, or about $500 billion, would go into new separate 401(k)-style retirement accounts.

Gene Sperling, Mr. Clinton's top economic adviser, said yesterday the White House plan foresees the stock-market money being placed in "broad-based, neutral forms of investments," with a diversified group of private-sector managers setting the investment strategy.

Noting the extensive debate over how best to shore up the retirement fund, Mr. Sperling told reporters: "The president is responding to the things he heard around the country and I think he struck a positive balance."

Horace Deets, head of the American Association of Retired Persons, the powerful senior citizens lobby, took no position on the stock-ownership plan. But he said Mr. Clinton's proposal "to add a universal retirement savings account on top of Social Security appears to be a constructive start toward greater retirement security for all Americans."

But critics took quick aim at other aspects of the president's reform plan, saying it does not address the program's fundamental problems of long-term insolvency and taxpayer liability, and would create a new entitlement that would add further costs to the system.

Many Republicans are backing competing plans to allow workers themselves to put part or all of their payroll taxes into their own retirement investment plans.

"The president's proposal is a disappointing political cop-out that does not save Social Security first, last or ever," said Sen. Phil Gramm, Texas Republican, who has introduced his own full-privatization plan with Senate Budget Committee Chairman Pete V. Domenici, New Mexico Republican.

"The president's plan continues to allow the government to plunder 75 cents out of every new dollar coming into the Social Security trust fund to pay for other unrelated government programs," Mr. Gramm said.

There also appeared to be major opposition to the third part of the plan to devote 11 percent of the coming surpluses to establish government-subsidized retirement accounts, because Mr. Clinton would exclude higher-income people from the plan and give higher benefits to lower-income people.

"It's one of the worst ideas I've heard in 20 years," said Paul Huard, senior vice president for policy at the National Association of Manufacturers. "All this does is create a new redistributional entitlement that the voters would come to expect [and] that doesn't do anything to fix the basic system."

"The only way to truly save Social Security is to start putting the Social Security surplus money into privately owned individual retirement accounts, because the government cannot raid your own retirement account the way the Social Security surplus has been raided over the last 15 years," said Stephen Moore, the libertarian Cato Institute's chief budget analyst.

The Washington Times

WEDNESDAY, JANUARY 20, 1999

Stem-cell research will get U.S. funding

Pro-life groups slam use of embryos

By August Gribbin
THE WASHINGTON TIMES

A1

The head of the National Institutes of Health announced yesterday that the federal government will fund pioneering but controversial stem-cell research that may provide cures for Alzheimer's, diabetes and other diseases.

Dr. Harold Varmus informed the National Bioethics Advisory Commission that a ban on federal funding of human embryo research does not apply because the cells used in the recently developed stem-cell experiments come from non-living fetuses.

Dr. Varmus, first among the scientists, ethicists and concerned citizens who will testify before the board, said that "the scientific potential here is tremendous and would clearly be limited" if government funding were denied.

The announcement drew quick criticism from Rep. Christopher H. Smith, New Jersey Republican, a foe of all research involving human embryos. He said the NIH proposes "to offer federal subsidies to researchers who will experiment with cells obtained from human beings ruthlessly killed in the first weeks of life." The research, he said, "depends on the

see CELL, *page A18*

mutilation of children."

The National Right to Life Committee argued the NIH was using a "subterfuge" to "do violence to the clear intent of the law."

The contested research involves microscopic human cells in the first phases of their existence. They were long known to exist and were finally isolated early in December.

Called "primitive" and "immortal" cells, they have the ability to divide limitlessly and to give rise to specialized cells that eventually can develop into toes, ears, brain cells, blood and other body parts.

Scientists speculate that further experimentation will lead to developing the ability to direct stem cells to grow into certain types of tissue that can be used to repair disease- or accident-damaged bodies. Injecting stem cells might delay certain aspects of aging, and the research appears likely to create a new form of medicine.

