Case No. 16-15360

IN THE

UNITED STATES COURT OF APPEALS

FOR THE NINTH CIRCUIT

NATIONAL ABORTION FEDERATION,

Plaintiff-Appellee,

v.

CENTER FOR MEDICAL PROGRESS, BIOMAX PROCUREMENT SERVICES, LLC, DAVID DALEIDEN, aka ROBERT DAOUD SARKIS, and TROY NEWMAN,

Defendants-Appellants.

On Appeal from the United States District Court
for the Northern District of California
Case No. 3:15-cv-03522-WHO
Hon. William H. Orrick, United States District Court Judge

Brief of *Amici Curiae* Fetal Tissue Researchers, Scientists, Physicians, Medical and Legal Ethicists and Academics in Support of Plaintiff-Appellee

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TABLE OF CONTENTS

Page

TABLE OF AUTHORITIES

Page(s)

CASES

STATUTES

RULES

OTHER AUTHORITIES

TABLE OF AUTHORITIES

Page

TABLE OF AUTHORITIES

Page

TABLE OF AUTHORITIES

Page

TABLE OF AUTHORITIES

Page

STATEMENT OF IDENTITY, INTEREST, AND AUTHORITY TO FILE[1]

The undersigned *amici curiae* ("*amici*") include fetal tissue researchers, scientists, physicians, medical and legal ethicists and academics.[2] Many of *amici's* careers focus on saving and improving life, using legally and ethically sourced fetal tissue to discover cures and prevention for devastating conditions such as birth defects including neural tube defects (spina bifida and anencephaly), microcephaly (small brain), childhood cancers including retinoblastoma (a childhood onset eye cancer which starts in utero) and childhood B-cell leukemia, developmental disorders including autism spectrum disorders, immunodeficiency disorders, neuropsychiatric diseases including schizophrenia and epilepsy, neurodegenerative diseases including Alzheimer's Disease, Parkinson's Disease, and Amyotrophic Lateral Sclerosis ("ALS", or Lou Gehrig's disease), and diseases of the nervous system including multiple sclerosis. *Amici* have also participated in drafting research guidelines and policies including the National Academies' Stem

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[1] Pursuant to Federal Rule of Appellate Procedure 29, undersigned counsel for *amici* certify that no party's counsel authored this brief in whole or in part, and that no party or person other than *amici* and their counsel contributed money towards the preparation or filing of this brief.

[2] *Amici's* biographies are attached as Appendix A. *Amici* sign this brief in their individual capacities. References to their institutions are for biographical purposes only.

Cell Guidelines and President Barack Obama's policies on research ethics, and served on advisory boards including the National Bioethics Advisory Commission under President William Jefferson Clinton and the California Institute for Regenerative Medicine's Ethics Standards Working Group.

As the District Court's injunction recognizes, this is an "exceptional case where the extraordinary circumstances and evidence to date shows that the public interest weighs in favor of granting the preliminary injunction." Order Granting Plaintiff's Motion for Preliminary Injunction at 39, *filed in National Abortion Federation v. Center for Medical Progress*, Case No. 3:15-cv-03522 (N.D. Cal. Feb. 5, 2016). The important work of *amici*—work that makes us all healthier—is the embodiment of this very real public interest.

But the actions of the Center for Medical Progress, Biomax Procurement Services, David Daleiden and Troy Newman have threatened that. As a result of the publishing of Appellants' misleading videos, there have been threats to doctors and researchers involved in fetal tissue procurement and research. *See* Appellee's Brief at 55 ("Dr. Nucatola and Ms. Dyer faced death threats and $10,000 rewards for their murders. Dr. Ginde faced threats of being 'publicly lynched' and was confronted at her home by picketers. Dr. Ginde's clinic was then attacked by a gunman who, after murdering two bystanders and a police officer, recited

defendants' credo of 'no more baby parts' to police. The list goes on.") (citations omitted). Moreover, after the videos were released, suppliers of fetal tissue feared being similarly targeted and "the supply of fetal tissue quickly dwindled." Danielle Paquette, *We Lose Money Doing This: Tiny Company Caught in Abortion Debate Takes on Congress*, The Washington Post (May 27, 2016) (quoting Cate Dyer, CEO of Biomedical Company StemExpress). The press further reports that Steven Goldman, a neurologist at the University of Rochester Medical Center in New York, noted that "the outrage—and anxiety—over becoming a target of [threats]—has delayed his research on multiple sclerosis. . . . 'This kind of delay' he said, 'results in the additional deaths of people who could have been rescued.'" *Id.* (quoting Steven Goldman, MD). *Amici* urge this Court to affirm the District Court. The District Court's injunction serves the public interest.

Counsel for *amici* have sought and obtained the consent of counsel for Defendants-Appellants to the filing of this brief.

SUMMARY OF ARGUMENT

Fetal tissue research, a research method used since the 1930s, has been key to scientific advances that have preserved the health and saved the lives of millions of people. It is both legal and ethical under long-established laws, policies and norms.

Until the development of the respective vaccines, polio was a frightening killer virus, and the rubella virus threatened the healthy pregnancies and the fetal development of expectant mothers. Both vaccines—common now—were discovered with fetal tissue research. Since 1988, the polio vaccine has prevented more than 650,000 deaths and 13 million cases of paralysis worldwide. *See* CDC, *The Time to Eradicate Polio Is Now* (last updated Mar. 3, 2014).

And the past is prologue: fetal tissue research is absolutely needed today to save lives threatened by diseases, viruses, and other health afflictions. "'[F]etal tissue continues to be a critical resource for important efforts such as research on degenerative eye disease, human development disorders such as Down syndrome, and infectious diseases . . .' [f]rom therapies for end-stage breast cancer, diabetes, and Parkinson's disease to a promising vaccine for Ebola, vital medical research depends on continued use of fetal tissue under current laws and regulations." Association of American Medical Colleges Statement in Support of Fetal Tissue Research (Mar. 18, 2016) ("AAMC Statement") (citing the United States. Department of Health and Human Services ("DHHS").[3] Leading researchers in the

[3] Signatories include:
American Association for the Advancement of Science
American Congress of Obstetricians and Gynecologists
(Continued…)

American Physiological Society
American Society for Reproductive Medicine
American Society of Hematology
Association of American Universities
Association of Anatomy Cell Biology and Neurobiology Chairs
Association of Chairs of Departments of Physiology
Association of Medical School Microbiology and Immunology Chairs
Association of Public and Land-Grant Universities
Association of University Radiologists
Beth Israel Deaconess Medical Center
Boston Children's Hospital
Boston University School of Medicine
California Northstate University College of Medicine
Cedars-Sinai Medical Center
Children's Hospital Los Angeles
Columbia University Medical Center
Duke University School of Medicine
Feinberg School of Medicine, Northwestern University
Florida Atlantic University
Harvard University
Jacobs School of Medicine and Biomedical Sciences at the University at Buffalo
Johns Hopkins University
Loma Linda University School of Medicine
Marshall University Joan C. Edwards School of Medicine Medical College of Wisconsin
Michigan State University College of Human Medicine
Mount Sinai School of Medicine and Health System
National Multiple Sclerosis Society
NYU Langone Medical Center
Oregon Health & Science University
The Perelman School of Medicine at the University of Pennsylvania
Research!America
Roy J. and Lucille A. Carver College of Medicine at the University of Iowa
Rutgers Robert Wood Johnson Medical School
Stanford University School of Medicine
(Continued…)

field have opined that fetal tissue research is the best vehicle to use in the critical search for a vaccine to the newest global threat to successful pregnancies and fetal/infant health—the Zika virus. *See* National Partnership for Women and Families, *CDC Issues New Zika Guidance; State, Federal Efforts Targeting Fetal Tissue Donation Could Thwart Zika Research* (Mar. 29, 2016) ("Basically the only insights we've had so far on Zika is with patients who have either lost a pregnancy

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Stony Brook Medicine
SUNY Upstate Medical University College of Medicine
Temple University School of Medicine
Tufts University School of Medicine
Tulane University School of Medicine
Universidad Central del Caribe
University of Alabama School of Medicine
University of Chicago
University of Colorado School of Medicine
University of Illinois Hospital & Health Sciences System
University of Maryland, Baltimore
University of Massachusetts Medical School
University of Michigan Medical School
University of Nevada School of Medicine
University of New Mexico Health Science Center
University of Pittsburgh School of Medicine
University of Puerto Rico School of Medicine
University of Rochester Medical Center
University of Washington
University of Wisconsin-Madison
Virginia Commonwealth University School of Medicine
Washington University in St. Louis
Weill Cornell Medical College
Wright State University Yale School of Medicine

or had miscarriages. . . . This is a situation where the vaccine is going to have to protect the woman and fetus, so [f]etal tissue is going to be needed to look at the effects.") (quoting high-risk obstetrical expert Patrick Ramsey of the University of Texas Health Science Center).

Amici submit this brief to make clear to the Court what fetal tissue research is and the laws and protocols that govern it. This brief answers the following questions: what is fetal tissue research; what is the law regulating its use; and why is it such an important tool in the fight for public health?

ARGUMENT

I. What is Fetal Tissue Research?

Fetal tissue research is medical/scientific research conducted using tissue from non-living human fetuses that would be otherwise discarded. *See* The American Society for Cell Biology, *Facts About Fetal Tissue Research* at 2 (Mar. 2000). While the fetal tissue used in research generally comes from legal, voluntary, induced abortions, it may also be a product of a spontaneous abortion ("miscarriage"). *Id.*

However, tissue from spontaneous abortions is not an adequate substitute for tissue from voluntary abortions. *See* Amy Maxmen, *Fetal Tissue Probe Unsettles Scientific Community*, 34 Nature Biotechnology 447, 447-48 (May 2, 2016).

Because spontaneous abortions often are a result of fetal genetic abnormalities, the tissue does not provide the proper vehicle for most fetal research. *See* Congressional Research Service, *Fetal Tissue Research: Frequently Asked Questions*, 3 (July 31, 2015). And because spontaneous abortions are just that—spontaneous—they generally do not occur in settings where the fetal tissues can be properly gathered and preserved. *Id.* In the ordinary course, researchers obtain the tissue from large and small-scale medical facilities and non-profit tissue banks, at least three of which receive federal funding from the National Institutes of Health ("NIH"). *Id.*

A. Why Fetal Tissue and Not Adult, Animal or Computer-Generated Material?

1. What Makes These Cells Unique?

"Fetal tissues and cells cannot be replaced by embryonic stem cells, reprogrammed stem cells, or adult stem cells." Lawrence Goldstein, Ph.D., Statement Before the Select Investigative Panel of the Committee on Energy and Commerce, United States House of Representatives at 3 (Mar. 2, 2016) ("Goldstein Statement"). Fetal tissue is "a flexible, less-differentiated tissue . . . allowing researchers to study basic biology or use it as a tool in a way that can't be replicated with adult tissue." Meredith Wadman, *The Truth*

About Fetal Tissue Research, 528 Nature 181 (Dec. 10, 2015) (quoting Carrie Wolinetz, NIH Associate Director for Science Policy).

Specifically, many subpopulations of fetal cells are uniquely capable of rapidly dividing and growing in culture; some are also pluripotent, that is, capable of developing into any type of cell or tissue. *See* J.T. Hansen & J.R. Sladek, Jr., *Fetal Research*, 246 Science 775, 777 (Nov. 10, 1989). Fetal cells also have unique genetic programs that are not expressed in adult cells.

For these reasons, fetal cells alone make possible the scientific achievements described below. *See infra* Section III. Additionally, fetal cells are uniquely suited (and used) to screen new drugs to evaluate safety, particularly safety for use by pregnant women. *See* Hansen at 777. This ability to experiment and test enables drug development without risking another "thalidomide tragedy,"[4] and could not be accomplished with adult cells. *Id.*

[4] "One need only recall the thalidomide episode of the 1960s for a grim reminder of the need for careful fetal screening before drugs are administered to pregnant (and nursing) women. Maternal intake of the sedative thalidomide early in pregnancy, as reported in Germany and England, led to an unusually high incidence of limb-reduction deformities. Once thalidomide was recognized as the causative agent, it was withdrawn from the market, but not before an estimated 3,000 malformed infants were born." Hansen at 778.

Fetal tissue for research cannot be replaced by non-human tissue, or for that matter, computer-generated material. "[G]ene regulation—the finely tuned symphony that controls when and where genes are active—can vary strikingly between species, so findings in other animals often do not hold true in humans." Wadman at 180 (citing Neil Hanley, an endocrinologist at the University of Manchester, UK). Animals "differ from humans in size, appearance, longevity, physiology, and performance."[5] Harry Ostrer, *et al.*, *Human Embryo and Early Fetus Research*, 70 Clin Genet 98, 98-99 (Aug. 2006) (citations omitted). Professor Paul Fowler put it plainly: "I get very frustrated when misinformed people go on about how it can all be done with computer models or cell cultures or stem cells or animals. . . . In some areas, the human is absolutely dramatically different than rodents." Wadman at 180 (quoting Fowler, a reproductive biologist at the University of Aberdeen Institute of Medical Sciences in the United Kingdom who recently published a study using

[5] "Mouse, the most popular model, diverged from a common ancestor 75-80 million years ago. This divergence has led to important differences in anatomy, even at the earliest developmental stages, and in some important biochemical pathways . . . . The laboratory mouse does not produce monozygotic [identical] twins naturally. Some human mutations . . . seem not to occur spontaneously in mice. The high rate of chromosomal [abnormality] in human zygotes is not found in mice." Ostrer at 98-99.

tissues from the livers of aborted fetuses to study the impact of maternal smoking on fetal liver development).

2. Why Is There No Substitute for Fetal Tissue Research on Human Development and Treating Infants and Newborns?

In two areas in particular, there will likely *never* be a substitute for fetal tissue research: the study of early human development and why human development sometimes goes wrong; and the promotion of early infant health and fetal intervention.[6]

Scientists understand that "[h]uman fetal tissue is likely never going to be replaced in some areas of research, particularly relative to fetal development[] . . . [because] unless you understand normal you're not going to understand abnormal." Wadman at 180 (quoting Carrie Wolinetz, NIH associate director for science policy).

"By studying normal and abnormal development in fetal tissue, scientists will learn more about . . . mental retardation, Down Syndrome, SIDS [Sudden Infant Death Syndrome], and defective eye development." The American

[6] Fetal tissue may someday be replaced with other materials and methods in some limited and specific research. Like fetal tissue, flexible cell types including embryonic stem cells, induced pluripotent stem (IPS) cells, and lab-created organoids are also being used to grow new organs. See Cassandra Willyard, *The Boom in Mini Stomachs, Brains, Breasts, Kidneys and More*, 523 Nature Int'l Weekly J. of Science 520, 520-22 (July 29, 2015).

Society for Cell Biology at 2. An NIH-funded study is also "probing gene activity in cells lining the fetal intestine to help explain excessive intestinal inflammation in premature babies." Wadman at 180. "By learning more about fetal development, doctors will [] be better prepared to conduct fetal surgery [to address developmental disorders, and] . . . gain new understanding of why some pregnancies are spontaneously aborted." The American Society for Cell Biology at 2.

And "[t]he application of such work goes far beyond understanding developmental disorders such as congenital heart disease or other malformations" that appear at birth. Wadman at 180 (citing Neil Hanley, endocrinologist at University of Manchester). Indeed, "[t]he genes responsible for some diseases of later life, such as Alzheimer's, prostate cancer and Type II diabetes, may be activated during fetal development." The American Society for Cell Biology at 2. Research also suggests that schizophrenia may have origins during early stages of fetal growth. *See* Thomas R. Insel, M.D., *Rethinking Schizophrenia*, 468 Nature 187, 188 (Nov. 2010). Researchers are striving to understand these genes, and to either alter their trajectory or suppress them entirely, and fetal tissue is the only resource available for this important work. *See* Wadman at 180.

Fetal tissue is also irreplaceable for developing treatments for infants with deadly genetic disorders and viruses, including developing therapies that can be administered *in utero*. *See* Maxmen at 447-48. The fetal immune system is particularly vulnerable to viruses, and fetal tissue researchers are working on ways to cure virus-infected fetuses *in utero*.[7] In fact, researchers have successfully used "fetal [cadaver] cells [to] treat another fetus *in utero*." Hansen at 779. This work is vital to fetal health because waiting until birth to treat some viruses is too late; by that point some viruses will cause irreversible, catastrophic harm. *See* Maxmen at 447-48.

All of these "advances have brought us to the point where we no longer stand by helplessly in the face of fetal malformation, nor are we left impotent to respond to treatable disorders." Hansen at 775.

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[7] The study of fetal blood cells has shown that immune cells present before birth vary greatly from those present at birth. *See* M.O. Muench, E.M. Pott Bärtsch, J.C. Chen, J.B. Lopoo & A. Bárcena, *Ontogenic Changes in CD95 Expression on Human Leukocytes: Prevalence of T-Cells Expressing Activation Markers and Identification of CD95-CD45RO+ T-cells in the Fetus*, 27 Dev. Comp. Immunol. 899, 900 (Dec. 2003). As such, studying umbilical cord blood cells is no substitute for studying fetal cells. *Id.*

II. What Laws and Regulations Apply to Using Fetal Tissue for Research?

A. What is the History of Fetal Tissue Research Laws?

American scientists have used fetal tissue in a broad range of research since the 1930s (discussed *infra* at Section III); the NIH has funded fetal tissue research since the 1950s.

Fetal tissue research continued for decades without political or legislative regulation or interference. But after *Roe v. Wade*, 410 U.S. 113 (1973), fetal tissue research became a target for political activism. *See* L.M. Sanders, L. Giudice & T.A. Raffin, *Ethics of Fetal Tissue Transplantation*, 159(3) West J Med. 400, 402-03 (Sept. 1993). A year after *Roe*, Congress passed a moratorium on fetal tissue research for transplantation which remained in place for over fifteen years; other areas of fetal tissue research were not impacted.

In 1988 under President Reagan, the NIH appointed an advisory panel to evaluate the "ethical, legal, and scientific issues" surrounding fetal tissue research. Report of the Advisory Committee to the Director, NIH, *Human Fetal Tissue Transplantation Research* at 1 (Dec. 14, 1988) ("Advisory Report"). This committee was chaired by the Honorable Arlin M. Adams, a retired federal judge and notably, an opponent of abortion. *See* James F. Childress, *Deliberations of the Human Fetal Tissue Transplantation Research Panel*, Biomedical Politics,

National Academy Press 215, 218 (1991). After extensive public hearings and months of deliberation during President George H.W. Bush's administration, this panel concluded that the use of human fetal tissue in research, following deliberate abortions, is "*acceptable public policy*."[8] *Id.* at 215 (citing DHHS/NIH, 1988:2) (emphasis added).

In 1992, Congress passed—with overwhelming bipartisan support[9]—the NIH Revitalization Act, which specifically authorized federal funds to be used for fetal tissue research. *See* Heather D. Boonstra, *Fetal Tissue Research: A Weapon and a Casualty in the War Against Abortion*, 19 Guttmacher Policy Rev. 9, 11 (Feb. 9, 2016). The moratorium was overturned by Executive Order in 1993. *See* Sanders at 402.

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[8] The panel also recommended, consistent with rules promulgated by DHHS in 1975, that "the decision and consent to abort must precede discussion of the possible use of fetal tissue" so that "a woman's abortion decision would be insulated from inducements to abort to provide tissue for transplant research and therapy," Advisory Report at 2-3, and that there be a prohibition on "payments . . . associated with the procurement of fetal tissue . . . except payment for reasonable expenses" to ensure there would be "no offer of financial incentives or personal gain to encourage abortion or donation of fetal tissues." *Id.* at 2.

[9] The Senate's final vote was 85 to 12, and the House vote was 260 to 148. *See* U.S. Senate Roll Call Votes 102nd Congress - 2nd Session (June 4, 1992); Final Vote Results for Roll Call 147 (May 28, 1992).

B. What Is the Current Law on Fetal Tissue Research?

Federal and state law operate in tandem in the area of fetal tissue research. The current federal law has two main provisions, 42 U.S.C. § 289g-1 and § 289g-2. The first, section 289g-1, addresses federally funded research on "the transplantation of human fetal tissue for therapeutic purposes"; the second, section 289g-2, expressly permits clinics and institutions that donate fetal tissue to receive "reasonable payments associated with the transportation, implantation, processing, preservation, quality control, or storage of human fetal tissue" for all areas of fetal tissue research. In addition, researchers may not knowingly acquire fetal tissue from a pregnancy initiated to provide tissue for research. *See* 42 U.S.C. § 289g-2(c)(1).

States regulate fetal tissue research and research for transplantation under the Uniform Anatomical Gift Act (UAGA), a version of which is in effect in every state. *See* Boonstra at 11-12. This is the same law that governs adult organ transplantation. *See* Joseph L. Verheijde, Mohamed Y. Rady & Joan L. McGregor, *The United States Revised Uniform Anatomical Gift Act (2006): New Challenges to Balancing Patient Rights and Physician Responsibilities*, 2(19) Philos. Ethics & Humanit. in Med. at 2 (Sept. 2007). In thirty-eight states and the District of Columbia, the UAGA "explicitly treat[s] fetal tissue the same way as other human

tissue," allowing fetal tissue to be donated by a woman for research, therapy, or education. Boonstra at 12.[10] The other twelve states' laws are silent, neither allowing nor disallowing fetal tissue donation. *Id.*

III. What Role Has Fetal Tissue Research Played in Modern Health?

The list of diseases and health challenges which are now treatable and/or preventable because of fetal tissue research is long and extraordinary. It includes polio, rubella, measles, Hepatitis A, chickenpox, adenovirus, rabies, arthritis, cystic fibrosis, and hemophilia. Potential breakthrough areas include fatal blood diseases (sickle-cell anemia, aplastic anemia, and leukemia), nervous system disorders including optic nerve damage, degenerative disorders of the brain, and spinal cord damage. Hansen at 779.

A. What Role Has Fetal Tissue Research Played in Vaccine Development?

Vaccines are the key component of modern preventive medicine: "[I]t is always better to prevent a disease than to treat it after it occurs." CDC, *Why Are Childhood Vaccines So Important?* (last updated May 19, 2014). Vaccines have eradicated or virtually eradicated some of the world's deadliest diseases and have

[10] Of these, twelve states explicitly prohibit profiting from donation or transfer of fetal tissue for research, and eight states require the woman's consent for research. *See* Boonstra at 12.

saved and continue to save millions of lives. Fetal tissue research has played (and continues to play) a key role in the development of many common, critical vaccines.[11]

The polio vaccine was one of the first. Polio is a highly contagious virus; it can penetrate the brain and spinal cord, causing paralysis and death. *See* CDC, *A Polio-Free U.S. Thanks to Vaccine Efforts* (last updated July 27, 2015). Its impact was felt globally; it infected young and old, rich and poor, powerful and powerless alike. In the early 1950s, researchers, infecting fetal kidney cells in petri dishes, were able to grow a sufficient quantity of the virus to harvest and purify for vaccination. *See* Rush Holt, Letter on behalf of the American Association for the Advancement of Science ("AAAS")[12] to Chairwoman Marsha Blackburn and Select Investigative Panel, House Energy and Commerce Committee at 1-2 (Apr.

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[11] In the early 1930s, researchers developed vaccine candidates "using material taken from polio-infected monkeys, such as monkey spinal cords. These candidates proved to be dangerous, sometimes causing paralysis in the limb where the vaccine was administered . . . . The trials ceased, and researchers moved on with the goal of finding another way to grow the virus for vaccine development." The History of Vaccines, *Early Tissue and Cell Culture in Vaccine Development* (last updated Jan. 4, 2016). Only after they began trials on human embryonic tissue did researchers find success.

[12] AAAS is the world's largest general scientific society and publisher of *Science* Magazine. *See* AAAS Annual Report: Innovation, Information and Imaging at C2 (2015).

25, 2016) ("Holt Letter").[13] The polio vaccine has been heralded globally. Because of the vaccine, polio has been eliminated in the United States and virtually eliminated globally, saving over half a million lives. *See* CDC, *A Polio-Free U.S. Thanks to Vaccine Efforts*; Jason Beaubien, *Wiping Out Polio: How the U.S. Snuffed Out a Killer*, National Public Radio (Oct. 15, 2012).

The rubella vaccine was also developed using fetal tissue. "The most serious complication from rubella infection is the harm it can cause a pregnant woman's unborn baby. If an unvaccinated pregnant woman gets infected with rubella virus she can have a miscarriage, or her baby can die just after birth. Also, she can pass the virus to her unborn baby who can develop serious birth defects such as heart problems, loss of hearing and eyesight, intellectual disability, and liver or spleen damage." CDC, *Rubella* (last updated Jan. 19, 2016).[14] The

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[13] These researchers, John Enders, Thomas Weller, and Frederick Robbins, won the 1954 Nobel Prize in Physiology or Medicine for their work. *See* E. Norrby & S.B. Prusiner, *Polio and Nobel Prizes: Looking Back 50 Years*, 61 Ann. Neurol. 385, 385 (May 2007).

[14] On the heels of a massive rubella epidemic in the 1960s, a researcher isolated the rubella virus and used fetal tissue to let it replicate. "[T]he virus had been grown through the cells 25 times at [a] low[] temperature [until] it was no longer able to replicate enough to cause illness in a living person, but *was* still able to provoke a protective immune response." History of Vaccines, *Human Cell Strains in Vaccine Development* (last updated June 1, 2016). This vaccine has been in use since 1970, (Continued…)

vaccine eliminates the virus' risk to fetuses, "has prevented thousands [of] abortions[,]" and made a normal life possible for those who, if infected, would have been born with severe disabilities. Meredith Wadman, *Medical Research: Cell Division*, 498 Nature 422, 425 (June 26, 2013).

Fetal tissue research is responsible for other vaccines currently used, including measles, Hepatitis A, chickenpox, shingles, adenovirus (administered to all US military recruits), and rabies. *See* AAMC Statement in Support of Fetal Tissue Research (Mar. 18, 2016).[15]

B. What Role Does Fetal Tissue Research Play in the Treatment of Devastating Diseases?

Fetal tissue research has been instrumental not only in preventing illnesses, but also in treating illnesses. Contributions from fetal tissue research include a "blockbuster" arthritis drug and therapeutic proteins that fight cystic fibrosis and hemophilia. *See* Wadman at 179. Fetal thymus tissue has been successfully used to treat patients with DiGeorge Syndrome, an immune deficiency caused by the lack of thymus and parathyroid tissue at birth. *See* Sanders at 401. Scientists are

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and in 2004, the CDC declared rubella eliminated from the U.S. *See* CDC, *Pregnancy and Rubella* (last updated March 31, 2016).

[15] This list will likely grow. For example, fetal tissue is currently being used to develop an Ebola vaccine. *See* AAMC Statement.

at the clinical trial stage for a potential prenatal stem-cell therapy to treat osteogenesis imperfecta—a debilitating genetic condition also known as or brittle bone disease.[16] *See* Holt Letter at 2. Early tests conducted in Sweden and the United Kingdom are promising. *Id.*

C. Where Is the Future Opportunity For Fetal Tissue Research?

Scientists are confident that fetal tissue is key to more preventive medicine, new vaccines and identifying treatments for today's most devastating conditions; research continues, and its course is impacted by global health threats.

Zika, a current global health threat,[17] is "caused by the Zika virus, which is spread to people primarily through the bite of an infected *Aedes* species mosquito."

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[16] "The therapy involves the use of mesenchymal stem cells (MSCs) from donated fetal liver that is infused through an umbilical vein that directly treats bone development of the fetus before birth." Holt Letter.

[17] The global media has robust coverage of the Zika threat. *See, e.g.*, Sonja A. Rasmussen, MD, *et al.*, *Zika Virus and Birth Defects—Reviewing the Evidence for Causality* (Apr. 13, 2016); Amir Attaran, *Off the Podium: Why Public Health Concerns for Global Spread of Zika Virus Means That Rio de Janeiro's 2016 Olympic Games Must Not Proceed*, Harvard Pub. Health Rev. Special Commentary- Zika Virus and Public Health Concerns (May 2016); California Department of Public Health, *Public Health Reports First Confirmed Zika Virus Case Acquired Through Sexual Transmission in California* (Mar. 25, 2016); Donald G. McNeil, Jr., *et al.*, *Short Answers to Hard Questions about Zika Virus*, The New York Times (Mar. 18, 2016); Ariana E. Cha & Lena H. Sun, *What Is Zika? And What Are The Risks As It Spreads?*, The Washington Post (Feb. 4, (Continued…)

CDC, *About Zika Virus Disease* (last updated May 5, 2016). If a woman contracts the Zika virus during pregnancy, the infection "can cause a serious birth defect called microcephaly, as well as other severe fetal brain defects." *Id.* Scientists are using fetal tissue to understand both the effect of the virus on pregnant women and how Zika causes birth defects. *Id.* "Scientists studying Zika have gathered strong evidence about the disease and its potential association with birth defects through fetal tissue analysis." Mark S. DeFrancesco, MD,[18] American College of Obstetrics & Gynecology ("ACOG") Statement In Support of Fetal Tissue Research, (Mar. 30, 2016) ("ACOG Statement").

Through fetal tissue research, scientists can begin testing potential therapies and treatments for safety and efficacy. *Id.* "[W]e must use the full potential of science, including fetal tissue research, if we hope to develop a vaccine or a medicine that will allow us to prevent serious birth defects and even deaths in the future." *Id.* Just a few weeks ago, Professor Lawrence Goldstein, a neurobiologist at the University of California, San Diego, School of Medicine, testified before Congress that *not* having fetal tissue as a resource to study Zika "would absolutely

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2016); David Quammen, *Why Zika Virus Is This Year's Scary Virus*, National Geographic (Jan. 28, 2016).

[18] Dr. DeFrancesco is the President of ACOG for the 2015-2016 term. *See* ACOG Statement.

delay [finding a cure]." Mike DeBonis, *In First Hearing, GOP Panel Casts Doubt on Fetal Tissue Research*, The Washington Post (Mar. 2, 2016).

With our growing aging population, a cure or treatment for Alzheimer's disease research is vital. "This devastating disease afflicts millions of Americans and costs the United States billions of dollars a year in health care costs." Goldstein Statement at 3; *see* Harry Johns,[19] Testimony before the Fiscal Year 2014 Appropriations for Alzheimer's-Related Activities at DHHS, Subcommittee on Labor, Health and Human Services, Education and Related Agencies Committee on Appropriations, United States House of Representatives at 4 (Mar. 13, 2013) ("Johns Testimony"). Research using fetal astrocytes, "which is a support cell type in the brain[,]" is promising. Goldstein Statement at 4. Professor Goldstein uses these cells for Alzheimer's research in his own lab: "These fetal astrocytes provide growth factors that keep nerve cells healthy and other factors that are not yet defined that help the neurons establish connections and maintain long-term growth and viability. . . . The fetal astrocytes are vital to these investigations, which I think will help conquer the terrible scourge of Alzheimer's disease." *Id.* "[M]edical researchers have [also] explored the feasibility of grafted

[19] Harry Johns has been the President and CEO of the Alzheimer's Association since 2005. *See* Johns Testimony.

fetal nerve cells to restore damaged neural circuits" in Alzheimer's patients. Hansen at 778.

Fetal tissue research also holds promise in the treatment of Parkinson's disease. Parkinson's causes a degeneration of neurons that produce the neuro-transmitter dopamine, which is crucial for normal movement. Alison Abbott, *Fetal-Cell Revival for Parkinson's*, 510 Nature Int'l J. of Science 195, 195 (June 12, 2014). Therapies using fetal cells aim "to replace the missing neurons with dopamine-producing [] cells from fetal brains or with those derived from human stem cells." *Id.* Harvard Stem Cell Institute researchers have found that "fetal dopamine cells transplanted into the brains of patients with Parkinson's disease were able to remain healthy and functional for up to 14 years, a finding that could lead to new and better therapies for the illness." *Id.* To achieve this end, the "fetal cell is the gold standard." *Id.* (citing neurologist Claire Henchcliffe, MD from the Weill Cornell Medical Center in New York).

And fetal tissue research is thought to be critical to developing an HIV/AIDS vaccine. The portion of NIH funding dedicated to this– more than one third of NIH funding for fetal tissue research—underscores its importance and promise. *See* Boonstra at 10. Due to the flexibility and adaptability of fetal tissue, and its rich supply of stem cells, researchers have developed a "new generation of

humanized mice [that] is rapidly opening new opportunities for pre-clinical and basic HIV research." Paul W. Denton, Ph.D. and J. Victor Garcia, Ph.D., *Novel Humanized Mouse Models for HIV Research*, 6 Curr. HIV/AIDS Rep. 1, 19 (Feb. 2009). The accessibility of these models to many investigators will certainly accelerate HIV/AIDS research. *See* Wadman at 178-81. The humanized mice are also key to research into hepatitis B and C; the mice help researchers to understand "how the viruses evade the human immune system and cause chronic liver diseases." *Id.*[20]

The past successes of fetal tissue research promise future breakthroughs; in addition to those described above, fetal tissue research has led to investigational therapies for end stage breast cancer and advances against cardiac causes. *See* R. Alta Charo, *Fetal Tissue Fallout*, 370(10) New Engl. J. Med. 890, 891 (Aug. 12, 2016). Fetal pancreatic islet cells are being pursued to treat diabetes. *Id.* And future goals for fetal tissue research include combatting ALS, spinal cord injuries,

[20] Other NIH-funded fetal tissue grants focus on developmental biology (ranging from the differentiation of myoblasts (the embryonic precursors to muscle cells) to development of the urogenital tract to gene activity in cells lining the fetal intestine that causes excessive intestinal inflammation in babies), eye development and disease, other infectious diseases, type 1 diabetes, *in utero* diseases, toxic exposures, and congenital conditions. *See* NIH Research Portfolio Online Reporting Tools, Funding: Project Listed by Category (last updated July 8, 2015).

macular degeneration (the most common cause of adult blindness), and building new organs.[21] *See id.*, Goldstein Statement at 5-6.

CONCLUSION

The District Court's order properly found that the public interest weighs in favor of granting the preliminary injunction. Fetal tissue research is legal, it is vital, and it is plainly in the public interest. *Amici* urge the Court to, like the District Court, accord that public interest factor great weight, and affirm the District Court's decision.

Dated: June 7, 2016 CROWELL & MORING LLP

/s/ Laura Schwartz
Laura Schwartz
Attorneys for *Amicus Curiae*
[signature block continued on next page]

[21] Organ building is particularly important to the 93,000 Americans on waiting lists for kidney transplants. *See* Goldstein Statement at 5-6. "Fetal tissue that would otherwise be discarded is vital to the future of this investigation as it is only by examining this fetal tissue that it will be possible to determine the earliest biochemical signals that cells use to tell some cells to make kidneys and other cells to make other organs." *Id.* at 3.

Erez Aloni
Hazel Beh
Ann Bonham
R. Alta Charo
Wendy K. Chung
F. Sessions Cole
Ron Clyman
Mitchell Creinin
Judith Daar
Gillian Dean
Jeffrey Dicke
Eleanor Drey
Jeffrey Ecker
Maxine Eichner
David Eisenberg
Mark I. Evans
Eric Feldman
Susan J. Fisher
Renée C. Fox
Arupa Ganguly
Steven Goldman
Rudolf Jaenisch
Bliss Kaneshiro
Jennifer Kerns
Antonella Lavelanet
Sylvia Law
David H. Ledbetter
Christopher Mason
Joseph M. McCune
Marcus Muench
David Mutch
Kim Mutcherson
Vivek R. Nerurkar
Mark Nichols
Siripanth Nippita
Robert Nussbaum
Paul Offit
David Orentlicher
Harry Ostrer
Maureen Paul
Sarah Prager
Maura Quinlan
Radhika Rao
Hope Riccioti
John A. Robertson
M. Elizabeth Ross
Jennifer Salcedo
Robert Schwartz
Nathaniel Snyder
Reni Soon
Phillip Stubblefield
Jennifer Tang

Appendix A
Amici Curiae

Institutional affiliations appear only for purposes of identification, and not as an indication of institutional support for the content of this *amici curiae* brief.

1. **Erez Aloni**: Dr. Aloni is an Assistant Professor at Whittier Law School. His scholarship focuses on the legal regulations surrounding the lives of the family. Dr. Aloni previously held the Center for Reproductive Rights Fellowship at Columbia Law School.

2. **Hazel Beh**: Dr. Beh, Ph.D., is a Professor of Law, Carlsmith Ball Faculty Scholar, and Co-Director of the Health Law Policy Center at the William S. Richardson School of Law at the University of Hawaii at Manoa. She previously clerked for Chief Justice Herman Lum of the Hawaii Supreme Court.

3. **Ann Bonham**: Dr. Bonham is the former Chief Scientific Officer of the Association of Medical Colleges (AAMC), where she directed the AAMC's array of programs that support all aspects of research and training. She was previously the Executive Associate Dean for Academic Affairs and Professor of Pharmacology and Internal Medicine at the University of California, Davis, School of Medicine.

4. **R. Alta Charo**: Ms. Charo is the Warren P. Knowles Professor of Law and Bioethics at the University of Wisconsin at Madison, where she is on the faculty of the Law School and the Department of Medical History and Bioethics at the Medical School. She was a member of President Clinton's National Bioethics Advisory Commission and was most recently a witness for the congressional panel on fetal tissue research. Ms. Charo is a member of the National Academy of Medicine.

5. **Wendy K. Chung**: Dr. Chung is a board certified geneticist and the Kennedy Family Associate Professor of Pediatrics in Medicine at Columbia University Medical College, where she is also the Director of the Clinical Genetics Program, Clinical Cancer Genetics program, and the Director of the fellowship program in Cytogenetics and Molecular Genetics.

6. **F. Sessions Cole**: Dr. Cole is the Park J. White, M.D., Professor of Pediatrics and Chief Medical Officer at St. Louis Children's Hospital, where he also serves as the Assistant Vice Chancellor for Children's Health, the Director of

the Division of Newborn Medicine, and the Interim Director for Pediatric Critical Care Medicine.

7. **Ron Clyman**: Dr. Clyman is a Professor of Pediatrics, Associate Director of the Pediatric Clinical Research Center, and a member of the Cardiovascular Research Institute at the University of California, San Francisco School of Medicine. Dr. Clyman is a member of the Society for Pediatric Research (SPR) and the American Pediatric Society (APS).

8. **Mitchell Creinin**: Dr. Creinin is a Professor and Director of Family Planning in the Department of Obstetrics and Gynecology at the University of California, Davis. He has received research funding from the NIH, USAID, WHO, CDC, private foundations and industry. Dr. Creinin is a founding member of the Society of Family Planning and served on the Executive Board from 2004-2011, including as Society President from 2007-2009.

9. **Judith Daar**: Ms. Daar is a Professor of Law at Whittier Law School and a Clinical Professor of Medicine at the University of California, Irvine (UCI), School of Medicine. She is Chair of the American Society for Reproductive Medicine Ethics Committee and a member of the UCI Medical Center Medical Ethics Committee, where she serves on the Bioethics Consultation Team. She has also served as a member of the Harbor-UCLA Hospital Institutional Review Board, and the ABA Coordinating Group on Bioethics.

10. **Gillian Dean**: Dr. Dean is an Associate Professor in Obstetrics and Gynecology and the Director of the Fellowship in Family Planning at the Icahn School of Medicine at Mount Sinai Hospital in New York City. She is also the Physician Director of Clinical Research Planned Parenthood of New York City.

11. **Jeffrey Dicke**: Dr. Dicke is a Professor of Obstetrics and Gynecology and the Vice Chair of Imaging at Washington University in St. Louis, School of Medicine. His subspecialty is Maternal-Fetal Medicine. He is a member of the National Medical Committee of the Planned Parenthood Federation of America.

12. **Eleanor Drey**: Dr. Drey is the Medical Director of the Women's Options Center at Zuckerberg San Francisco General Hospital and a Professor in the Department of Obstetrics, Gynecology and Reproductive Sciences at the University of California, San Francisco.

13. **Jeffrey Ecker**: Dr. Ecker is the Chief of the Department of Obstetrics and Gynecology at Massachusetts General Hospital and a Professor at Harvard Medical School. He is a former Chair of both the Committee on Ethics and the

Committee on Obstetric Practice for the American College of Obstetricians and Gynecologists.

14. **Maxine Eichner**: Dr. Eichner, Ph.D., is the Reef C. Ivey II Professor of Law at the University of North Carolina School of Law, focusing on family relationships, social welfare law and policy; feminist theory; sexuality; and the relationship of the family, the workplace, and market forces.

15. **David Eisenberg**: Dr. Eisenberg, a board certified obstetrician and gynecologist, is an Associate Professor in the Department of Obstetrics and Gynecology, Divisions of Family Planning and Clinical Research at Washington University in St. Louis, School of Medicine.

16. **Mark I. Evans**: Dr. Evans is President of the Fetal Medicine Foundation of America, Professor of Obstetrics & Gynecology at Mt. Sinai School of Medicine, President of the International Fetal Medicine and Surgery Society Foundation, and President of Comprehensive Genetics, PLLC. He has multiple NIH grants including one as principal investigator for the search for fetal cells in maternal blood.

17. **Eric Feldman**: Dr. Feldman, Ph.D., is a Professor of Law at the University of Pennsylvania Law School, focusing on Japanese law, comparative public health law, torts, bioethics, and law and society. He has received grants and fellowships from the Robert Wood Johnson Foundation, the American Bar Association, the National Science Foundation, and the Social Science Research Council.

18. **Susan J. Fisher**: Dr. Fisher, Ph.D., is a Professor in the Department of Obstetrics, Gynecology and Reproductive Sciences, School of Medicine, University of California, San Francisco (UCSF). She is jointly appointed in the Department of Anatomy. Dr. Fisher is the Director of the UCSF Human Embryonic Stem Cell Program and Faculty Director of the Sandler-Moore Mass Spectrometry Core Facility.

19. **Renée C. Fox**: Dr. Fox, Ph.D., is Professor Emerita in Sociology, the Annenberg Professor Emerita of the Social Sciences, and an Emerita Senior Fellow of the Center for Bioethics at the University of Pennsylvania. She is a member of the American Academy of Arts and Sciences, the American Philosophical Society, and the Institute of Medicine of the National Academy of Sciences, and is a Fellow of the American Association for the Advancement of Science.

20. **Arupa Ganguly**: Dr. Ganguly is a Professor of Genetics and the Director of the Genetic Diagnostic Laboratory at the Hospital of the University of Pennsylvania. Her research is in the area of two eye cancers – retinoblastoma, a childhood onset cancer, and uveal melanoma, an adult onset cancer.

21. **Steven Goldman**: Dr. Goldman is the University of Rochester Medical Center Distinguished Professor of Neuroscience and Neurology, Chief of the Department's Division of Cell and Gene Therapy, and Co-Director of Rochester's Center for Translational Neuromedicine at University of Rochester Medical Center. He holds additional appointments as a Professor of Neurosurgery and as the Dean Zutes Chair in Biology of the Aging Brain, is a former chairman of Neurology at Rochester, and has a joint appointment as Professor of Neuroscience at the University of Copenhagen in Denmark.

22. **Rudolf Jaenisch**: Dr. Jaenisch is a Professor of Biology at MIT, where he is also a founding member of the Whitehead Institute. His research focuses on understanding epigenetic regulation of gene expression. He was appointed to the National Academy of Sciences in 2003.