To date, however, stem-cell research breakthroughs have come only from laboratories funded by the biotechnology industry and private clinics. That's because it was presumed such research fell under the federal funding ban, which applies to universities and research organizations accepting federal grants.

The ban meant that some of the nation's foremost university scientists could not engage in stem-cell research, and that promising lines of investigation were being ignored.

The bioethics advisory commission was asked to study the situation and make recommendations regarding the moral and ethical issues involved in the experiments.

Yesterday, the board heard scientists plead for a recommendation that the research be funded. The researchers argued for a policy that allows the current research and permits laboratory creation of research embryos. Academicians and theologians provided advice on how to evaluate the conditions under which the use of embryos would be appropriate.

However, some appearing before the board backed Mr. Smith and insisted such research should never be allowed. A group called Collegians Activated to Liberate Life and others from pro-life groups expressed the view that there can be no compromise.

Arguing that life begins with conception, they say that experiments with human embryonic cells are the moral equivalent of murder. They tie the research to the abortion issue.

Others, including Patricia King of the Georgetown University School of Law, ethicist Erik Parens of the Hastings Center and Ted Peters from the Center for Theology and the Natural Sciences, advised the commission to consider distinctions between various types of human embryos.

Miss King, a member of previous government bioethical ethical committees, urged the advisory board to consider that "there will not be a consensus on the morality of abortion in our lifetime."

But she said there can be an "overlapping consensus" on stem-cell research based on values that most people do agree on. That would include wide agreement that people need the treatments and cures such research can facilitate, and that a distinction can be made between embryos that could never develop into a person and those that could.

The Washington Times

WEDNESDAY, JANUARY 20, 1999

Deborah:
Not particularly well written. Repetitive & choppy, but not wrong or overly problematic. Please allow to quickly review if you have not already.
Thanks.

DRAFT * DRAFT * DRAFT

Response to House Letter

Thank you for your letter dated February 11, 1999, concerning the recent announcement by the Director of the National Institutes of Health (NIH) regarding federal funding for research utilizing human pluripotent stem cells. The recent isolation of human pluripotent stem cells is a powerfully important scientific advance for human biology and medical research. As you know, this research has the potential to lead to great progress in our treatment of debilitating and deadly diseases, our understanding of human development and our ability to develop and test new drugs. Stem cell research is richly promising, yet the prospect of this research raises important ethical and legal issues. Therefore, Dr. Varmus and his colleagues at the National Institutes of Health (NIH) will proceed with great caution to ensure that the highest standards are set before moving forward in this area.

In keeping with the important ethical concerns that must be considered before any federal funds could be committed to research utilizing pluripotent stem cells, the NIH plans to proceed in a careful and deliberate fashion to develop rigorous guidelines. A working group of the Advisory Committee to the Director of NIH will develop guidelines for the conduct of research using pluripotent stem cells and will recommend an oversight mechanism for protocol review. The National Bioethics Advisory Commission is studying these issues and will provide us with advice that -- together with counsel from outside experts, Congress and other interested parties -- will help ensure appropriate oversight.

First and foremost, these guidelines will ensure that any research funded in this area is consistent with the prohibition on federal funding for human embryo research contained in section 511 of the HHS appropriations law. Since this prohibition was first enacted in 1996, the Department of Health and Human Services (HHS) has conscientiously adhered to its strictures. For example, we have included the restriction on the use of funds in the NIH Grants Policy Statement and have issued notices reminding NIH intramural staff and the extramural research community that they must observe the prohibition. When necessary, we have not and will not hesitate to take appropriate enforcement action. I am firmly committed to our continued adherence to the law.

Your letter makes specific inquiries regarding a legal memorandum on this subject from the HHS General Counsel. You suggest that the legal analysis is problematic because it relies on a new definition of human embryo that would undermine the Congressional prohibition. In fact, the memorandum relies on the definition provided in the statute itself. The statute defines human embryo as "any organism ... that is derived ... from one or more human gametes or diploid cells." The legal memorandum, relying on the scientific definition of the word "organism", concludes that the stem cells at issue are not organisms and therefore cannot be considered human embryos under section 511 of the HHS appropriations law.

The prohibition on federal funding for human embryo research bars the expenditure of federal funds for the creation of a human embryo for research purposes or for research in which a human embryo is destroyed, discarded or knowingly subject to greater than minimal risk. You suggest

that this provision should be read to also bar federal funding for research which follows or depends upon the destruction of or injury to a human embryo. The plain language of the statute supports the opinion issued by the General Counsel. The law applies by its terms to research in which "a human embryo or embryos are destroyed, discarded" or subjected to more than minimal risk, and not to research preceding or following such research projects. Moreover, I have been advised that there is nothing in the legislative history to suggest that the provision was intended to prohibit funding for research in which embryos -- organisms -- are not involved.

I have reviewed our Department's position and am reassured that proceeding cautiously with research on existing pluripotent stem cell lines is both legal and appropriate. Further, it will allow the NIH to foster world-class research on stem cells, assure appropriate oversight, and bring together the finest minds and facilities to further medical and scientific advances. Allow me to assure you that the NIH understands and respects the deep convictions of people in the research, academic and religious communities, and in Congress, and intends to seek the advice and comment of those communities as we move ahead. I look forward to working with you to ensure that the legal and ethical issues involved in this extremely promising area of research are addressed.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
THE GENERAL COUNSEL
PHONE: 202/690-7741
FAX: 202/690-7998

TO: Chris Jennings

DATE: February 22 1999

DEPARTMENT/OFFICE:

PHONE: (202) 456-5560

FAX: (202) 456-5557

FROM: **HARRIET S. RABB**
GENERAL COUNSEL

COMMENTS: We need your comments tonight. Please call Marcy Wilder at (202) 690-6318 by 7:00 PM. If you have any changes.

PAGES INCLUDING COVER: 3

DRAFT * DRAFT * DRAFT

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March 18, 1999

Stem Cell Research Supported

A.P. INDEXES: TOP STORIES | NEWS | SPORTS | BUSINESS | TECHNOLOGY | ENTERTAINMENT

Filed at 6:45 p.m. EST

By The Associated Press

WASHINGTON (AP) -- Seventy-three prominent scientists, including 67 Nobel prize winners, signed a letter supporting plans by the National Institutes of Health to consider financing research with stem cells that originated from human embryos.

The letter, to be published Friday in the journal Science, said that despite the opposition of more than 70 members of Congress, the NIH position on human stem cell research ``is both laudable and forward-thinking.''

Stem cell research, the scientists said, could be used to treat heart disease and brain disorders and could ``perhaps even cure'' diabetes.

The letter is the latest volley across a growing chasm of disagreement separating medical researchers who say stem cell research offers great promise from members of Congress who believe the research is immoral because it starts with aborted human embryos. The lawmakers support a ban on federal funding of human embryo research and say that ban includes stem cells.

Pluripotent stem cells are the master cells from which all body tissue develops. During gestation, the cells change into the 210 types of cells that make up the human body.

Privately funded researchers recently took cells from aborted or unused embryos no longer needed for invitro fertilization and they grew colonies of pluripotent stem cells. In some experiments, the cells differentiated into other types of cells, supporting the theory that heart, brain and other tissue could be grown from such cells.

Citing the promise of stem cell research, Dr. Harold Varmus, director of the National Institutes of Health, proposed in January that the agency consider funding such studies. He said the research may not violate the federal ban because it would use existing stem cell colonies and not involve working directly with embryos. An

NIH committee is being selected to evaluate the ethical concerns.

In their letter in Science, the 73 scientists said Varmus' plan ``succeeds in protecting the sanctity of human life without impeding biomedical research that could be profoundly important to the understanding and treatment of human disease."