23. **Bliss Kaneshiro**: Dr. Kaneshiro is an Associate Professor in the Department of Obstetrics and Gynecology at the University of Hawaii John A. Burns School of Medicine, where she is also Co-Director of the Fellowship in Family Planning and Director of the Division of Family Planning. She is also the Medical Director of Family Planning for the Hawaii State Department of Health.

24. **Jennifer Kerns**: Dr. Kerns is an Assistant Professor in the Department of Obstetrics, Gynecology and Reproductive Sciences at the University of California, San Francisco School of Medicine. She is also the Director of Research of the Women's Options Center at Zuckerberg San Francisco General Hospital.

25. **Antonella Lavelanet**: Dr. Lavelanet is an Instructor of Medicine in the Department of Obstetrics and Gynecology at the Boston University School of Medicine. Board certified in obstetrics and gynecology, she also holds a law degree and a Master's degree in public health.

26. **Sylvia Law**: Ms. Law is the Elizabeth K. Dollard Professor of Law, Medicine and Psychiatry at New York University School of Law. In 1984, Ms. Law became the first lawyer in the United States selected as a MacArthur Prize Fellow. In 2004, she was elected to the American Academy of Arts and Sciences.

27. **David H. Ledbetter**: Dr. Ledbetter is the Executive Vice President and Chief Scientific Officer of the Geisinger Health System. He was previously the Robert W. Woodruff Professor and Director of the Division of Medical Genetics in the Department of Human Genetics at Atlanta's Emory University School of Medicine. Dr. Ledbetter previously held academic and leadership positions at the University of Chicago, the National Center for Human Genome Research (now NHGRI) at NIH and Baylor College of Medicine.

28. **Christopher Mason**: Dr. Mason is an Associate Professor in the Department of Physiology and Biophysics at the Institute for Computation Biomedicine at Weill Cornell Medical College at Cornell University. He is also a WorldQuant Foundation Research Scholar, and an Affiliate Fellow of Genomics, Ethics, and Law at the Information Society Project at Yale Law School.

29. **Joseph M. McCune**: Dr. McCune is a Professor of Medicine and Chief of the Division of Experimental Medicine at the University of California, San Francisco School of Medicine. He is board certified in internal medicine. He was awarded the Elizabeth Glaser Pediatric AIDS Foundation Scientist Award in 1996, the Burroughs Wellcome Fund Clinical Scientist Award in Translational Research in 2000, a MERIT Award from the NIH in 2001, and the NIH Director's Pioneer Award in 2004.

30. **Marcus Muench**: Dr. Muench is a Senior Scientist in the Cell Therapy Core at the Blood Systems Research Institute in San Francisco, focusing on the development of new cellular therapies, mostly for prenatal and neonatal transplantation.

31. **David Mutch**: Dr. Mutch is the Ira C. and Judith Gall Professor of Obstetrics and Gynecology and the Vice Chair of Gynecology at the Washington University in St. Louis, School of Medicine. He is on the Editorial Board of *Gynecologic Oncology* and *Journal of the Society of Gynecologic Investigation*.

32. **Kim Mutcherson**: Ms. Mutcherson is a Professor and the Vice Dean at Rutgers Law School. She has been a fellow with the Rutgers Institute for Research on Women/Institute for Women's Leadership Interdisciplinary Seminar on Health and Bodies and a board member for the Women's Law Project in Philadelphia.

33. **Vivek R. Nerurkar**: Dr. Nerurkar is a Professor and Chair of the Department of Tropical Medicine, Medical Microbiology and Pharmacology and the Director of the Biocontainment Facility at the University of Hawaii John A.

Burns School of Medicine. Dr. Nerurkar's major area of research interest is in infectious diseases.

34. **Mark Nichols**: Dr. Nichols is a Professor in Obstetrics and Gynecology at Oregon Health and Sciences University, where he previously served as the Chief of the Division of General Gynecology and Obstetrics for 25 years. He served as the Medical Director of Planned Parenthood of the Columbia/Willamette (PPCW) for 19 years. He has worked with several NGOs in family planning programs internationally and most recently served as a Visiting Professor in the Obstetrics and Gynecology Department at Mekelle University, Ethiopia.

35. **Siripanth Nippita**: Dr. Nippita is an Instructor in Obstetrics, Gynecology, and Reproductive Biology at Harvard Medical School and serves as the Director of the Ryan Residency Training Program at Beth Israel Deaconess Medical Center.

36. **Robert Nussbaum**: Dr. Nussbaum, a board certified internist and medical geneticist who specializes in the care of adults with hereditary disorders, was for nine years the Holly Smith Professor of Medicine and Chief of Genomic Medicine at University of California, San Francisco (USCF) Medical Center until August 2015 when he transitioned to emeritus status and became Chief Medical Officer at Invitae. Prior to joining UCSF, Dr. Nussbaum was chief of the Genetic Disease Research Branch of the National Human Genome Research Institute.

37. **Paul Offit**: Dr. Offit is the Director of the Vaccine Education Center and a Professor of pediatrics in the Division of Infectious Diseases at The Children's Hospital of Philadelphia. He is the Maurice R. Hilleman Professor of Vaccinology at the Perelman School of Medicine at the University of Pennsylvania. Dr. Offit was a member of the Advisory Committee on Immunization Practices to the Centers for Disease Control and Prevention.

38. **David Orentlicher**: Dr. Orentlicher is Samuel R. Rosen Professor and Co-Director of the Hall Center for Law and Health at the Indiana University Robert H. McKinney School of Law. He is also an Adjunct Professor of Medicine at Indiana University School of Medicine. Dr. Orentlicher previously served as Director of the Division of Medical Ethics at the American Medical Association for six-and-a-half years and was a member of the Indiana House of Representatives from November 2002 to November 2008.

39. **Harry Ostrer**: Dr. Ostrer is a Professor of Pathology and Pediatrics at the Albert Einstein College of Medicine, with research focusing on the use of modern genomics to help understand the roles of human genetic variation in the progression of disease and the individual responses to therapies.

40. **Maureen Paul**: Dr. Paul is Director of the Family Planning Division at Beth Israel Deaconess Medical Center in Boston, and Associate Professor in the Department of Obstetrics, Gynecology and Reproductive Biology at Harvard Medical School. She previously served as Medical Director at Planned Parenthood affiliates in Massachusetts, San Francisco, and New York City, where she oversaw the affiliates' clinical, training and research programs. She currently serves on the Board of Directors for the Society of Family Planning.

41. **Sarah Prager**: Dr. Prager is an Associate Professor in the Department of Obstetrics and Gynecology at the University of Washington School of Medicine, where she is also the Director of the Family Planning Division and Family Planning Fellowship. She is board certified with the American Board of Obstetrics and Gynecology.

42. **Maura Quinlan**: Dr. Quinlan is an Assistant Professor in Obstetrics and Gynecology at the Northwestern University Feinberg School of Medicine. She is also Chair, Illinois Section of the American Congress of Obstetricians and Gynecologists (ACOG).

43. **Radhika Rao**: Ms. Rao is a Professor of Law at the University of California, Hastings College of the Law, where she teaches and writes in the areas of biolaw, constitutional law, comparative constitutional law, and property. Ms. Rao was a member of the California Advisory Committee on Human Cloning, and currently serves as a member of the California Human Stem Cell Research Advisory Committee. She previously clerked for Judge Cudahy at the United States Court of Appeals for the Seventh Circuit and Justices Harry Blackmun and Thurgood Marshall at the United States Supreme Court.

44. **Hope Riccioti**: Dr. Ricciotti is both Chair and Residency Program Director in the Department of Obstetrics and Gynecology at Beth Israel Deaconess Medical Center in Boston and is an Associate Professor at Harvard Medical School. Dr. Ricciotti is co-chair of the Resident as Teacher Interest Group for the Harvard Medical School Academy, the obstetrician/gynecologist Clerkship Committee chair for Harvard Medical School, and a member of the Harvard Medical School Curriculum Committee.

45. **John A. Robertson**: Mr. Robertson is the Vinson and Elkins Chair at The University of Texas School of Law at Austin. He has served on or been a consultant to many national bioethics advisory bodies, and is currently Chair of the Ethics Committee of the American Society for Reproductive Medicine. He was a member of the National Institutes of Health Panel on Fetal Tissue Transplantation Research.

46. **M. Elizabeth Ross**: Dr. Ross is the Nathan Cummings Professor of Neurology and Neuroscience at Weill Cornell Medical College, where she also directs the Center for Neurogenetics in the Brain and Mind Research Institute, which supports research into the genetic causes of neurological disorders in children and adults.

47. **Jennifer Salcedo**: Dr. Salcedo is the Associate Residency Program Director and Family Planning Course Director in the Obstetrics & Gynecology Department at the University of Hawaii, where she also serves as an Associate Professor.

48. **Robert Schwartz**: Mr. Schwartz is a Senior Visiting Professor at University of California, Hastings College of the Law and a Visiting Professor (Psychiatry) at University of California, San Francisco. He is also Weihofen Professor of Law Emeritus at the University of New Mexico. He was President of the ACLU of New Mexico from 1995 to 2000, and has served as Chair of New Mexico's Health Policy Commission and General Counsel to the State's Human Services Department. He began his legal career as law clerk to the High Court of American Samoa in Pago Pago.

49. **Nathaniel Snyder**: Dr. Snyder is an Assistant Professor at the A.J. Drexel Autism Institute. He uses fetal tissue in his research on identifying and measuring modifiable risk factors for autism spectrum disorder. Dr. Snyder staffs the Exposure Science Lab at the Autism Institute.

50. **Reni Soon**: Dr. Soon is an Assistant Professor in the Department of Obstetrics, Gynecology, and Women's Health at the University of Hawaii John A. Burns School of Medicine, where she is also the Co-Director of the Fellowship in Family Planning. She is the Hawaii Medical Director at Planned Parenthood.

51. **Phillip Stubblefield**: Dr. Stubblefield is Emeritus Professor of Obstetrics and Gynecology at the Boston University School of Medicine. He has maintained an association with the Planned Parenthood League of Massachusetts,

serving as Board Member, Board President, and most recently as Interim Medical Director.

52. **Jennifer Tang**: Dr. Tang is an Assistant Professor in the Division of Global Women's Health in the Department of Obstetrics & Gynecology at the University of North Carolina. She has been based at UNC Project-Malawi in Lilongwe, Malawi since August 2012 and is an Honorary Lecturer in the Department of Obstetrics and Gynecology at the Malawi College of Medicine.

CERTIFICATE OF SERVICE

I hereby certify that on June 7, 2016, I electronically filed the foregoing *Amicus Curiae* brief with the Clerk of the Court for the United States Court of Appeals for the Ninth Circuit by using the CM/ECF system. I certify that all participants in the case are registered CM/ECF users and that service will be accomplished by the CM/ECF system.

Dated: June 7, 2016 CROWELL & MORING LLP

s/ Laura Schwartz
Laura Schwartz
Attorneys for *Amici Curiae*

TABLE OF CONTENTS

Page

TABLE OF CONTENTS

Page

TABLE OF CONTENTS

Page

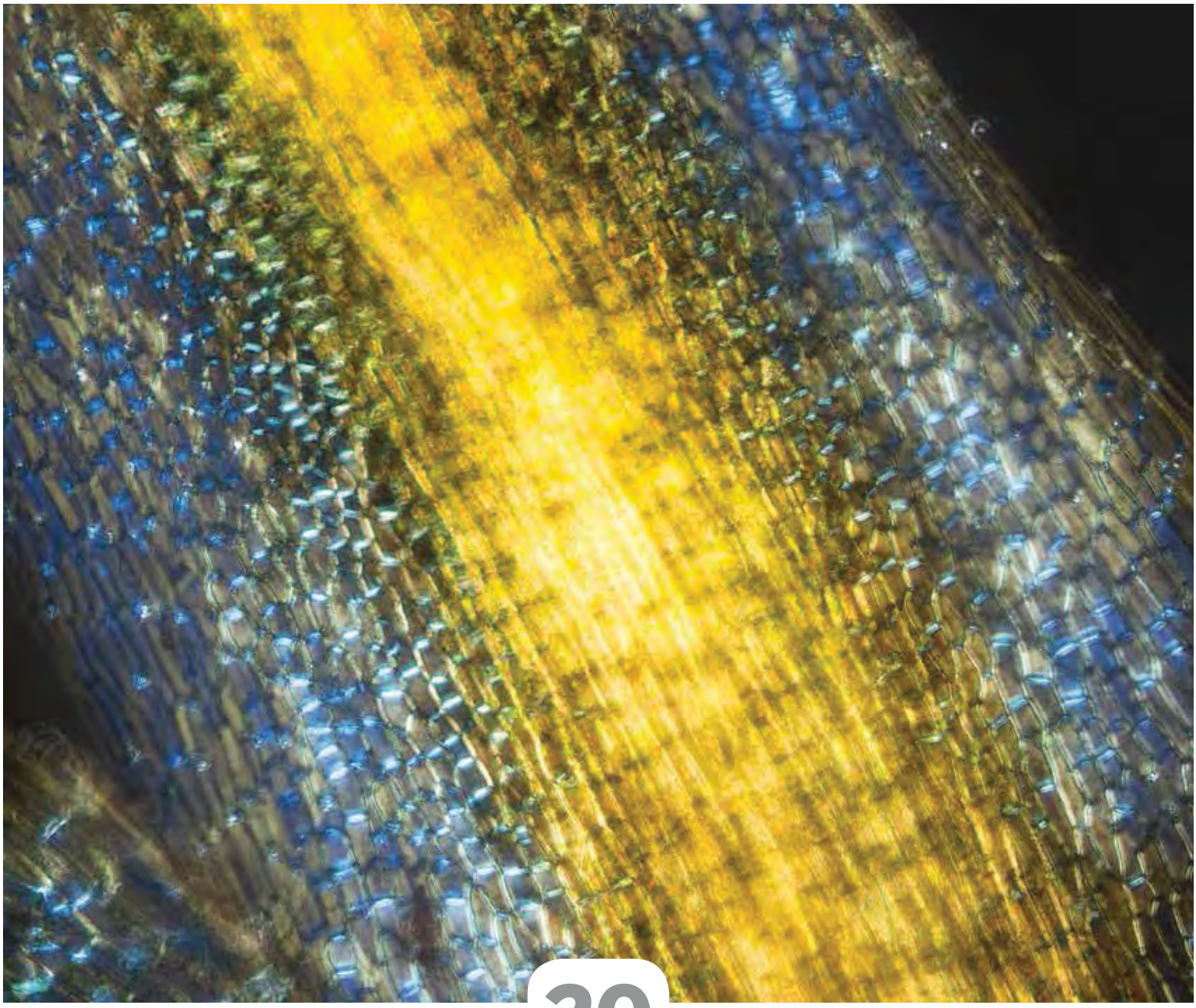
TABLE OF CONTENTS

Page

TABLE OF CONTENTS

Page

AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE



2015

ANNUAL REPORT

INNOVATION, INFORMATION, AND IMAGING

AAAS

AAAS

The American Association for the Advancement of Science (AAAS) is the world's largest general scientific society and publisher of the journal *Science* (www.sciencemag.org) as well as *Science Translational Medicine*, *Science Signaling*, a digital, open-access journal, *Science Advances*, and beginning in 2016, two new journals—*Science Robotics* and *Science Immunology*. AAAS was founded in 1848 and includes some 250 affiliated societies and academies of science, serving 10 million individuals. *Science* has the largest paid circulation of any peer-reviewed general science journal in the world. The non-profit AAAS (www.aaas.org) is open to all and fulfills its mission to "advance science and serve society" through initiatives in science policy, international programs, science education, public engagement, and more. For the latest research news, log onto EurekAlert! (www.eurekalert.org), the premier science-news website, a service of AAAS.

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▶ On the Cover:
Polarizing micrograph of leaf cells from *Diphyscium* moss.

PHOTO: ADOBE STOCK IMAGES

◀ *Diphyscium foliosum,* a leafy moss, thrives across eastern North America.

PHOTO: HERMANN SCHACHNER

[FSC MixedSources logo / Rainforest Alliance Certified / 100 percent green power logo] PRINTER WILL ADD

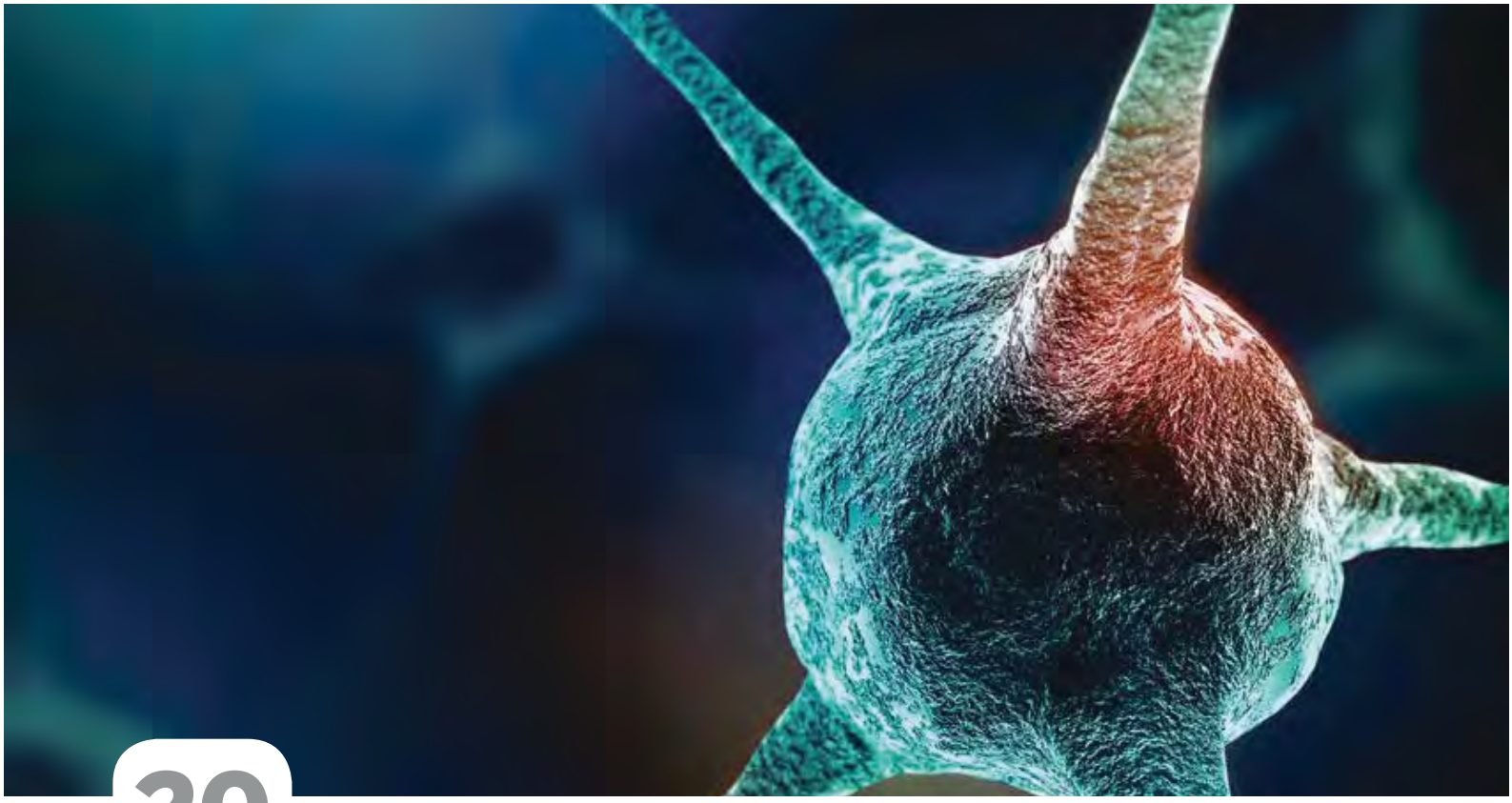

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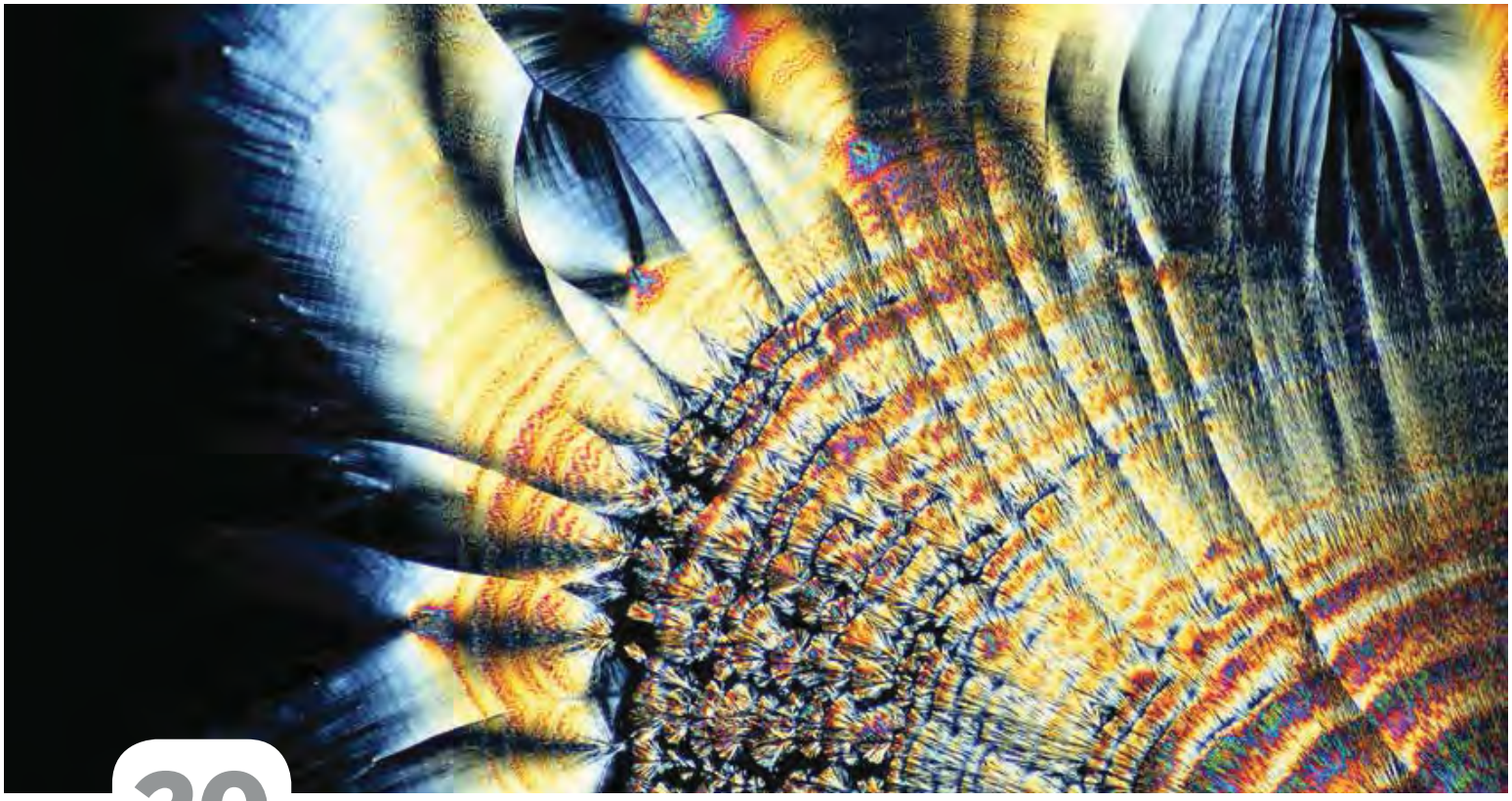
Table of Contents



2015 Welcome

Through microscopes and telescopes, new scientific and engineering insights allow us to see worlds we never knew existed, and drive innovation to improve people's lives. The blurry microscopes of the 1920s gave way to a revolution in imaging that vividly revealed 46 human chromosomes, making it possible to identify the cause of genetic conditions such as Down's syndrome. The sequencing of the human genome, coupled with the power of computer-generated pattern recognition, uncovered the genetic flaws that cause diverse childhood leukemias, many of which are now treatable.

AAAS and the *Science* family of journals are working to further such scientific progress by advocating for the research enterprise, and by bringing scientists and engineers together worldwide to address urgent societal concerns. As part of an ambitious Transformation Initiative, AAAS in 2015 began focusing more intensively on advocacy and service to members. We spoke out against barriers to women in science, for example, and we helped scientists and engineers more effectively communicate key scientific findings. We also worked to improve science education, and we engaged directly with the public, through such events as Family Science Days. AAAS has transformed its journals, too, by adopting digital-first strategies to enhance scientific communication. Trellis, a new digital communication and collaboration platform, is being developed to make it easy for individuals, collaborations, and organizations to work together and share scientific information.

AAAS exerts a unique influence by informing the public and our representatives about the importance of science to our nation and the world. As part of those efforts, the association advocates for science diplomacy and international research collaboration while promoting inclusiveness and diversity in science. In 2015, for instance, the association administered travel awards for women scientists participating in an international Gender Summit, through a National Science Foundation (NSF) program, Mentoring Women in International Research Collaborations (MWIRC) in STEM. Also in 2015, AAAS built upon its historic 2014 agreement with the Cuban Academy of Sciences. Collaboration across three fields of neuroscience, supported by the Lounsbery Foundation and others, will result in a scientist-exchange program between the two countries (see pages 12-13).

Vitamin C ascorbic acid crystals displayed on a microscope glass slide.

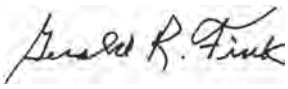
PHOTO: ADOBE STOCK IMAGES

To further encourage inclusiveness and reward innovation globally, AAAS in 2015 launched the Marion Milligan Mason Awards, honoring early-career women in the chemical sciences (page 31), and it again administered the Global Innovation through Science and Technology (GIST) competition, a U.S. State Department effort to encourage young entrepreneurs (13). AAAS provided essential recognition for talented journalists who communicate scientific advances and issues to the public, too: For the first time since 1945, the historic AAAS Kavli Science Journalism Awards program (9 and 35) expanded to accept international entries, thanks to a generous doubling by The Kavli Foundation of the program's endowment. The AAAS Mass Media Science and Engineering Fellows program, dating to 1974, also continued to promote excellence in science journalism, by dispatching science and engineering scholars to newsrooms (27).

Communicating the scientific reality of global climate change was the focus of a policy briefing on Capitol Hill and a related AAAS symposium, hosted by the Carnegie Institution for Science. "Climate Science, 50 Years Later," supported by the American Meteorological Society and the Linden Trust for Conservation, commemorated the 50th anniversary of the first official climate-change warning to a U.S. President and reaffirmed the 2014 AAAS *What We Know* report. The symposium also marked the launch of the Alan I. Leshner Leadership Institute, which announced the first cohort of 15 fellows—all climate scientists with an interest in promoting science-society dialogue. The Leshner Leadership Fellows will be supported by the AAAS Center for Public Engagement with Science and Technology, and the association's popular Communicating Science workshops, which have provided training for more than 6,700 scientists and engineers since 2008 (9).

AAAS advocacy work in 2015 included strong opposition to ideological attacks on climate-change scientists and their findings, a call for research to better understand the root causes of gun violence, media interviews on the value of federal investments in science, and more (4-7). Our advocacy efforts were bolstered by programs that help to bring scientific insight to the policymaking process. These included the association's well-respected analysis of U.S. research and development funding trends (18), and the AAAS Science & Technology Policy Fellowships, which in 2015 sent 280 scientists and engineers to work with Congress and many executive-branch agencies or departments as well as the Bill and Melinda Gates Foundation (15). To prepare the next-generation of civic-minded innovators, AAAS also supported a wide range of capacity-building programs, from efforts to improve K-12 science curriculum, to the NSF's Emerging Researchers National Conference in STEM (24-27).

In 2015, scientific reports published by the growing *Science* family of journals—including *Science Translational Medicine*, *Science Signaling*, the open-access journal *Science Advances*, and coming soon, *Science Robotics* and *Science Immunology*—described a promising new melanoma vaccine trial, an enhanced lithium-air battery design, genetic tools to combat elephant poaching, a new hominin mandible that raised fascinating questions about human evolution, and much more. (Incidentally, a 2015 *Science Advances* study on the sixth mass extinction made its way into the top 5% of all research outputs ever tracked on Altmetric.com, a metrics reporting site for scholarly content.) Every member of AAAS plays an integral role in accelerating such advances, by supporting the association's nonprofit programs, advocacy work, and scientific communication. AAAS members and donors allow us to serve as a voice and force for science worldwide, helping us to advance science in service to society.



Gerald R. Fink
AAAS Chair (2015-2016)
Margaret and Herman Sokol Professor of Genetics, Massachusetts Institute of Technology/Whitehead Institute

Rush D. Holt
AAAS CEO and Executive Publisher of the *Science* Family of Journals

(PHOTO: CHET SUSSLIN/*NATIONAL JOURNAL*)

2015 Public Statements on Key Issues

AAAS continued in 2015 to advocate for the scientific enterprise through testimony, letters to policymakers, op-ed articles, and other outreach efforts. In particular, the association urged adequate, sustained U.S. federal support for research and development; action to address global climate change; broader international research cooperation; advances in science education; and more.

Advocacy for the Scientific Enterprise

21 April. In a letter to U.S. policymakers, AAAS expressed concern about the America COMPETES Act, noting that it did not follow key principles for steady and sustained real growth in the major federal research agencies. AAAS had earlier teamed up with other organizations to develop a set of Guiding Principles for reauthorization of the COMPETES Act. The AAAS letter urged policymakers to reconsider language that seemed to restrict the National Science Foundation's ability to build new major research facilities, while barring Department of Energy-supported research from being used in evidence-based federal policymaking.

21 April. Responding to a U.S. Government Accountability Office report on the detrimental impacts of policies that have prevented many federal employees from participating in scientific conferences, AAAS and dozens of other leading organizations decried the restrictions: "Current policies are reducing government scientists' and engineers' participation in scientific and technical conferences while the administrative cost of overseeing these activities has *increased* significantly," the group wrote to top policymakers.

27 April. AAAS President Geraldine Richmond expressed deep concerns about unintended

consequences of the Secret Science Reform Act of 2015, in a letter to policymakers. Language in the legislation would prevent the Environmental Protection Agency from using research conducted during one-time events such as the Deepwater Horizon oil spill, she noted. The legislation would also require a level of reproducibility that would be impossible for very long-term studies, which are usually tested and verified using statistical modeling. While transparency and high research standards are essential, Richmond said, unrealistic requirements could have a chilling effect on research, and increase costs. Earlier in 2015, AAAS and more than two-dozen other organizations sent a similar letter to the U.S. House Majority Whip. Richmond also wrote to the Chairman of the House Science, Space, and Technology Committee about the same issue.

1 June. Gerry Fink, AAAS chair, wrote to policymakers to oppose appropriations language that singled out four National Science Foundation (NSF) research directorates for increased funding, yet left out the important work of the Geosciences and Social, Behavioral and Economic Sciences area. Fink referenced the AAAS Geospatial Technologies Project as an example of exemplary work in the overlooked fields. Such projects "provide critical information on the impact of remote, isolated conflicts on civilians; a host of human rights violations; damage to sites of cultural heritage; environmental and social justice issues; cross-border conflicts; and indigenous rights," Fink pointed out.

19 June. The 21st Century Cures Act was commended by the AAAS chair, in a letter to members of the House of Representatives. The legislation "authorizes roughly $1.5 billion in increases over three years and creates an Innovation Fund of $2 billion per year over five years," significantly supplementing regular appropriations to the U.S. National Institutes of Health (NIH), Gerry Fink noted. "Robust, sustained funding for NIH is the pathway to progress."

25 October. AAAS CEO Rush Holt appeared on MSNBC's "Up With Steve" program, arguing for more sustained, robust U.S. federal funding for science and technology. "In every area of human welfare, there are real gains to be made" through scientific research, Holt said. "We are nowhere close to investing as much as we could productively invest."

11 November. In an op-ed for *New Scientist*, the AAAS CEO urged policymakers to "unshackle U.S. science," by dropping spending caps that were suppressing funding for research and development. "Science and technology are the wellspring of innovation, new jobs and economic progress, but the United States is underinvesting in them," Rush Holt wrote. A bipartisan budget deal reached in late October provided much-needed relief for federal science agencies, he noted. However, the deal was set to expire after two years, meaning that it was only a temporary solution to the spending caps known as "sequestration," which took effect in 2013.

Communicating Climate Science

29 October. Five decades after the first official climate-change warning to a U.S. President, and shortly before a historic summit in Paris, AAAS organized a daylong symposium and a related policymaker briefing to call for action. "Climate Science, 50 Years Later" featured presentations by more than a dozen prominent scientists who described the impacts of climate change, based on scientific evidence, and evaluated options for the future. "The climate is changing at a pace and in a pattern that is not explainable by natural influences," said John P. Holdren, a past AAAS president who serves as Assistant to the President for Science and Technology and Director of the White House Office of Science and Technology Policy. "We know that with global temperature about 0.9 degrees Celsius above pre-industrial temperatures, these changes are already causing significant harm to life."

24 November. AAAS and seven other leading organizations expressed "grave concern" about a Congressional inquiry that unfoundedly called into question the integrity of federal scientists whose research, published in *Science*, seemed to debunk claims of a global-warming slowdown or "hiatus." In a letter to Rep. Lamar Smith (R-Texas), chairman of the House Committee on Science, Space, and Technology, the group acknowledged the importance of appropriate congressional oversight of federally funded research, but emphasized that "scientists should not be subjected to fraud investigations or harassment simply for providing scientific results that some may see as politically controversial."

7 December. As members of the Senate Committee on Commerce, Science, and Transportation prepared for a hearing on the magnitude of human impacts on the Earth's climate, the AAAS chair sent a letter to Capitol Hill, confirming the scientific consensus on the reality of human-caused climate change. "Climate change is occurring, and rigorous scientific research demonstrates that the greenhouse gases emitted by human activities are the primary driver," Gerry Fink wrote, referencing an earlier statement of the AAAS Board of Directors.

Gun-Violence Research

3 December. In response to news headlines about mass shootings, AAAS once again called for a better understanding of the root causes of gun violence by freeing up research funding for the U.S. Centers for Disease Control and Prevention. The research funding had been essentially frozen for two decades. "It is time for Congress to approve sensible steps to study gun violence as a public health issue," the AAAS CEO said. "Quite aside from the ongoing political debates over gun control, it is essential that unbiased scientific research be used to gather data on this spreading epidemic that claims so many lives each year. The epidemiology of gun violence has been underfunded for far too long." Holt added that there also is a role for science to play in providing technological solutions to gun violence, including safer guns that can only be fired by authorized users.

International Engagement

19 August. Marty Moss-Coane, whose popular public radio program offers insights on an eclectic range of topics, spoke with the AAAS CEO and then Chief International Officer Vaughan Turekian about the U.S.-Iran nuclear agreement, Cuba, climate change, Ebola, and more. The conversation, which aired on WHYY's RadioTimes program, also included historian Audra Wolfe. Scientific progress "depends on the free flow of ideas, and evidence-based thinking is central to it," CEO Rush Holt said. "Those things have democratizing and civilizing effects. Science can actually advance diplomacy and improve political and diplomatic relations."

11 September. Science diplomacy was also the focus of a Science Friday segment in which host Ira Flatow interviewed the AAAS CEO and the Chief International Officer. CEO Holt, who had earlier joined other leading physicists in signing a letter to President Obama that endorsed the Iran Nuclear Deal, noted that being a scientist comes with both benefits and civic obligations to communicate science to the public, and to policymakers.

Science Education For All

25 September. The world needs talented scientists to solve the problems of the 21st century, but talent is wasted when women and minorities face obstacles that keep them out of the field, said Shirley Malcom

of AAAS, in a live-streamed TEDxMidAtlantic talk. Malcom, who also serves as co-chair of the Gender Advisory Board of the United Nations Commission on Science and Technology for Development, and of Gender InSITE, called for Americans to recognize that talent can come from "every nook and cranny of this country," and to value diverse perspectives in the sciences. "Today, in 2015, we have got to make a decision as a nation," she said. "Do we choose to use the talent that is available, or do we choose to give in to the stereotypes about who does or does not belong?"

7 December. With the U.S. Supreme Court set to hear arguments on a case challenging the use of race-conscious admissions at the University of Texas at Austin, AAAS joined the American Educational Research Association (AERA) and nine other organizations in filing an *amicus curie* (or "friend of the court") brief, noting that "student body diversity leads to significant educational benefits and prevents the harms of social isolation." Shirley Malcom, director of Education and Human Resources at AAAS, also took part in a media briefing organized by the AERA.

Scientific Rights, Responsibilities, and Freedoms

31 March. In response to news headlines regarding challenges to the integrity of science, AAAS reaffirmed its commitment to robust, independent peer review as well as the sharing of research results through publications and public discourse, in accordance with well-crafted transparency policies and procedures. "AAAS remains dedicated to promoting the responsible conduct and use of science, and it asks individual scientists and engineers to remain vigilant in ensuring the transparency of the scientific enterprise," the AAAS CEO wrote in a statement.

Women in Science

13 August. Institution leaders and others in the science community must do more to create welcoming environments for women, minorities, and other underrepresented groups, and "call out unfairness whenever and wherever it appears," the AAAS director of Education and Human Resources wrote in a *Science* editorial. "The science community prizes objectivity, but research indicates that this isn't necessarily reflected in the behavior and choices of scientists," Shirley Malcom wrote. She noted that AAAS and the *Science* family of journals were looking internally to make improvements, while also looking outward to society colleagues so as to evaluate larger structural barriers to equality and diversity in science.

4 November. In response to a letter from U.S. Representative Jackie Speier (D-California), who had expressed concerns about gender bias, sexual harassment, and assault against women in science across the community, AAAS President Geraldine Richmond announced that AAAS would play a leadership role in combating such injustices. Noting that such cases are "abhorrent, unacceptable, and inconsistent with the long-standing values of AAAS," Richmond announced that the association would organize a national Forum on Implicit Bias in Peer Review, to encompass grant-making and publication. She also described a wide range of long-standing AAAS efforts to advance the careers of women in STEM fields.

2015 Communication and Public Engagement

AAAS multiplies the impact of research by communicating information about scientific advances and promoting scientific knowledge among audiences worldwide. Each year, AAAS hosts the world's largest general-science meeting, attracting researchers, policymakers, journalists, and families. It shares information on the latest advances with media, provides communication training to scientists and engineers, and promotes collaboration among researchers across disciplines and borders.

2015 Annual Meeting

Advances in imaging technology and information analysis are increasing the speed of scientific discovery, from light-activated proteins that make neural pathways visible, to 3-D printing of fossil artifacts that facilitate shared exploration of evolutionary advances. These and many other developments were explored in the public lectures and technical sessions during the 181st AAAS Annual Meeting, organized around the theme, "Innovation, Information, and Imaging."

Held for the first time in San Jose, California, the 12-16 February meeting drew more than 9,800 attendees, including researchers, journalists, and students. AAAS's Family Science Days, two days of free hands-on activities and demonstrations for children and adults, attracted more than 5,000 people.

Massachusetts Institute of Technology geneticist and then AAAS President Gerald Fink described during his presidential address how human chromosomes were initially miscounted when researchers first viewed their fuzzy outlines under a microscope. Improved imaging revealed their actual number as well as the small defects that can lead to disease. Later, geneticists learned that only 2% of genes are actively used to make proteins, while the function of the other 98% remains a mystery, he said.

"That new vision is exciting because it reveals an unknown world that stimulates our curiosity

The 2015 Communicating Science Seminar at the AAAS Annual Meeting connected scientists and public-engagement experts.

PHOTO: ©2015 ATLANTIC PHOTO—BOSTON

and spawns new fields," Fink said. "But it's also threatening because a new picture can destroy our past understanding of our universe, a universe we thought we understood only yesterday."

50 Years of Communicating About Climate Change

In a continuation of the "What We Know" climate-change communication series launched in 2014 (whatweknow.aaas.org), AAAS and the Carnegie Institution for Science organized a scientific symposium marking the 50th anniversary of the first official warning about climate change to a U.S. president. More than a dozen prominent scientists discussed climate-change impacts, including habitat loss and increased extreme-weather events, and how to best respond to, and communicate about these challenges.

In 1965, President Lyndon Johnson's science advisors issued a report saying that the accumulation of atmospheric carbon dioxide from the burning of fossil fuels would "almost certainly cause significant changes" to the environment. By 1990, "We really knew enough scientifically to justify the kinds of actions that we're only now talking about today 25 years later," said John P. Holdren, Assistant to the President for Science and Technology, and Director of the White House Office of Science and Technology.

Following the symposium, supported by the American Meteorological Society and the Linden Trust for Conservation, AAAS organized a briefing for legislators in the U.S. Capitol Senate Visitors Center, in conjunction with Sen. Ed Markey (D-Mass.). AAAS also provided live video of the symposium, which celebrated the launch of the Alan I. Leshner Leadership Institute. The first 15 Leshner fellows are all climate scientists and communicators.

AAAS Kavli Science Journalism Awards

The 2015 AAAS Kavli Science Journalism Awards marked the first time in the program's 70-year history that entries were accepted from journalists around the world. Almost 40% of all submissions were from international reporters, with a comparable number of international winners. The Kavli Foundation made the change possible by doubling the endowment that funds the awards program.

Independent panels of science journalists selected the two best examples of science reporting for a general audience in eight categories. Winning stories were published or broadcast by *The New York Times*, *Baltimore Sun*, PBS NewsHour, *Le Monde*, *Nature*, Minnesota Public Radio, and other media outlets. The prizes, $5,000 for a gold award, and $3,500 for a silver award, were given out at the 2016 AAAS Annual Meeting in Washington, D.C.

Communication Tools for Scientists & Engineers

AAAS is providing tools for scientists and engineers who want to more effectively communicate about their research and its implications. More than 1,500 of them were trained and given a chance to practice, during AAAS Communicating Science workshops held in 2015.

Staff in the Center for Public Engagement with Science and Technology organized 33 workshops and 17 invited talks, which were held at universities and government agencies, and at business and professional meetings. Workshop leaders taught participants to use different communication tools to engage a variety of audiences, including the public, reporters, and policymakers. They then had opportunities to refine their messages and build confidence through small-group discussions and practice.

Visitors at the 2015 Family Science Days explored scientific phenomena and met a diverse range of scientists and engineers, from anthropologists to zoologists.

PHOTO: ©2015 ATLANTIC PHOTO—BOSTON

The Center also organized two communication seminars during the 2015 Annual Meeting that drew about 300 attendees. During "Scientists Communicating Challenging Issues," presenters offered social science research about why some scientific issues, like climate change, are prone to controversy, and how scientists can navigate those tensions. A second workshop, entitled "Public Engagement for Scientists: Realities, Risks, and Rewards," also drew on research to explore the methods and possible results of public outreach.

The Communicating Science program has reached more than 6,700 scientists and engineers since it was founded in 2008.

EurekAlert! Reaches Out Worldwide

EurekAlert!, the AAAS-operated science news service, continued to expand its international reach in 2015. It saw a dramatic increase in news releases from Japanese universities and science institutions after EurekAlert! staff visited several institutions in Japan. The staff also promoted an updated English-Japanese website. Afterward, Japanese institutions used the site to post four times more often than in 2014, and visits to the bilingual site more than quadrupled.

▼ In October, Brian Lin of EurekAlert! at AAAS (standing) worked with public information officers who tried their hands at writing news headlines, at the first EurekAlert! seminar held in China.