Stem cells, the letter said, could be used to make ``a long list of cells and tissues that could be used for transplantation." New cells could be injected to restore ailing hearts, or to correct damage by Parkinson's disease, or to replace failed insulin-producing cells, and, thus, cure diabetes, they said.

If Congress blocks this research, the letter said, ``these tremendous scientific and medical benefits may never become available to the patients who so desperately need them."

In reply, the leader of an antiabortion group in Congress, Rep. Christopher H. Smith, R-N.J., said: ``Some scientists resent any moral limits on their use of taxpayer funds for harmful experiments."

``I reject the claim that a degree in science -- even a Nobel Prize in science -- makes scientists our supreme arbiters of morality and human dignity," said Smith, who leads a group of 70 Congress members who have written two letters opposing Varmus' plans.

The congressman said medical experimenters have committed ``horrific abuses" in the past.

Addressing the scientists, Smith said: ``Americans will not endorse lethal experiments on infants just because you claim it would be useful. We should not start down that road now."

Among those who signed the scientists' letter were Nobel laureates Dr. Robert F. Furchgott of State University of New York, 1998 winner for discovery the action of nitric oxide in the body; Eric F. Wieschaus of Princeton, 1995 winner for studies of genes in developing fetuses; Joseph E. Murray of Harvard, 1991 winner for studies on cell and organ transplantation, and James D. Watson of Cold Spring Harbor Laboratories, co-discoverer in 1953 of the DNA molecule.

January 19, 1999

Ban on Embryo Research Limited

A.P. INDEXES: TOP STORIES | NEWS | SPORTS | BUSINESS | TECHNOLOGY | ENTERTAINMENT

Filed at 11:03 a.m. EST

By The Associated Press

WASHINGTON (AP) -- A federal ban on human embryo research does not apply to studies using the new ``master cell'' technology that might one day treat heart disease, diabetes and other killers, the head of the National Institutes of Health announced today.

NIH director Harold Varmus said his agency will soon finance such research.

At issue are embryonic stem cells, the basic or primordial cells from which all of a body's tissues and organs develop. With private funding, these cells have recently been derived from embryonic tissue and then grown in laboratories.

The hope is that scientists can learn how to use them to treat disease, but researchers have recently warned that without federal financing to do so, the work would take many more years.

Congress has banned federal money for research that involves human embryos. But Varmus announced today that a legal evaluation of that ban concluded that these laboratory-grown cells -- which could never grow into an entire human being -- do not constitute an embryo. Thus, the NIH can finance research to use them to hopefully create new treatments, Varmus said.

``The scientific potential here is tremendous and we would clearly be limited'' if the NIH could not participate in such research, Varmus told President Clinton's National Bioethics Advisory Commission.

``It is appropriate for NIH to support this research and we intend to do so,'' Varmus said.

The advisory commission is studying the scientific and ethical implications of research involving human embryonic stem cells. Some anti-abortion groups contend that cell research is morally unacceptable because it begins with the destruction of human embryos.

Two researchers have been successful in isolating and growing human stem cells. Scientists at Johns Hopkins University, using tissue from aborted fetuses, culled stem cells from the tissue and then caused the stem cells to multiply in a

lab. Scientists at the University of Wisconsin used early-stage embryos that had been donated by couples undergoing fertility treatments at ``in vitro'' fertilization clinics and who had consented to their unused embryos being used in the research.

It also may be possible for scientists to use cloning techniques to derive stem cells, but that hasn't been done yet.

Scientists don't yet know how to use these stem cells to create treatments. However, these cells naturally would go on to form various tissues and organs in the body.

If scientists can learn how to control that process and switch on the proper genes to direct which tissues the cells form, they might one day be able to grow heart tissue that could, for example, replace the damaged tissue of someone with congestive heart failure. Or, researchers could grow new pancreas cells for a diabetic.

Varmus cautioned that the NIH will not immediately start handing out money for the research. Over the next few months, the agency, with guidance from the bioethics commission and Congress, will draw up guidelines that must be strictly followed for scientists to win NIH funding for their research.