PHOTO: CHINESE ACADEMY OF SCIENCES

EurekAlert! also offered its first international training for public information officers, in collaboration with the Chinese Academy of Sciences. The training, held in Chengdu, China, helped communicators practice linking their news to issues of interest to international reporters and audiences.

The EurekAlert! service provides free access to news about research in science, health, medicine, and technology to about 12,000 journalists worldwide.

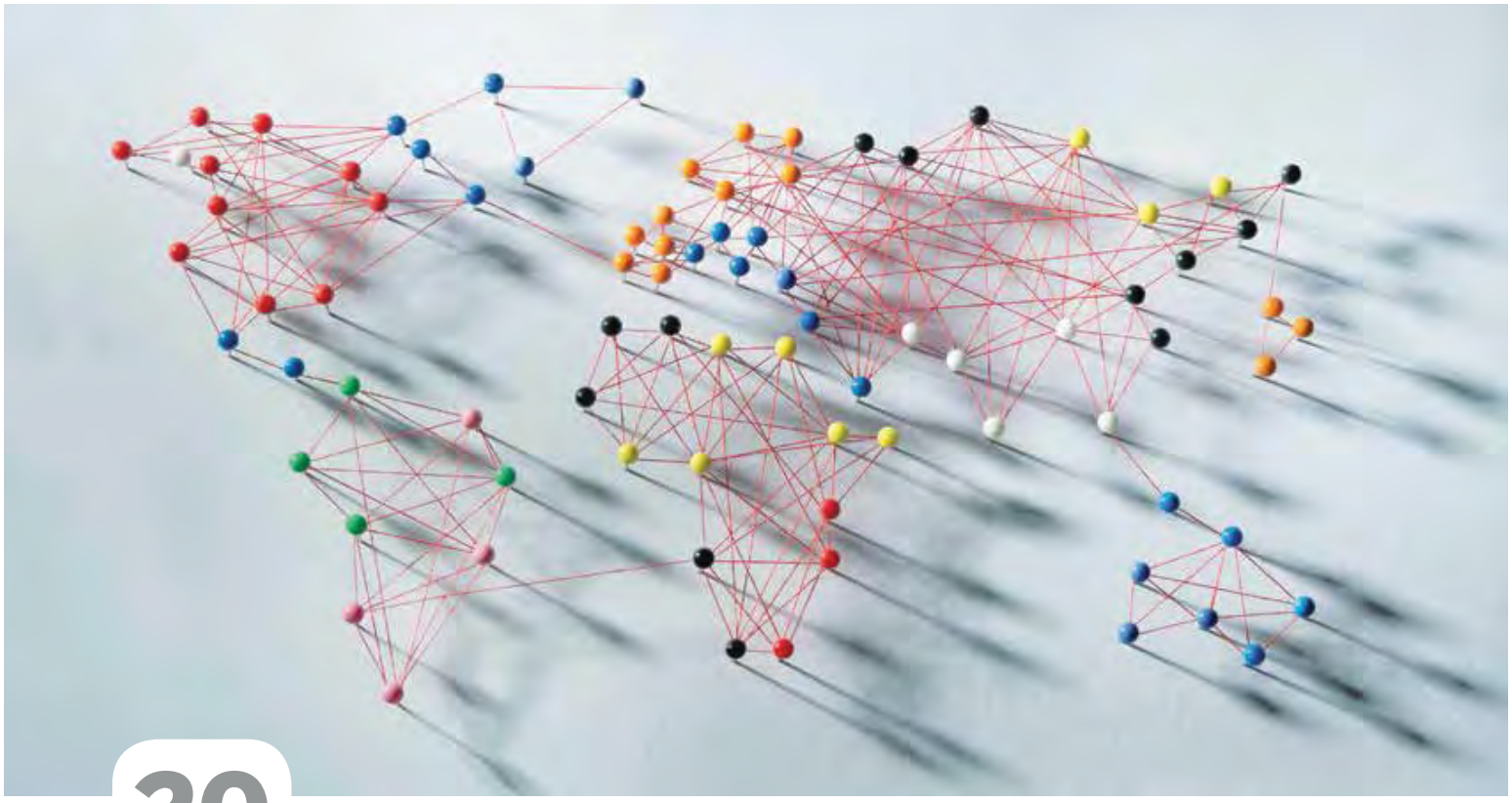
AAAS Colloquium Series Takes Off

As part of the association's ongoing Transformation Initiative, AAAS launched a new Colloquium Series, organized by staff volunteers, to provide a forum for exploring topics relevant to science and society. Initial Colloquium Series lectures, intended to engage staff, AAAS members, and the public, featured topics ranging from the state of Iranian science—the focus of a *Science* news feature by journalist Richard Stone—and the destruction of cultural heritage in Syria and Iraq, to U.S. science policy challenges and opportunities, and more.

Trellis: Increasing Research Collaborations

Research efforts increasingly cross disciplines, and they rely upon collaborations between institutions and across international boundaries. Some 80% of AAAS members surveyed said they wanted better ways to connect with other scientists online. In response, AAAS launched an online communication and networking platform called Trellis to promote discussions and research collaborations. A beta version of the website went live in December 2014, and added 5,700 users in 2015.

AAAS will also begin training community managers—people who can help facilitate collaborations between researchers within and outside their fields using platforms such as Trellis. Using a $773,000 grant from the Alfred P. Sloan Foundation, the AAAS Community Engagement Program will begin a one-year pilot program to train as many as 18 fellows in 2017.



2015 International Engagement

AAAS promotes the use of science and engineering to address challenges that span regions and cross disciplines. It has forged new international relationships, supported research collaborations, and encouraged innovation in developing countries. AAAS serves as a resource for science diplomacy training, and provides a forum for finding new ways to use science and engineering to connect nations.

Scientific Drivers for Diplomacy

The AAAS Center for Science Diplomacy continues to promote international engagement to facilitate research, and to leverage research as a way to bring together countries to address broader issues.

"The principles of science—transparency, open communication, and evidence-based thinking—go a long way to diffusing difficult situations, breaking through barriers, and developing relationships," said Rush Holt, CEO of AAAS, in an address at the first annual conference on science diplomacy, held at AAAS headquarters in April. More than 200 people participated, including representatives from the U.S. Department of State and other federal agencies, UNESCO, The World Academy of Sciences, and the Academy of Sciences of Cuba.

Conference panelists discussed the need for trans-boundary cooperation and information-sharing to address public health and environmental issues, such as cholera outbreaks, biodiversity loss, and climate change. Participants also related ways to foster cooperation during times of political strain, by working with shared resources, and the roles of institutions and networks in science diplomacy.

First Poland-U.S. Science Award

Two structural biologists who worked to develop AIDS treatments were honored with the first Poland-U.S.

Science Award in April 2015. The award, established in 2013, is given to a pair of scientists working in Poland and the United States for outstanding scientific achievements resulting from their collaboration. AAAS and the Foundation for Polish Science will grant the award every two years.

Prof. Mariusz Jaskólski of Adam Mickiewicz University in Poznań, Poland, and Dr. Alexander Wlodawer of the National Cancer Institute began working together in 1988 to understand the structure of retroviral proteins. That work led to the development of the first protease-oriented drugs for AIDS patients. Their continued collaboration has generated 37 joint publications to date.

Science Diplomacy Boot Camp

The second annual Course on Science and Diplomacy was held in June in Trieste, Italy, drawing together participants from 30 countries. The week-long meeting, organized by the AAAS Center for Science Diplomacy and The World Academy of Sciences (TWAS), provided science diplomacy training to 56 researchers and administrators.

The attendees learned how science diplomacy can be carried out, how to educate the public and policymakers about risks, and how some countries are already using science diplomacy.

Sir Peter Gluckman, science advisor to New Zealand's prime minister, delivered the Paolo Budinich Lecture as part of the course. New Zealand is an example of how smaller countries can use their strengths in scientific research to gain global influence and advance their own policy interests, Gluckman said.

The 2015 AAAS-TWAS course was sponsored by the Golden Family Foundation, the Organization for Women in Science for the Developing World, the Swedish International Development Cooperation Agency, and the U.S. Agency for International Development.

U.S. and Cuban Researchers Begin Neuroscience Collaborations

United States and Cuban researchers will soon begin collaborating to improve magnetic resonance imaging technology, to advance neuroinformatics and neurodevelopment research, and to investigate the establishment of an international non-human primate research center in Cuba.

A U.S. delegation of researchers, academics, policymakers, and representatives of industries and foundations met with their Cuban counterparts at a December 2015 meeting in Havana to plan the research collaborations. The meeting was the first outcome of a 2014 agreement between AAAS and the Cuban Academy of Sciences to promote scientific cooperation between their countries.

Participants at the meeting, organized by AAAS and the Cuban Neurosciences Center (CNEURO), discussed research advances in neurodegenerative and psychiatric disorders, brain mapping techniques, imaging, and treatments.

AAAS in 2015 also began planning to launch a fellowship program for early and midcareer scientists from Cuba. The Cuban biomedical research fellows could begin research collaboration in the United States in 2016, under a program administered by the AAAS Center for Science Diplomacy.

▼ The 2015 GIST Tech-I competition finalists hailed from 23 developing countries.

PHOTO: EPHOD VISUAL & AUDIO ENTERPRISES

That program is supported by a grant from the Lounsbery Foundation. AAAS staff members are still seeking funding to bring U.S. scientists to Cuba.

Global Competition Propels Innovation

An international competition for innovators, administered by AAAS, is helping entrepreneurs to develop low-cost solar-powered hearing aids in Botswana and a lemongrass-derived compound to protect stored crops from insects in Nigeria, while also providing role models to spur innovation in developing countries.

The Global Innovation through Science and Technology (GIST) Tech-I competition was held in Nairobi, Kenya in July 2015, and was organized by the AAAS Office of International and Security Affairs and the Research Competitiveness Program. The U.S. Department of State began the GIST initiative in 2011 to support scientific and technological innovation in the developing world.

Participants who apply for the program must go through an extremely competitive, multistep selection process to reach the finals, where they receive training and mentoring from leaders in industry, funding agencies, and other sectors. Thirty people from 23 developing countries competed to be one of the 13 winners, who took home almost $140,000 in cash prizes.

The finals were part of the annual Global Entrepreneurship Summit, which received a visit by President Barack Obama. GIST alumni who have commercialized their inventions have generated $110 million in revenue, according to State Department figures.

Mentoring Women in International Research Collaboration

Women and underrepresented groups trying to succeed in STEM fields may find themselves up against a "polycarbonate ceiling" to career advancement, said chemist and AAAS President Geraldine Richmond. It's one they must find a way around, since it's almost impossible to break.

AAAS has several programs to help women navigate the barriers that prevent them from fully participating in science, technology, engineering, and mathematics (STEM) careers, including some that also promote international research. Under one such program, Mentoring Women in International Research Collaborations (MWIRC) in STEM, AAAS has administered 15 research grants of $20,000 each to allow women to mentor graduate students or postdocs and carry out research in another country. The grants are funded by the National Science Foundation. In addition, the program began sponsoring travel awards to send two women scientists to the international Gender Summit, beginning with the April 2016 summit in South Africa.

The Elsevier Foundation Awards for Women in Science in the Developing World—supported also by Gilbert S. Omenn, a past AAAS president, and Martha Darling—provide five early-career women scientists with $5,000 and support for travel to the AAAS Annual Meeting. The 2015 winners were from Nigeria, Sudan, and Vietnam, and were selected for their contributions to nanoparticle physics, atmospheric physics, medical physics, and computational mathematics, as well as their efforts to encourage other young women to pursue STEM careers.

The L'Oréal awards, which AAAS administers, provide five women each year with $60,000 grants to fund postdoctoral research. And in October, four women were awarded the first AAAS Marion Milligan Mason Awards for Women in the Chemical Sciences, which provide funding for early-career researchers. (See also the Education, Outreach, and Careers section on pages 26-27.)

Science & Diplomacy Update

The AAAS Center for Science Diplomacy's quarterly policy journal, *Science & Diplomacy*, published 21 articles plus editorials, perspectives, and letters in 2015. It attracted more than 36,000 readers, more than half of whom were outside the United States.

Popular articles included one by the executive director of the Academy of Sciences of Cuba detailing Cuba's research history and its periods of collaboration with the United States, as it anticipates improved relations once again. An editorial by AAAS CEO Rush Holt on the relationship of science to diplomacy has also been viewed more than 1,000 times.

2015 Science, Policy, and Society

The AAAS Center of Science, Policy, and Society Programs (CSPSP) brings scientific and engineering expertise to policymakers, promotes wise investments in research, and advances scientific freedom and responsibility. Through a selective fellowship program and a prestigious annual forum, it shares insights with the federal agencies and Congressional offices where public policy is made and interpreted. CSPSP also organizes programs that promote ethical research practices, provides technical expertise on human rights issues, and encourages dialogue about science and religion.

2015 Science & Technology Policy Forum

Concern about cuts to basic research funding was the overriding message during the 40th AAAS Forum on Science & Technology Policy. The two-day meeting, held in Washington, D.C. in April, drew more than 400 elected officials, government and business leaders, foreign embassy staff, researchers, and educators.

Funding for basic-science research in the United States is threatened by limits on "discretionary" spending due to budget sequestration, said John P. Holdren, director of the White House Office of Science and Technology Policy, in his keynote address. France Córdova, National Science Foundation director, questioned whether funding for basic research should continue to rely on the nation's discretionary spending budget. "Our nation's future, including our preparedness for that future, depends on innovation," Córdova said. "Innovation in turn depends, in large part, on discovery, and discovery is fueled by basic research. This pursuit is not discretionary."

The Forum saw the start of a new lecture series, the Gilbert S. Omenn Grand Challenges Address, intended to draw attention to the most pressing needs and goals at the intersection of science and society. Dr. Omenn, past president of AAAS, gave the 2015 address, encouraging consideration of "aspirational and inspirational" research challenges to "energize not only the scientific and engineering community, but

also students, journalists, the public, and their elected representatives, to develop a sense of the possibilities, an appreciation of risks, and an urgent commitment to accelerate progress."

Additional speakers addressed how scientists can better engage with a skeptical public, how data can be used for the public's benefit, and how the U.S. educational system can increase the number of workers prepared to take science, technology, engineering, and mathematics (STEM) jobs.

Protecting Antiquities and Predicting Conflict

Sites and objects with irreplaceable cultural value often become targets during armed conflicts, both for ideological reasons and for their value to collectors. The AAAS Geospatial Technologies Project assisted groups trying to protect sites in Syria and Iraq by analyzing recent satellite images with earlier ones to document the status of the sites. Some sites, such as one in Apamea, Syria, are so covered with pits and tunnels dug by looters that they appear to have been carpet-bombed, AAAS reported.

Sometimes sites are damaged or destroyed to remove reminders of a cultural heritage that terrorists or other groups oppose, or to demoralize the local people, said Katharyn Hanson, a visiting scholar with the Geospatial Technologies Project, in a November colloquium. Hanson and AAAS contributed to the Safeguarding the Heritage of Syria and Iraq (SHOSI) Project, which physically protects sites from bombings, using sandbags and other methods.

The Geospatial Technologies Project also studied the use of satellite imagery to better understand and help prevent border conflicts. With a grant from the United States Institute of Peace, it aggregated and correlated large amounts of information from previous cross-border conflicts, including satellite imagery, media reporting, and eyewitness accounts, to create a retrospective geospatial analysis. That process allowed it to identify trends that could contribute to the future detection, management, and peaceful de-escalation of similar incidents.

Science & Technology Policy Fellowships

The 2015-16 class of Science & Technology Policy Fellows includes researchers and engineers of all types, from all stages in their careers, who have one shared goal: to apply their science and technology skills to policy solutions. The program places doctoral-level scientists, or engineers with a Master's degree, into various offices within the executive, legislative, and judicial branches of federal government and Congress for a year.

"Scientists have such an important role to play in society beyond the bench," said Sapana Vora, who served as a fellow at the State Department.

Of the 280 fellows, 163 fellows were new fellows, 99 had renewed their fellowship for a second year, and 18 were in special alumni fellowships. Thirty-

▲ The AAAS Science & Technology Policy Fellows, class of 2015-16, included 280 competitively selected fellows.

one fellows served in Congress; 245 served in the executive branch among 18 agencies or departments, including overseas missions with the U.S. Agency for International Development; and four were placed with the Bill and Melinda Gates Foundation in Seattle.

In August, the fellows had a chance to meet with S&T Policy Fellowship alumnus Rush Holt, CEO of AAAS. A physicist by training, Holt called his fellowship experience "life-changing," and said that it led to his serving for 16 years in the U.S. House of Representatives. He told the fellows that he hopes to enlist their help in advocating for science for years to come.

Promoting Research Competitiveness

The AAAS Research Competitiveness Program (RCP) has worked for 20 years to build capacity for STEM systems through its work on peer-reviewed competitions, program and institutional assessment, trainings, and innovation and entrepreneurship initiatives.

In 2015, RCP finished the first phase of support for grant competitions of the King Abdulaziz City for Science and Technology (KACST) in Saudi Arabia. For seven years, RCP had solicited more than 15,000 reviews for about 5,000 proposals for KACST. It continues to provide review of grantee progress reports. RCP also in 2015 solicited reviews for more than 100 applications to the Connecticut Bioscience Innovation Fund, which has awarded $4.5 million since 2014 to five universities and four companies.

Since 1996, RCP has organized expert assessments for more than $1 billion spent on science initiatives in the United States and worldwide. In 2015, the program helped states implement and sustain multi-institutional, interdisciplinary research programs, encompassing assessments of five programs funded by the National Institutes of Health (in Louisiana, Mississippi, New Hampshire, Rhode Island, and Oklahoma), and two programs funded by the National Science Foundation (in Maine and South Dakota).

In its work on innovation and entrepreneurship, RCP assumed leadership of the Global Innovation through Science and Technology (GIST) Tech-I competition, and organized the training and judging for the 2015 Tech-I finals held at the Global Entrepreneurship Summit in Nairobi, Kenya. RCP was also awarded funding in 2015 for three GIST Women's Village workshops on networking for science and technology entrepreneurs, to be held in Côte d'Ivoire, Nigeria, and Mozambique in 2016.

Science for Religion Reporters

The AAAS Dialogue on Science, Ethics, and Religion program (DoSER) convened independent judges who selected eight writers and broadcasters to receive the first Science for Religion Reporters Award, given during the 2016 AAAS Annual Meeting. The $2,000 awards recognize journalists whose audiences are attentive to religion and culture, and who demonstrate an interest in reporting about science.

The award-winning journalists reach a wide range of audiences, through reporting distributed by such media outlets as CBS, the Religion News Service, *The Atlantic*, and Sojourners, among others. The program is funded by a grant from The John Templeton Foundation, with support from AAAS.

▲ AAAS staff members Christine Scheller (far left) and Jennifer Wiseman (far right) celebrated the first eight winners of the AAAS Science for Religion Reporters Awards (L-R): Kimberly Winston, Liz Kineke, Kelsey Dallas, Renee Gadoua, Emma Green, Cathy Lynn Grossman, Patti Miller, and Catherine Woodiwiss.

PHOTO: AAAS

2015 Government Relations

AAAS Government Relations shares the wide-ranging value of the scientific enterprise with policymakers by communicating directly with Congressional representatives, offering Capitol Hill briefings, and providing evidence-based science and technology updates. It sponsors training to equip and encourage scientists and engineers to become more active in communicating and advocating for science. The group also offers authoritative, ongoing analysis of federal investments in science and engineering research and development.

AAAS Protests Climate-Science Inquiry

AAAS led a protest of an inappropriate Congressional inquiry into federal climate-science research that threatened to violate federal scientists' academic freedom. In June, a research group from the National Atmospheric and Oceanographic Administration (NOAA) published findings in the journal *Science*, showing that what had previously appeared to be a 15-year slowdown in the rate of global warming early in the 21st century was likely due to incorrect estimates of surface temperatures, and that warming had continued at the same rate during that period.

The chairman of the U.S. House Committee on Science, Space, and Technology sent subpoenas in October to NOAA, requesting "all documents and communications" related to the *Science* paper. AAAS and seven other science societies sent a letter in support of federal scientists, stating that needlessly intrusive Congressional inquiries can inhibit scientific discovery, particularly if scientists are threatened with legal action.

"Science cannot thrive when policymakers—regardless of party affiliation—use policy disagreements as a pretext to attack scientific

conclusions without public evidence," the coalition's letter said. "We are concerned that establishing a practice of inquests directed at federal scientists ... could well have a chilling effect on the willingness of government scientists to conduct research that intersects with policy-relevant scientific questions."

The letter acknowledged the importance of appropriate Congressional oversight of federally funded research, and suggested that the House committee use other established mechanisms for assessing technical information, such as advisory reports of the National Academies of Sciences, Engineering, and Medicine.

AAAS also held a symposium and Congressional briefing in October to discuss advances in climate science and strategies for communicating about climate change, while marking the 50th anniversary of the first warning to a U.S. president of the threat posed by climate change.

Neuroscience, Human Health, and Policy

The AAAS Neuroscience and Society series organized four public lectures and four Capitol Hill briefings on topics ranging from the treatment of mental illness in people of all ages, to the complexity of chronic pain. Each of the public events, held at AAAS headquarters, drew up to 100 people.

Researchers also addressed policymakers in briefings about topics including how increased access to marijuana in states where it has been legalized is affecting teens, and how schools can improve learning for children with disabilities such as attention deficit hyperactivity disorder and dyslexia. The Capitol Hill neuroscience briefings were hosted in conjunction with Rep. Chaka Fattah (D-Pennsylvania).

The Neuroscience and Society series is supported by a grant from The Dana Foundation.

Golden Goose Awards

Created to honor odd-sounding basic research that has led to important benefits for society, the 2015 Golden Goose Awards were given to seven researchers who studied self-control strategies, how the brain interprets visual stimuli, and the distribution of people at various altitudes.

One winner, psychologist Walter Mischel, designed the "marshmallow test" in the late 1960s to see how young children can delay gratification to get a larger reward later. He found that distraction works best, and over the next 30 years, he and his colleagues followed up with some of the original subjects of the research. They found that having self-control strategies did correlate with greater academic and social success later in life, and that such strategies can be taught to improve children's later outcomes.

Rep. Jim Cooper (D-Tennessee) and a coalition of organizations, including AAAS, the Association of American Universities, and the Association of Public- and Land-grant Universities, created the Golden Goose award in 2012. Cooper and a bipartisan group of Congressional representatives attended the September awards ceremony at the Library of Congress.

"These awards remind us that scientific breakthrough rarely follows the straight and narrow path," said Sen. Chris Coons (D-Delaware), and "how important it is that we continue to support the basic research that only the federal government can sustainably fund."

Analyzing U.S. R&D Funding Trends

The AAAS R&D Budget and Policy Program has been tracking federal spending for research and development since 1976 by following Congressional debates and bills, and by parsing the President's yearly budget proposals. There has been much to follow of late, as spending caps on discretionary spending created by the Budget Control Act of 2011 allowed for only a 0.2% increase in spending, before factoring in inflation.

The National Science Foundation and the Department of Energy's laboratories did have small budget increases in 2015, but the National Institutes of Health's overall budget continued a decade-long decline. After multiple budget adjustments, Congress eventually passed an omnibus spending bill for fiscal year 2016 that added 5.2% to the discretionary spending allowance, and provided about an 8% increase in R&D spending.

Matt Hourihan, the AAAS program's director, gave R&D budget briefings on Capitol Hill and at the association's 40th annual Forum on Science & Technology Policy, in addition to publishing periodic analyses. He told Hill attendees that the United States remains the largest global contributor to R&D, spending more than twice as much (in dollars) as China, the next largest funder. Two-thirds of U.S. R&D spending is generated by industry, with the remainder coming from the federal government.

However, there has been "a very clear shift from west to east" in recent years, Hourihan said. China, Singapore, Taiwan, Japan, and South Korea collectively increased their share of global R&D spending from 24% in 2000 to 36.8% in 2012. Analysts believe that China may surpass the United States in total R&D funding from all sources by 2019.

AAAS Joins Rally for Medical Research

AAAS was one of more than 300 organizations that sent researchers, physicians, and patients to speak with their Congressional representatives in support of biomedical research on 17 September. The Rally for Medical Research was an effort to reverse a decade-long decline in federal spending for the National Institutes of Health (NIH), whose $29.5 billion budget for 2015 was 22% lower than its 2003 peak, after adjusting for the high rate of inflation in the biomedical sciences.

People with many conditions, including cancer, influenza, Ebola, and AIDS, are relying on NIH-funded research to find a cure, said NIH Director Francis Collins during a rally reception. The NIH is the largest funder of medical research in the world.

Among rally participants appealing to Congress were graduate students who participated in the AAAS Catalyzing Advocacy in Science and Engineering (CASE) event, a three-day workshop that provides policy, advocacy, and communication training. Close to 80 students representing 43 institutions participated in the second annual CASE workshop.

The program was created in response to repeated requests from graduate students who were interested in science policy and advocacy. It encourages attendees to continue their involvement in science policy. Alumni have gone on to become a California Science and Technology Policy Fellow and to participate in similar programs.

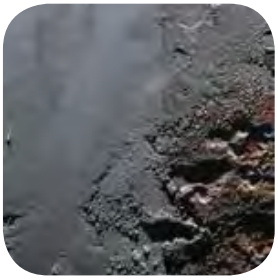
Engaging Scientists and Engineers in Policy

AAAS and a coalition of universities and science and engineering societies are working to help researchers, science and technology professionals, and students become more involved in policy initiatives. The Engaging Scientists and Engineers in Policy (ESEP) website provides a list of fellowships, internships, graduate programs, trainings, degree programs, websites, publications, and more.

The ESEP program has conducted several workshops at AAAS meetings. ESEP also began a webinar series that allowed participants to ask questions and interact with experts in real time. Speakers included AAAS CEO Rush Holt (a former member of Congress), government affairs representatives for science societies, and lobbyists who described the tools they use to advocate for science policy, and how to use them most effectively.

2015 The *Science* Family of Journals

Science headlines encompassed research advances across the biological, physical, and social sciences, plus penetrating news and analysis meant to expand our knowledge of technology's role in making traditional notions of privacy obsolete, issues stemming from the emergence of the world's last isolated tribes from the Amazon rainforest, and Einstein's 100-year-old general theory of relativity, which continues to underpin cutting-edge physics today, including efforts to trace the origin of the universe.



2015 Research News

First Scientific Results from Flyby of Pluto
In the first published results from the flyby of the Pluto-Charon system in 2015, researchers reported that the surface of the dwarf planet is marked by plains, troughs, and peaks that appear to have been carved out by geological processes that have been active for a very long period and continue to the present. (Stern *et al.*, *Science*, 16 October)

Fast, Continuous, 3D-Printing Out of Liquid Bath
Researchers developed a method for growing detailed solids out of a liquid bath at rates that dwarf three-dimensional (3D) print speeds. Their method makes it possible to convert 3D designs into parts in minutes instead of hours. (Tumbleston *et al.*, *Science*, 20 March)

A Global Look at Plastic in the Oceans
Using comprehensive data from 192 coastal countries, researchers estimated that between five and 13 million tons of plastic waste wind up in the world's oceans every year. Based on their

projections, this amount could increase tenfold in the next decade, the researchers said. (Jambeck *et al.*, *Science*, 13 February)

Personalized Vaccines Target Skin Cancer's Mutations
Researchers who tailored vaccines for different melanoma patients expanded the number and the reach of these patients' cancer-fighting T cells—providing a shot in the arm for cancer immunotherapy. (Carreno *et al.*, *Science*, 3 April)

The Oldest Fossil of the *Homo* Genus
This analysis of a partial hominin mandible found in Ethiopia with five of its teeth still intact suggests that the *Homo* genus arose by about 2.8 million years ago—almost half a million years earlier than previous evidence had indicated. (Villmoare *et al.*, *Science*, 6 March)

DNA from Illegal Ivory Points to Poaching Hotspots
New genetic tools helped researchers trace illegal ivory back to the African elephant populations from which it came, creating a mechanism by which to assist law-enforcement officials in cracking down on poaching in the future. (Wasser *et al.*, *Science*, 19 June)

Measles Risk in Countries Hit by Ebola
Researchers uncovered how healthcare services in Liberia, Sierra Leone, and Guinea were disrupted by the Ebola outbreak, adversely affecting routine vaccination of children against measles—an infection that often follows such humanitarian crises. (Takahashi *et al.*, *Science*, 13 March)

Virally Cleansing the Pig Genome with CRISPR
In an effort to enable organ transplants into humans, researchers used the CRISPR gene-editing technique to inactivate all 62 copies of a retrovirus in a pig cell line, a significant step on the road to generating pig organs for possible xenotransplantation. (Yang *et al.*, *Science*, 16 October)

New England Cod Collapse Linked to Warming Waters
Scientists revealed how rapid warming in the Gulf of Maine correlated to the near collapse of New England's cod stocks, despite cuts to fishery activity. The results reveal how a warming climate complicates fisheries management. (Pershing *et al.*, *Science*, 30 October)

Sequencing Tumor Alone May Misidentify Mutations
In perhaps the largest-scale evaluation of its kind, a study of 815 patients across 15 cancer types revealed that compared to genomic analysis of tumors alone, analysis of both tumor and normal tissue from the same patient more accurately identified cancer-causing mutations. (Jones *et al.*, *Science Translational Medicine*, 15 April)

"Designer Cell" Implants Detect and Treat Psoriasis
Designer cells programmed to serve as miniature disease-sensors and drug factories showed promise against psoriasis. Researchers built and implanted into mice synthetic cells capable of detecting psoriasis, automatically producing therapeutic proteins, and effectively treating the condition. (Schukur *et al.*, *Science Translational Medicine*, 16 December)

Infants Lacking "Good" Bacteria at Greater Asthma Risk
Infants with low levels of four protective bugs in their gut microbiome are more likely to develop asthma, this study of 300 children showed. The findings pave the way to designing a diagnostic screen and probiotic therapy to prevent at-risk babies from developing asthma. (Arrieta *et al.*, *Science Translational Medicine*, 30 September)

Burning All Fossil Fuels Could Eliminate Antarctic Ice Sheet
Researchers who performed a long-term modeling study estimated that if all of the currently available carbon resources were burned, the Antarctic Ice Sheet would melt entirely and trigger a global sea-level rise of more than 50 meters. (Winkelmann *et al.*, *Science Advances*, 30 September)

Uncontacted Amerindians Exhibit Extremely Diverse Microbiomes
The microbiome of Amerindian villagers from the Venezuelan Amazon with no documented contact with Western peoples contains perhaps the highest levels of bacterial diversity ever reported in a human group, researchers reported. (Dominguez-Bello *et al.*, *Science Advances*, 30 September)

More Than Half of All Amazonian Tree Species Threatened
More than half of all tree species in the Amazon may be at risk for extinction, this study revealed. The results increase the number of threatened plant species on Earth by approximately 22%, and could have implications for land-use policy. (ter Steege *et al.*, *Science Advances*, 20 November)

Methylation Takes Signaling Down a Notch
Researchers showed that chemically tagging the Notch protein with a methyl group helped curb Notch signaling activity, which controls many developmental processes. The finding offers a potential strategy for turning off the pathway and sheds light on why Notch—when defective—drives many cancers and developmental disorders. (Hein *et al.*, *Science Signaling*, 24 March)

Other *Science* Highlights

Powerful Special Issues: *Science* published 14 substantive special issues on a range of topics, from "The End of Privacy," to "General Relativity at 100," to "Isolated Tribes in the Amazon." On 4 September, a special issue, "Science in Iran," explored the scientific challenges and triumphs of a country that has experienced international isolation in recent years. As *Science* International News Editor Richard Stone explained, though decades of economic sanctions have deprived Iranian scientists of critical scientific resources and collaboration, these researchers have persevered, using homespun ingenuity to create their own resources from scratch.

February marked the launch of AAAS's first open-access journal, *Science Advances*. Scientific reports published in the journal during its first year described the creation of electronic plants that could be used to speed up plant-based drug development, a smartphone system for early earthquake and tsunami warnings, and how exposure to space radiation may put astronauts at risk for cognitive problems. A 2015 *Science Advances* study on the sixth mass extinction made its way into the top 5% of all research outputs ever tracked on Altmetric.com, a metrics-reporting site for scholarly content.

In 2015, AAAS also laid the foundation for the publication of *Science Immunology* and *Science Robotics*, both set to launch in 2016. *Science Immunology* will feature interdisciplinary research focused on the understanding of problems in cellular and clinical immunology, including links to microbiology. *Science Robotics* will highlight new advances in complex engineered systems for exploration of and intervention in environments as diverse as the body, a factory, land, air, sea, and space.

The blog, In the Pipeline, an editorially independent commentary on drug discovery and the pharma industry by medicinal chemist Derek Lowe, moved to the *Science Translational Medicine* website, attracting a wide readership.

Finally, *Science* in the Classroom, a program launched in October 2011 with support from the National Science Foundation, received a considerable boost in funding. The program continues to help students across the country better understand core science concepts through a freely available site that features specially developed learning exercises and *Science* research articles annotated by student volunteers.

Honors we brought in

Three *Science* news reporters received prestigious journalism prizes. For her story, "Eavesdropping on ecosystems," *Science* staff writer Kelly Servick was awarded the 2013-2014 Acoustical Society of America's Science Writing Award. *Science* staff writer Eric Hand received the Gold EXCEL Award for the best in-depth exploration of a single topic for "Martian obsession," published 28 November, 2014.

Judges of the D.C. Science Writers Association Newsbrief Award for short journalism recognized *Science* staff writer Emily Underwood with honorable mention for her story, "Rats forsake chocolate to save a drowning companion."

Honors we gave out

The Grand Prize winner of the international competition for the *Science* & SciLifeLab Prize for Young Scientists was Allison Clearly of Pennsylvania State University, recognized for her research on how breast cancer cells cooperate to enable tumor growth. Established in 2013, the $25,000 prize is awarded annually to one young scientist for outstanding life science research. Cleary's winning essay, "Teamwork: The tumor cell edition" describes how her team's innovative approach unraveled a mysterious feature of human breast cancer biology—the interactive relationship between tumor cell subpopulations within single tumors, which is needed for tumors to grow. The prize is a coordinated effort of *Science*/AAAS and four Swedish universities comprising the *Science* for Life Laboratory, a Swedish national center for molecular biosciences with a focus on health and environmental research.

On July 31, AAAS and the journal *Science Translational Medicine* honored Nicholas Navin, an assistant professor of genetics and bioinformatics at MD Anderson Cancer Center, with the AAAS Martin and Rose Wachtel Cancer Research Award, now in its third year. This $25,000 prize recognizes outstanding work by young scientists performing breakthrough cancer research. Navin created the first method for sequencing the genome of an individual cell, which has given scientists a new view into the inner workings of tumors.

The 2014-2015 AAAS Newcomb Cleveland Prize was awarded to Eric Betzig and colleagues for the report, "Lattice light-sheet microscopy: Imaging molecules to embryos at high spatiotemporal resolution," published in *Science* on 24 October 2014. This microscopy advance provides an unprecedented understanding of the inner workings of live cells. According to *Science* Editor-in-Chief Marcia McNutt, "There are several criteria that the selection committee looks for in an outstanding Newcomb Cleveland awardee, and this year's winner had it all: a major advance in the field, a well-communicated contribution, and broad potential application beyond a narrow sub-discipline." The association's oldest award, the AAAS Newcomb Cleveland Prize was established in 1923. Now supported by The Fodor Family Trust, it acknowledges an outstanding paper published in *Science's* Articles, Research Articles, or Reports sections.

2015 Improving Science Literacy

Through its long-term science-education initiative, Project 2061, AAAS endeavors to improve science, mathematics, and technology literacy for everyone. Project 2061 carries out research and development of tools and curricula to help improve the quality of K–12 science curricula, instruction, and assessments. It collaborates with organizations devoted to science education to promote an approach to learning that helps students understand essential science ideas as they engage in the kinds of activities scientists use every day to answer questions about the world.

Global Influence of Science Literacy Efforts

In 2015, Project 2061's leaders participated in international conferences about promoting science literacy and science, technology, engineering, and mathematics (STEM) innovations, and shared results from some of the Project's work. George DeBoer, Project 2061's deputy director, was a keynote speaker at the 2015 Shanghai International Forum on Science Literacy for Adolescents in September. He described the evolution of science standards for education in the United States, and the challenges of taking a more integrated approach to teaching STEM.

Director Jo Ellen Roseman spoke in July at the U.S.-Korea Conference on Science, Technology, and Entrepreneurship about the project's efforts to promote science literacy for all, and the role of scientific organizations such as AAAS in reforming education. Inspired by Project 2061's publication, *Science for All Americans*, which defined what a science-literate adult should know and be able to do, the Korea Foundation for the Advancement of Science and Creativity (KOFAC) is working to create a similar document for Koreans.

Bringing Energy Concepts to Teens

Project 2061 received a grant from the U.S. Department of Education's Institute of Education Sciences to develop a six-week curriculum unit for high-school biology students. The new unit will help

develop students' understanding of energy transfer and conservation in both living and non-living systems so that they can explain fundamental processes in living organisms, a major topic in most high-school biology courses.

"Energy concepts are quite abstract and can be very difficult for students, especially in a life-science context," said Jo Ellen Roseman, Project 2061's director. "Many middle-school students and college undergraduates share some of the same misunderstandings about energy, so it's clear that a whole new approach is needed."

To help make ideas about energy more concrete, the new unit will use a variety of analogies, beginning with phenomena drawn from more familiar physical systems such as combustion and charging a cellphone battery. Building on these experiences, the unit will then help students understand that the same energy-releasing and energy-requiring chemical reactions also occur in living organisms—they are just more complex and difficult to observe. Examples of biological energy transfers include cellular respiration, and creating a charge across a membrane in mitochondria and nerve cells.

The unit will also have students work with a range of models, such as interactive simulations and virtual labs, designed to help them think about and explore energy phenomena and make sense of their observations.

Over the course of the three-year curriculum project, the research team will design a professional-development program and materials for teachers, plus a set of assessments for evaluating students' understanding of the concepts presented in the new unit.

Workshops for Educators

Science teachers, curriculum and assessment specialists, and education researchers continued to turn to Project 2061 for help in improving their students' learning. Nearly 70 educators attended Project 2061 workshops in 2015 to learn more about developing and using high-quality science curricula and assessments, including those that are designed to support *Next Generation Science Standards*. Attendees also included middle-school teachers who were getting ready to use the project's new *Toward High School Biology* curriculum unit.

In addition to introducing the Project's research and development efforts, the workshops gave participants a chance to try out its tools and resources for themselves. They engaged in activities from the new curriculum unit, for example, and used diagnostic test items from the Project's science-assessment website.

New Weather@School Website Launched

A new website developed by Project 2061, WeatherSchool@AAAS (weatherschool.aaas.org), uses real-world data collected from around the globe to teach fundamental concepts of weather and climate. In a series of interactive modules that include graphing tools, data sets, guided activities, and quizzes, middle- and high-school students can learn how moving air masses cause day-to-day temperature variations, how geographic factors such as elevation above sea level influence temperature, and how the movement of the Earth in relation to the sun affects temperatures over the course of a year.

The new site is consistent with recommendations in the *Next Generation Science Standards*, and it encourages teachers to integrate the core ideas that students are learning with the practices of science, such as generating data, creating graphs and tables, and looking for relationships and patterns.

Searching for Standards-Aligned Curricula

While 12 states and the District of Columbia have adopted new *Next Generation Science Standards* (NGSS) for K-12 classrooms, educators are struggling to find teaching materials and curricula that fit with the standards' goals. In response, Project 2061 in April led a symposium at the annual meeting of the National Association for Research in Science Teaching. Three case studies were presented, in which curriculum materials were analyzed using the Educators Evaluating the Quality of Instructional Products (EQuIP) Rubric developed by Achieve, an organization that helped to create the NGSS.

"Everyone is desperately looking for examples of what [NGSS] looks like in curriculum materials and teaching," said Jo Ellen Roseman, director of Project 2061. Educators are also going to need tools and measures they can use to evaluate textbook publishers' claims that their materials are "NGSS-aligned," she said. The NGSS standards emphasize three main dimensions of science learning: science practices for investigating the world, crosscutting concepts common to all scientific topics, and core ideas within scientific disciplines.

Roseman and her colleagues reported that the EQuIP tool helped them to identify strengths and weaknesses of curricula in several key ways, and engaging in the EQuIP analysis deepened their understanding of the NGSS and its vision for science teaching and learning.

2015 Education, Outreach, and Careers

Improving education and opportunities for students and professionals in science, technology, engineering, and mathematics (STEM) is a primary goal of AAAS. This not only benefits individuals, but society, which needs science-literate citizens and a well-trained STEM workforce. The Education and Human Resources Programs team at AAAS oversees internships, awards, training programs, and conferences that reach out to women and underrepresented groups to ensure that society will have access to a full spectrum of STEM talent.

Emerging Researchers

More than 1,000 students, researchers, professors, and administrators from 240 colleges and universities attended the 2015 Emerging Researchers National (ERN) Conference in STEM, hosted by AAAS and the National Science Foundation (NSF). The ERN conference, held annually in Washington, D.C., provides an opportunity for undergraduate and graduate students in STEM fields to enhance their science-communication skills through poster and oral presentations, and to benefit from career-information sessions on topics such as applying to graduate schools, funding higher education, and STEM career trends.

Many of the students attending the ERN conference participate in programs funded by the NSF's Division of Human Resources Development, which provides opportunities for underrepresented minorities, women, and persons with disabilities to pursue research and education in STEM fields.

The conference tries to provide a supportive, encouraging space for students who face additional barriers to entering science to present their research, often for the first time, said Shirley Malcom, director of AAAS Education and Human Resources Programs. "This is a wonderful entrée into being able to see yourself as part of the scientific community," she told attendees.

AAAS-Lemelson Invention Ambassadors

Seven men and women from academia and industry joined the second class of AAAS-Lemelson Invention Ambassadors in July. Formed by a partnership between AAAS and The Lemelson Foundation, the program is designed to cultivate a new and diverse generation of inventors, and to increase understanding of the role of invention in creating new products and establishing new businesses.

The Ambassdors, who together hold more than 220 patents, were selected for their high regard for the role of invention, their success with invention, their accomplished professional careers, a commitment to invention's role in impacting environmental sustainability, and their interest in speaking to different audiences. "All of us have an inventor inside of us," said Ambassador Lisa Seacat DeLuca, the most prolific woman inventor in IBM history.

EntryPoint! Widens the S&T Pipeline

Twenty-seven undergraduate students with disabilities got a chance to try out working in STEM positions, through internships facilitated by the AAAS EntryPoint! Program. Launched in 1996, the program has recruited students to work in industry, universities, and government agencies, including at NASA, Georgia Tech, and Johns Hopkins University.

Of the 580 alumni of the program, more than 80% are now working in STEM fields, and alumni sometimes mentor new students, said Laureen Summers, the program's coordinator. It is the only such program for disabled college students that focuses on STEM jobs, she said.

Changing the Face of Science

While the number of women entering STEM careers, including faculty positions in academia, has been growing, women, along with minorities and persons with disabilities, are still underrepresented in these fields. AAAS sponsors several awards to help women succeed in science.

Four women were awarded the first AAAS Marion Milligan Mason Awards for Women in the Chemical Sciences in October. The award is named for a long-time AAAS member and chemist who left a $2.2 million bequest to provide funding for early-career women researchers. The $50,000 awards, which help winners do research and attract and mentor graduate students, will continue to be awarded to three women every two years for the next 20 years.

At an awards ceremony at AAAS, four winners spoke with appreciation for the mentors who helped to steer them on their course. "As I evaluate all the mentorship that I had during my chemistry career, I would like to pass that along to my students," said Luisa Whittaker-Brooks, an assistant professor of chemistry at the University of Utah. She became interested in science as a high-school student in Panama, thanks in large part to an enthusiastic teacher who told her that she had a bright future in chemistry.

AAAS also administers the L'Oréal USA for Women in Science Fellowship, which awarded five women with $60,000 research grants in October. The recipients were an exoplanet astrophysicist, a marine microbiologist, a synthetic biologist, a cancer bioengineer, and a condensed matter physicist.

The Elsevier Foundation Awards for Women in Science in the Developing World, with its partners, the Organization for Women in Science for the Developing World and the World Academy of Sciences, also recognize early-career women scientists. Each year, five women are awarded $5,000 and a trip to the AAAS Annual Meeting. The 2015 winners from Nigeria, Sudan, and Vietnam were selected for their contributions to nanoparticle physics, atmospheric physics, medical physics, and computational mathematics, and their efforts to encourage other women to pursue STEM careers. Gilbert S. Omenn, a past AAAS president, and Martha Darling helped to support the awards.

Mass Media Fellows March On

Most of the 2015 AAAS Mass Media Science and Engineering Fellows began their 10-week internships at *Scientific American*, *Slate*, *WIRED*, the *Los Angeles Times*, NPR, and other outlets having little or no journalism experience—just a knowledge of science and a desire to share it while improving their communication skills. Afterward, about two-thirds said that they would like to continue to work in journalism, and many of those who will return to science say they want to continue to use the skills they honed to communicate about science with the public.

"This program helps in both ways. Not only do we have some of the best science journalists anywhere who have come out of this program and now give back to this program, but we also have dynamic scientists who have come out of this program, and they are also excellent communicators," said Shirley Malcom, director of Education and Human Resources Programs at AAAS. The highly competitive fellowship is open to upper-level undergraduate students, graduate students, or post-doctoral scholars in STEM fields.

2015 AAAS Divisions

The three divisions of AAAS serve as regional networks for scientists and engineers. Through annual meetings and other events, the Divisions also provide a forum for scientists and local communities to discuss issues that benefit from scientific input. In 2015, AAAS Divisions addressed the health of Arctic coastal regions in the face of climate change, international research collaborations with Cuba, and the effects of human population growth and development, particularly in the Galápagos Islands.

Caribbean Division

The 30th annual meeting of the AAAS Caribbean Division convened 12 September in San Juan, Puerto Rico. Carlos A. Torres Ramos, an assistant professor at the University of Puerto Rico School of Medicine, and president of the AAAS Caribbean Division, welcomed more than 150 scientists, educators, and students who attended the day-long event, which had three concurrent sessions on themes of science education and sustainability.

Sergio Jorge Pastrana, the executive director and secretary of foreign affairs at the Academy of Sciences of Cuba, gave the keynote address on the Academy of Sciences of Cuba and its role in international scientific collaborations. Established in 1861, the Academy was the first association of its kind in the New World.

Two centuries later, following the Cuban Revolution, the country intensely focused on building its capacities in education, science, and medicine. Today, Cuba's biotechnology industry exports a number of important vaccines and other biomedical technologies, and the country's infant mortality rates and average lifespans are roughly comparable to those in the United States.

Pastrana has been a key figure in many science-related partnerships between Cuba and other countries, including the United States. He

participated in an April conference on science diplomacy, held at AAAS headquarters, and earlier, he took part in a meeting between the Cuban Academy of Sciences and a AAAS-led delegation in Havana. That conference resulted in a joint agreement to foster joint cooperation in biomedical research (for more information, see page 12).

Arctic Division

The health and sustainability of near-shore zones and estuaries in the face of climate change was the focus of the 2015 Arctic Science Conference, which took place 1-3 October. These areas, where freshwater and oceans meet, serve as a gateway for fish and other migratory animals. They are increasingly important and vulnerable as climate change affects their chemistry and biology, and as it opens new sea routes.

The conference, which was hosted by the University of Alaska Anchorage, also served as the annual meeting of the AAAS Arctic Division. Researchers from the life, physical, and social sciences as well as artists and educators attended the meeting.

The Arctic is warming twice as fast as the lower latitudes, according to the Arctic Report Card, prepared by the National Oceanic and Atmospheric Administration (NOAA). As a result, scientists are trying to track the changes it is undergoing to learn what may eventually occur in more populated southern regions, said Larry Duffy, executive director of the AAAS Arctic Division.

"What we see happening in the north within the biota and the physical environment will happen later at lower latitudes, but with a much bigger impact," said Duffy, a professor of biochemistry at the University of Alaska Fairbanks. "When we talk here about a village of 500 people being eroded away, that's a problem. But when we talk about New York and New Jersey losing a portion of their coast due to sea-level rise—that's a big problem."

The warming temperatures also create stress on the 4 million people who live in the Arctic region, many of whom are indigenous people who rely on subsistence hunting and fishing. Arctic communities are seeing more frequent and severe extreme weather events, changing animal migration patterns, disappearing traditional ice paths, increasing tree lines, and eroding riverbanks, reported Mary Dallas Allen, associate professor at the University of Alaska Anchorage School of Social Work. Arctic communities are losing what it means to be home, she said.

Pacific Division

With a special focus on the 180th anniversary of Darwin's visit to the Galápagos Islands, the AAAS Pacific Division explored "Science in the Anthropocene" during its 14-17 June annual meeting at San Francisco State University. The gathering also began a celebration of the 100th anniversary of the year when the Pacific Division was founded.

Approximately 450 scientists, educators, students, and science enthusiasts from across the western United States attended the event, which was open to the public. Richard Cardullo, president of the AAAS Pacific Division and professor of biology at the University of California, Riverside, gave the Pacific Division presidential address on the science of human population growth and control.

The three-day symposium featured more than 30 speakers who discussed new research and a range of issues related to the Galápagos Islands, with sessions on the ecological impacts of human activities, and the status and conservation of the islands' native plant and animal species. The program also included a variety of symposia on other topics, including building relationships between racially diverse communities and police departments, 3D printing and open-source technology in science, technology, engineering, and mathematics education, as well as factors driving the emergence of vector-borne diseases.

The Pacific Division's annual meeting was co-sponsored by the California Academy of Sciences and Sigma Xi, The Scientific Research Society.

2015 Advancing Science Through Philanthropy

Philanthropic support and strategic partnerships allow AAAS to speak up on behalf of science, engineering, and society as opportunities and challenges arise. Our donors demonstrate strong vision and a deep commitment to the future of science through contributions to our Flexible Action Fund and support for specific programs.

A Transformative Gift from the Golden Family Foundation

Last fall, Lifetime Giving Society donor Sibyl R. Golden revealed her intention to make a gift of $4 million to AAAS, through the Golden Family Foundation. News of one of the most generous gifts in AAAS history generated significant excitement in the William T. Golden Center for Science and Engineering—the AAAS headquarters building in Washington, D.C.

Ms. Golden's gift honors her late father, William T. Golden, who was well-known for his contributions to science policy and his long career of public service and philanthropy. His input led to many milestones for the science enterprise, including the appointment of the first Science Advisor to the President and the Secretary of State, and the creation of the Office of Science and Technology in the Executive Office of the President (now the Office of Science and Technology Policy), the President's Science Advisory Committee (today, the President's Committee of Advisors on Science and Technology, or PCAST), and the National Science Foundation.

His influence was also a transformational force for AAAS. Mr. Golden served as AAAS Treasurer from 1969 to 1999, and as Honorary Treasurer until 2007. Over those 30 years, his generosity and foresight led to the creation of many of our best-known programs, including the signature Science and Technology Policy Fellowships program, which has been placing scientists in executive, legislative, and judiciary branch offices since 1973.

AAAS CEO Rush Holt is one of more than 3,000 alumni of that program. "Bill Golden's legacy is unparalleled. He has transformed the science-policy world, AAAS, and even my own career," Holt said.

The recent Golden Family Foundation contribution is second in magnitude only to Mr. Golden's 2003 gift of $5.25 million, which established the William T. Golden Fund for Program Innovation. At the time, Mr. Golden said, "I have great respect for the AAAS, as well as great affection and admiration for it, and I believe that the organization can become even more useful to society." His gift was intended to serve as the catalyst for creative, new, high-impact ideas that would not otherwise be funded as part of the association's budget.

And so it has, for just over a decade. In its first 12 years, more than 40 projects have received support from the Golden Fund, ranging from the popular Leadership Seminar in Science and Technology Policy—a one-week "crash course" designed for those who need to know how S&T policy works, to communication tools and training for scientists; and a Chinese-language portal for EurekAlert!, the science-news consortium established by AAAS for some 12,000 reporter-registrants; as well as key activities to build capacity for philanthropy.

Ms. Golden's 2015 contribution in her father's memory, which brings the William T. Golden Fund for Program Innovation to more than $9 million, creates opportunities for initiatives not otherwise possible, and will enhance AAAS's ability to pursue creative, innovative endeavors well into the future.

Leshner Leadership Institute Fellows Announced

AAAS has announced the first fellows of the Alan I. Leshner Leadership Institute for Public Engagement with Science. All are climate scientists with an interest in promoting dialogue between science and society.

The fellows will plan and implement climate communication activities with assistance from AAAS and work to promote public engagement within their institutions and professional communities. In June 2016, the Leshner fellows will convene at AAAS headquarters for a week of public engagement and science communication training, networking, and plan development.

The Leshner Leadership Institute was established in 2015 with support from more than 130 philanthropic gifts. The first cohort will focus on climate change; the second will address infectious disease. Subsequent fellows will focus on other areas of science. To learn more about this work and how to support it, contact the Office of Philanthropy and Strategic Partnerships at 202-326-6636.

First AAAS Marion Milligan Mason Awards Honor Early Career Women Chemists

In October 2015, the first AAAS Marion Milligan Mason Awards for Women in the Chemical Sciences were awarded to four outstanding women. The awards, made possible by a $2.2 million bequest to AAAS, provide each chemist with $50,000 to ramp up their research projects while mentoring their own students. Marion Mason's gift honors her family's commitment to higher education for women. (See also the Education, Outreach, and Careers section of this report.)

▲ Marion Milligan Mason Award Winners: From left, Rush Holt, Shirley Malcom, and Geraldine Richmond, representing AAAS, joined winners Luisa Whittaker-Brooks, Kristin Parent, Katherine Mackey, and Alison Fout. At right is AAAS Board Member Laura Greene.

PHOTO: MICHAEL COLELLA/COLELLADIGITAL.COM

2015 AAAS Awards and Prizes

The AAAS awards celebrate the achievements of extraordinary scientists, engineers, educators, and journalists. We congratulate each of our distinguished winners.

Eric Lander

AAAS PHILIP HAUGE ABELSON PRIZE

PHOTO: TONY CENICOLA/THE NEW YORK TIMES/REDUX

The Philip Hauge Abelson Prize, established in 1985, is awarded to a public servant in recognition of sustained exceptional contributions to advancing science, or to a scientist whose career has been distinguished both by scientific achievement and other notable services to the scientific community.

Dr. Eric Lander was recognized for advancing science and serving society through his extraordinary contributions to science, and for his ability to explain science to the public and students as well as his work bringing science to bear in serving the public.

Sir Peter Gluckman

AAAS AWARD FOR SCIENCE DIPLOMACY

Established in 2010, the AAAS Award for Science Diplomacy recognizes an individual or a limited number of individuals working together in the scientific and engineering or foreign affairs communities to make an outstanding contribution to furthering science diplomacy.

Professor Sir Peter Gluckman was recognized for transforming the theory and practice of science diplomacy in New Zealand and internationally, and for uniting national science advice by successfully bringing both fields together into a global network to strategically address global challenges.

Rita Elmore of AAAS, with Eric Lander, winner of the AAAS Philip Hauge Abelson Prize.

PHOTO: ©2016 ATLANTIC PHOTO—BOSTON

Jean Maria Arrigo

AAAS AWARD FOR SCIENTIFIC FREEDOM AND RESPONSIBILITY

The AAAS Award for Scientific Freedom and Responsibility, established in 1980, honors scientists, engineers, and their organizations whose exemplary actions, sometimes taken at significant personal cost, have served to foster scientific freedom and responsibility.

Dr. Jean Maria Arrigo was honored for her courage and persistence in advocating for ethical behavior among her fellow psychologists, the importance of international human rights standards, and against torture.

Mark Rosin

AAAS EARLY-CAREER AWARD FOR PUBLIC ENGAGEMENT WITH SCIENCE

The AAAS Early-Career Award for Public Engagement with Science, established in 2010 through the generosity of several AAAS donors, recognizes early-career scientists and engineers who demonstrate excellence in their contribution to public engagement with science activities.

Dr. Mark Rosin was honored for his broad range of creative and sustainable public-engagement strategies that target audiences who may not be actively seeking science information.

Mark Miodownik

AAAS AWARD FOR PUBLIC ENGAGEMENT WITH SCIENCE

The AAAS Award for Public Engagement with Science, formerly the Award for Public Understanding of Science and Technology, was established in 1987 and recognizes working scientists and engineers who make outstanding contributions to the "popularization of science."

Dr. Mark Miodownik was recognized for his enthusiastic and successful commitment to public engagement, and for igniting a sense of wonder about the world by unveiling the interplay between science, engineering, and the society.

Christine Grant

AAAS MENTOR AWARD

The AAAS Mentor Award, established in 1996, honors AAAS members who have mentored significant numbers of students from underrepresented groups, or who have changed the climate of a department, college, or institution to significantly increase the diversity of students pursuing and completing doctoral studies in the sciences. This award is directed toward individuals who have mentored students for less than 25 years.

Dr. Christine Grant was recognized for facilitating dramatic education and research changes that are leading to a significant production of African American doctorates and females in chemical engineering.

Saundra Yancy McGuire

AAAS MENTOR AWARD FOR LIFETIME ACHIEVEMENT

The AAAS Mentor Award for Lifetime Achievement, established in 1991, honors AAAS members who have mentored significant numbers of students from underrepresented groups, or who have changed the climate of a department, college, institution, or field to significantly increase the diversity of students pursuing and completing doctoral studies in the sciences. This award is directed toward individuals with more than 25 years of success in mentoring students.

Dr. Saundra Yancy McGuire was recognized for her transformative impact and contributions toward creating a diverse doctorate workforce in the field of chemistry.

AAAS NEWCOMB CLEVELAND PRIZE

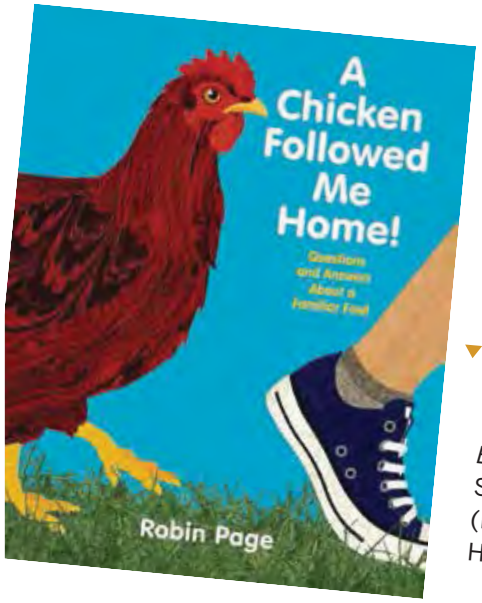
Supported by The Fodor Family Trust

The Association's oldest award, the AAAS Newcomb Cleveland Prize was established in 1923 with funds donated by Newcomb Cleveland of New York City. Now supported by The Fodor Family Trust, the Prize acknowledges an outstanding paper published in the Articles, Research Articles, or Reports sections of *Science*.

The 2014-2015 Newcomb Cleveland Prize was awarded to Bi-Chang Chen, Wesley R. Legant, Kai Wang, Lin Shao, Daniel E. Milkie, Michael W. Davidson, Chris Janetopoulos, Xufeng S. Wu, John A. Hammer III, Zhe Liu, Brian P. English, Yuko Mimori-Kiyosue, Daniel P. Romero, Alex T. Ritter, Jennifer Lippincott-Schwartz, Lillian Fritz-Laylin, R. Dyche Mullins, Diana M. Mitchell, Joshua N. Bembenek, Anne-Cecile Reymann, Ralph Böhme, Stephan W. Grill, Jennifer T. Wang, Geraldine Seydoux, U. Serdar Tulu, Daniel P. Kiehart, and Eric Betzig for their outstanding research article, "Lattice light-sheet microscopy: Imaging molecules to embryos at high spatiotemporal resolution," published in *Science* 24 October 2014.

AAAS/SUBARU SB&F PRIZES FOR EXCELLENCE IN SCIENCE BOOKS

The AAAS/Subaru SB&F Prizes for Excellence in Science Books, established in 2005, celebrate outstanding science writing and illustration for children and young adults.



CHILDREN'S SCIENCE PICTURE BOOK

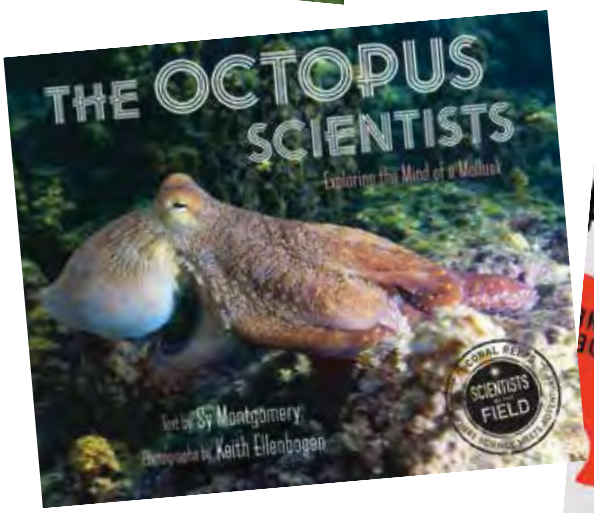
A Chicken Followed Me Home! Questions and Answers About a Familiar Fowl
Robin Page, Author and Illustrator
(Beach Lane Books)

MIDDLE GRADES SCIENCE BOOK

The Octopus Scientists: Exploring the Mind of a Mollusk
Sy Montgomery
(Houghton Mifflin Harcourt)

HANDS-ON SCIENCE BOOK

A Kid's Guide to Keeping Chickens
Melissa Caughey
(Storey Publishing)



YOUNG ADULT SCIENCE BOOK

How to Clone a Mammoth: The Science of De-Extinction
Beth Shapiro
(Princeton University Press)

AAAS KAVLI SCIENCE JOURNALISM AWARDS

These awards, endowed by the late Fred Kavli and The Kavli Foundation, recognize excellence in reporting for a general audience and honor individual reporters for their coverage of the sciences, engineering, and mathematics. A generous doubling of the program endowment by The Kavli Foundation permitted two awards in each of the eight categories for the first time—a Gold Award and a Silver Award—and opened the competition to entries from journalists worldwide.

LARGE NEWSPAPER—CIRCULATION OF 150,000 OR MORE

Gold Award
Andrea K. McDaniels
The Baltimore Sun

Silver Award
Nathaniel Herzberg
Le Monde

SMALL NEWSPAPER—CIRCULATION LESS THAN 150,000

Gold Award
Matthew Miller
Lansing State Journal

Silver Award
Helga Rietz
Neue Zürcher Zeitung (Switzerland)

MAGAZINE

Gold Award
Alexandra Witze
Nature and *Science News*

Silver Award
Amanda Gefter
Nautilus

TELEVISION SPOT NEWS/FEATURE REPORTING (20 MINUTES OR LESS)

Gold Award
Katie Campbell
KCTS 9 (Seattle)

Silver Award
Miles O'Brien
PBS NewsHour

IN-DEPTH REPORTING (MORE THAN 20 MINUTES)

Gold Award
Jonathan Renouf and Alex Freeman
BBC

Silver Award
Lone Frank and Pernille Rose Grønkjær
Danish Broadcasting Corporation

RADIO

Gold Award
Rami Tzabar and Angela Saini
BBC Radio 4 and BBC World Service

Silver Award
Dan Kraker and Elizabeth Dunbar
Minnesota Public Radio

ONLINE

Gold Award
Mark Harris
Backchannel

Silver Award
Kevin Sack, Sheri Fink, Pam Belluck and Adam Nossiter, with Daniel Berehulak, Dan Edge (for Frontline), and *The New York Times* graphics team
The New York Times

CHILDREN'S SCIENCE NEWS

Gold Award
Stephen Ornes
Science News for Students

Silver Award
Joan Cartan-Hansen
Idaho Public Television

2015 AAAS Fellows

AAAS Fellows are elected annually by the AAAS Council for meritorious efforts to advance science or its applications. Fellows have made significant contributions in areas such as research, teaching, technology, services to professional societies, and the communication of science to the public. The following members, presented by Section affiliation, were elected Fellows in fall 2015. AAAS congratulates them and thanks them for their services to science and technology.

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The AAAS Board of Directors gratefully acknowledges the individuals and organizations whose commitment to AAAS has sustained our efforts to advance science in the service of society and supported new activities in 2015.

Lifetime Giving Society

The Lifetime Giving Society recognizes individuals who have contributed a cumulative total of $100,000 or more during the course of their involvement with AAAS.

Stephen & Janelle Fodor
Sibyl R. Golden
Fred Kavli†
Alan & Agnes Leshner
Edith D. Neimark
Gilbert S. Omenn & Martha A. Darling
Daniel Pinkel
The Pitts Family
Carol Raugust†
The Roger & Ellen Revelle Family
David E. Shaw & Beth Kobliner Shaw
William F. Ward†

Edison Society

The Edison Society recognizes individuals who pave the way for the success of AAAS and our efforts on behalf of science and society through their leadership gifts throughout the year.

$100,000 and above

Sibyl R. Golden & the Golden Family
Daniel Pinkel
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"I support AAAS because of its critical role in educating lawmakers so that they better understand the science behind policy decisions." – Kenneth A. Cowin

†Deceased

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Each year, contributions from our President's Circle donors support our most timely and important activities.

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Hsiu S. Lin
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G. Lafayette Maynard
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Lester Newman
Pauline Newman
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Thomas W. Newton
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Martinus H. Nickerson
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Robert Nishikawa
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Dag Nummedal
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Rada Petrinjac-Nenadic
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Pat Phillips
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Donald & Donna Pulitzer
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Paul B. Reichardt
Frank Reichenbacher
Peter J. Reichl
Leonard Reiffel
Jakob Reiser
Minocher C. Reporter
Robert W. Rex
Solon L. Rhode

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Richard A. Rhoden
Joseph Rhodes
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Rollin C. Richmond
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AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE

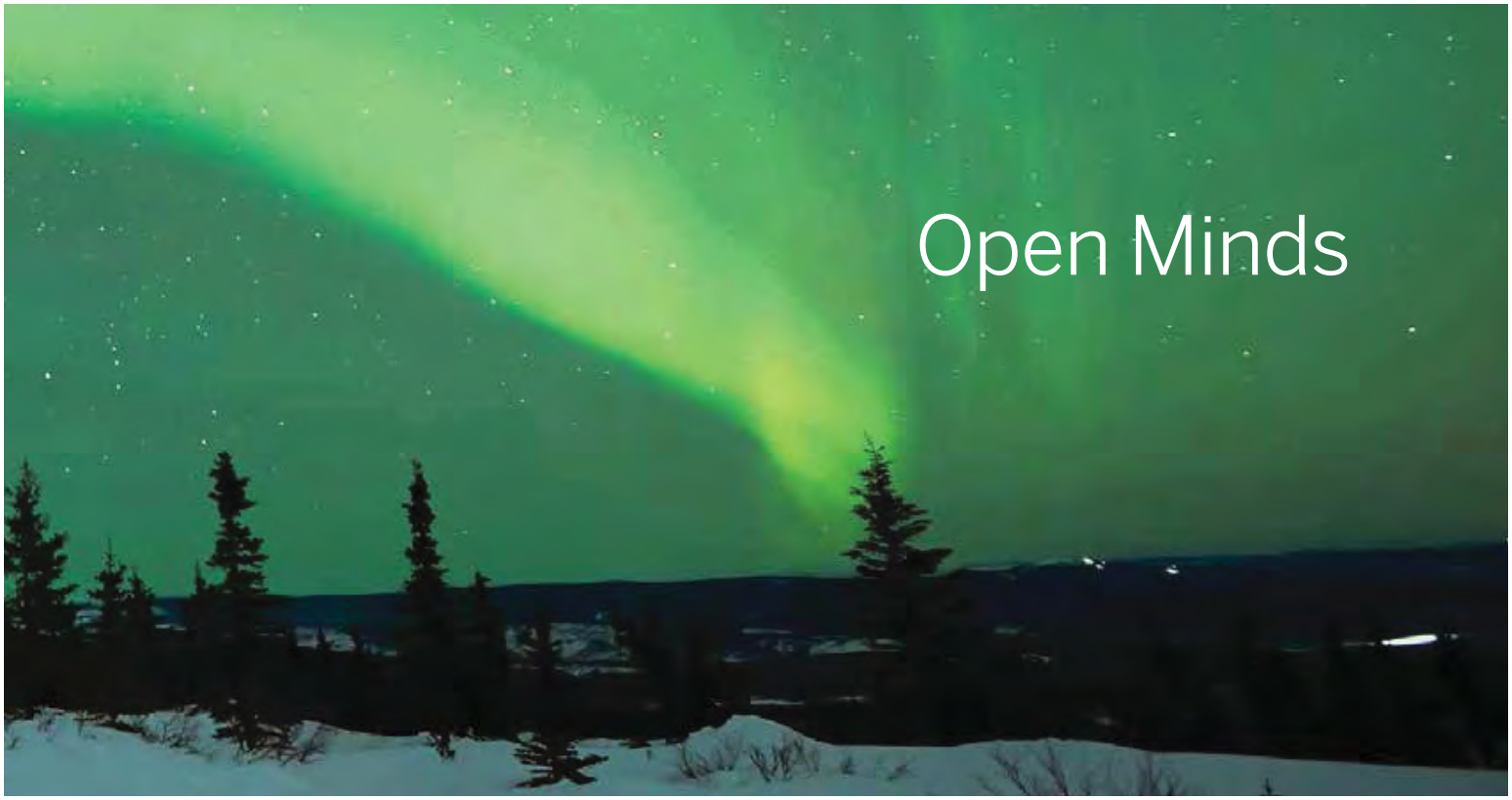
2015 By Joining AAAS, Members Become a Voice for Science

Research published in the *Science* family of journals in 2015 described advances in cancer immunotherapy and personalized vaccines, new insights to climate-change impacts, and the first fascinating flyby of the dwarf planet Pluto and its moon, Charon. At the same time, AAAS dispatched 280 Science & Technology Policy Fellows to Capitol Hill and elsewhere, bringing science to bear in policy decisions. The association also provided awards and mentoring programs to help uplift women in science, worked to improve science education, leveraged science diplomacy, and spoke forcefully on the urgent need to address climate change and to fully fund research and development. AAAS members remain essential to these and many other high-impact activities. By becoming members of AAAS, scientists, engineers, teachers, and others become a force for advancing science to serve society, and a voice for the scientific enterprise worldwide.

The benefits of AAAS membership include the *Science* journals, but also much more—particularly now, as the association has been transforming itself to better serve its members. In addition to becoming a member-facing organization, the Transformation Initiative calls on AAAS to ramp up advocacy efforts, and to adopt innovative, "digital-first" approaches to scientific communication. Already, AAAS has made significant strides toward becoming a truly digital-first enterprise, through a comprehensive redesign of the *Science* website, the rollout of an open-access journal, *Science Advances*, and plans for two new journals, *Science Robotics* and *Science Immunology*.

AAAS has also made meaningful progress toward putting members first. Engaging every AAAS member more fully in the association and its contributions to society, while also substantially increasing the number of members who help give science a voice on pressing global issues, will remain key priorities for the new Membership Engagement and Development Office. This has meant finding ways to better serve members both by improving member services, and by providing members with what they need and want to advance their careers throughout their lives—from kindergarten through the post-doctoral and professional stages.

How is AAAS improving member services? By the end of 2016, a new AAAS Member Platform will provide long-time and new members alike with much more



intuitive access to AAAS, thereby enhancing the member experience. Specifically, the new Member Platform will allow users to maintain a single log-in, learn how they can become more involved with AAAS, update their membership profile, and more easily renew their relationship with the association, 24-7. Already, the membership-renewal process has been streamlined and simplified. The association's public website, www.AAAS.org, is meanwhile being merged with MemberCentral to provide a smoother user experience across all AAAS online sites.

New career services and products are also being launched, including certificate-level online courses to help members avoid common errors in proposal writing, understand the federal R&D budget process, effectively work with policymakers, communicate science to non-scientists, and engage with the public on science-society issues. (See Careerdevelopment.AAAS.org.)

Members make it possible for AAAS to help broaden the science and technology talent pool, build bridges toward international research cooperation, and communicate the value of science—and scientific investments—to society. AAAS is therefore working to dramatically expand its membership, by reaching out to sectors that may have been less engaged with AAAS in the past, such as those working in industry, students and faculty at community colleges, early-career professionals, high-school students, and eventually, the science-interested public. As part of a new Employee Ambassadors Program, every member of the AAAS staff has become a member of AAAS so that they can experience firsthand what it means to be a member. Employees are also being challenged to help expand the ranks of AAAS. Every existing member can be a positive force for science, too, by spreading the word about the good work that AAAS is doing. Help to give scientists and engineers an influential voice worldwide. For AAAS membership information, log onto **www.aaas.org/join**.

AAAS

2015 Financial Statements

Consolidated Statements of Financial Position for the years ended December 31, 2015 and 2014
($ in thousands)

	2015	2014
ASSETS		
Cash	5,311	5,860
Accounts receivable, net	3,345	2,929
Grants and contributions receivable, net	11,064	6,316
Prepaid expenses and other	2,800	2,307
Investments	77,169	92,335
Property, plant and equipment	57,490	58,046
Total assets	**157,179**	**167,793**
LIABILITIES AND NET ASSETS		
Liabilities:		
Accounts payable and accrued expenses	10,629	13,169
Deferred dues, subscriptions revenue and other	22,133	24,465
Bonds payable, net	7,471	9,209
Total liabilities	40,233	46,843
Net assets:		
Unrestricted	83,611	93,986
Temporarily restricted	18,309	17,776
Permanently restricted	15,026	9,188
Total net assets	116,946	120,950
Total liabilities and net assets	**157,179**	**167,793**

Consolidated Statement of Changes in Net Assets for the years ended December 31, 2015 and 2014
($ in thousands)

	2015	2014
Revenues:		
Member dues	9,446	9,914
Publishing	49,891	49,748
Grants and other program support	29,023	29,077
Leasing, investments and other	10,185	11,771
	98,545	100,510
Expenses:		
Publishing	47,198	46,711
Education, policy and other programs	38,424	38,987
General and administrative expenses	16,398	15,642
	102,020	101,340
Operating income, before tax	(3,475)	(830)
Provision for income tax	58	221
Nonoperating revenue and expense	(6,841)	(3,399)
Change in unrestricted net assets	(10,374)	(4,450)
Change in restricted net assets	6,370	(644)
Change in net assets	(4,004)	(5,094)
Net assets, beginning of year	120,950	126,044
Net assets, end of year	116,946	120,950

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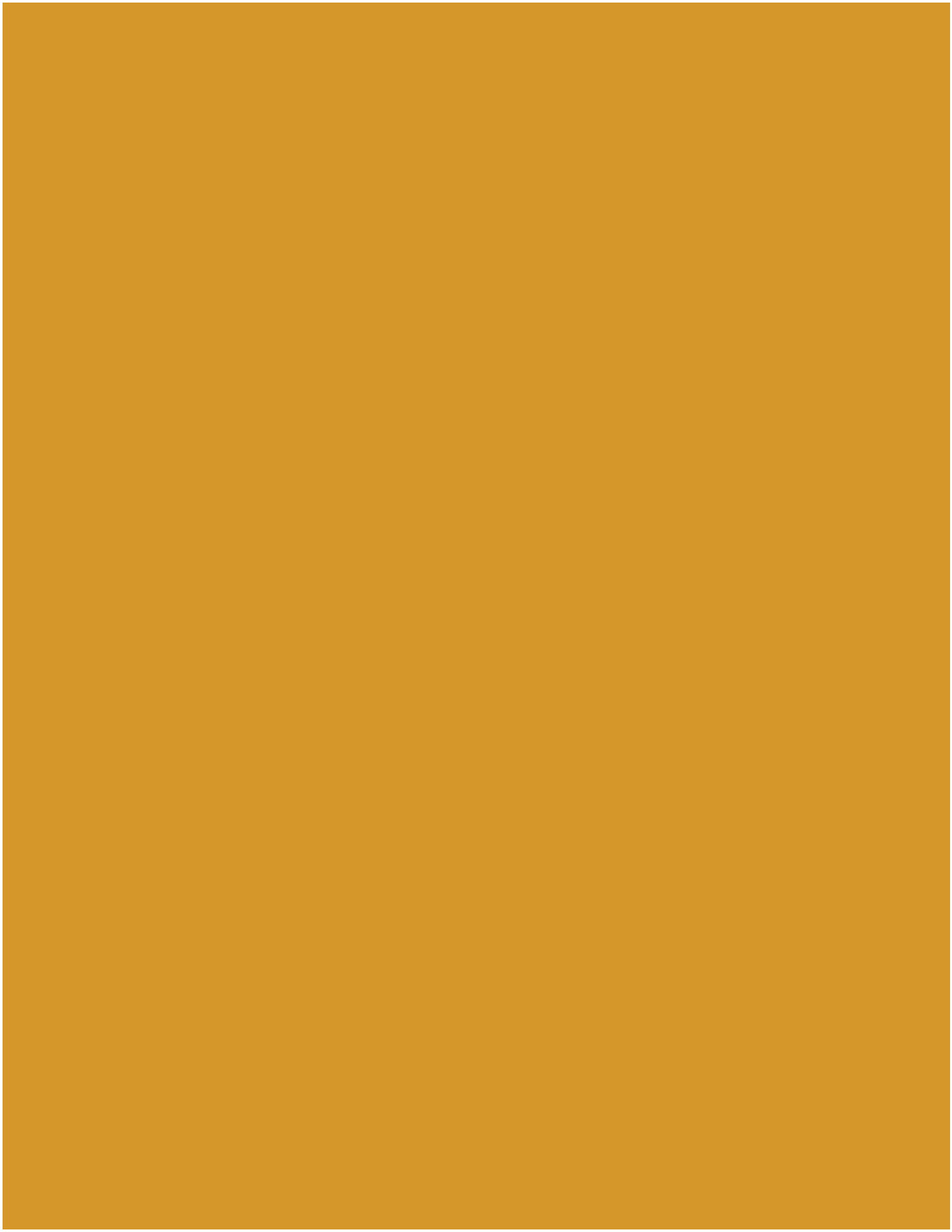

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March 18, 2016

As leading academic medical centers and scientific and medical societies who conduct and support life-saving research, we have grave concerns about legislative proposals to restrict the use of fetal tissue for research.

From therapies for end-stage breast cancer, diabetes, and Parkinson's disease to a promising vaccine for Ebola, vital medical research depends on continued use of fetal tissue under current laws and regulations. Fetal tissue continues to be an important resource for biomedical research. Fetal tissue is used when scientists need a cellular system that is less differentiated than adult cells. According to the U.S. Department of Health and Human Services, "fetal tissue continues to be a critical resource for important efforts such as research on degenerative eye disease, human development disorders such as Down syndrome, and infectious diseases, among a host of other diseases." Since the 1930's, fetal tissue has been used in a broad range of research that has led to lifesaving discoveries. In the past, human fetal tissue research has been critical in establishing permanent cell lines for use in vaccine research for diseases such as polio, hepatitis A, measles, mumps, rubella, chickenpox, and rabies. These established cell lines are currently being used to develop an Ebola vaccine.

Legislative proposals that halt research from cells already developed from fetal tissue and/or restrict scientists' access to new tissue or cell lines would have serious downstream consequences:

- They would limit new research on vaccines not yet developed, for treatments not yet discovered, for causes of diseases not yet understood.
- Some research questions cannot be answered using previous cell lines that have been immortalized; such proposals would prevent research that requires tissue that has been obtained more recently.
- Such proposals would restrict research only to organs or tissues for which cell lines currently exist, preventing new avenues of research exploring differences between tissue types.
- Such proposals would restrict access to new tissue necessary for the development and validation of novel research tools and technologies – essential to cutting-edge research.
- Organs and tissues are not just composed of a single type of cell, but rather an environment of multiple cell types; proposed restrictions would prevent scientists from studying the behavior of cells as they exist in our bodies.

As a prominent bioethicist has observed, the legal and ethical rules enforced for fetal tissue donation are similar in many respects to the ethics of organ donation. The ability to donate fetal tissue for medical research is not linked to an increase in the number of abortions practiced. Nor can we reasonably expect a limitation on fetal tissue donation or research to reduce the number of abortions. Rather, it will prevent the use of tissue that would otherwise be destroyed, hindering efforts to better understand, diagnose, and treat diseases.

We understand and share some of the concerns that have been raised in response to recent headlines, and our institutions endorse strong ethical practices that will address these concerns without shutting down vital research. We oppose any efforts to profit from the sale or distribution of human fetal tissue. Additionally, we embrace the best ethical practices that separate the decision to have an abortion from the decision to donate tissue for research.

As physicians and scientists, we work every day to save and improve lives. We urge lawmakers to support our ability to continue this important work by rejecting any proposals that restrict access to fetal tissue for research that has the potential to save countless lives.

American Association for the Advancement of Science
American Congress of Obstetricians and Gynecologists
American Physiological Society
American Society for Reproductive Medicine
American Society of Hematology
Association of American Universities
Association of Anatomy Cell Biology and Neurobiology Chairs
Association of Chairs of Departments of Physiology
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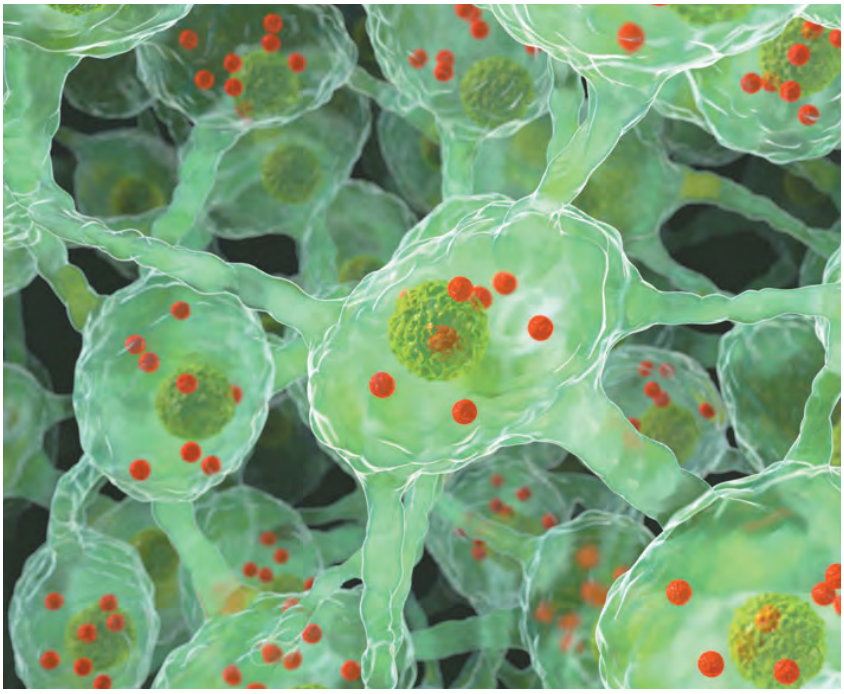
NEWS IN FOCUS

SPACE Uncertainty over future triggers push in space-station research **p.196**

GENETICS Competition over breast-cancer tests hots up a year after patent ban **p.198**

ACOUSTICS Marine signal offers lead in hunt for missing plane **p.199**

SOUTH AMERICA Seeds of success build hope for stronger science **p.201**



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Defective brain neurons are responsible for the mobility problems seen in people with Parkinson's disease.

REGENERATIVE MEDICINE

Fetal-cell revival for Parkinson's

Moratorium on controversial therapy lifted as stem cells emerge as alternative source of treatment.

BY ALISON ABBOTT

A neurosurgery team will next month transplant cells from aborted human fetuses into the brain of a person with Parkinson's disease. The operation breaks a decade-long international moratorium on the controversial therapy that was imposed after many patients failed to benefit and no one could work out why.

But the trial comes just as other sources of replacement cells derived from human stem cells are rapidly approaching the clinic. And this time, scientists want to make sure that things go better. So the teams involved in all the planned trials have formed a working group to standardize their research and clinical protocols in the hope that their results will be more easily interpretable.

People with Parkinson's disease suffer from a degeneration of neurons that produce the neurotransmitter dopamine, which is crucial for normal movement. This often leaves patients with severe mobility problems. Standard treatment includes the drug L-dopa, which replaces dopamine in the brain but can cause side effects. The cellular therapies aim to replace the missing neurons with dopamine-producing (dopaminergic) cells from fetal brains or with those derived from human stem cells.

The moratorium on replacement-therapy trials was introduced in 2003 because the early fetal-cell studies had produced varying results that were impossible to interpret.

"We want to avoid a repeat of this situation," says neurologist Roger Barker at the University of Cambridge, UK, who helped to organize the working group's inaugural meeting in London last month. The group, known as the Parkinson's Disease Global Force, includes scientists from the European, US and Japanese teams about to embark on the trials. At the meeting, they pledged to share their knowledge and experiences.

The first human transplantation of fetal brain cells took place in 1987 at Lund University in Sweden, where the technique was pioneered. Surgical teams took immature fetal cells destined to become dopaminergic neurons from the midbrain of aborted fetuses and transplanted them into the striatum of patients' brains, the area of greatest dopamine loss in Parkinson's disease.

More than 100 patients worldwide received the therapy as part of clinical trials before the moratorium. "But centres used different procedures and protocols — it was impossible to work out why some patients did very well and others didn't benefit at all," says Barker.

In 2006, Barker, together with neuroscientist Anders Björklund at Lund University, set up a network to bring together the original seven teams that had performed the transplants, to assess all protocol details and patient data retrospectively.

The teams worked out that the procedure tended to be most effective in patients who were relatively young and whose disease was at an early stage. In addition, post-mortem analysis of patients' brains showed that those who benefited most had at least 100,000 dopamine-producing cells of fetal origin integrated into their brains. Cells from at least three fetuses are needed to achieve these numbers, the neuroscientists concluded.

The retrospective analysis encouraged the European scientists, including Barker and ▶

Björklund, to launch a new trial, which is funded by the European Union, involving fetal dopaminergic-neuron transplants. Known as TRANSEURO, it will monitor disease progression in 150 patients in the United Kingdom, Sweden, France and Germany. The first patient is due for transplantation next month at Addenbrooke's Hospital in Cambridge. In line with the retrospective findings, the average age of trial participants at recruitment was 55, and their average disease duration just 4 years. None had displayed dyskinesias — uncontrolled muscle movements that can be a side effect of L-dopa treatment.

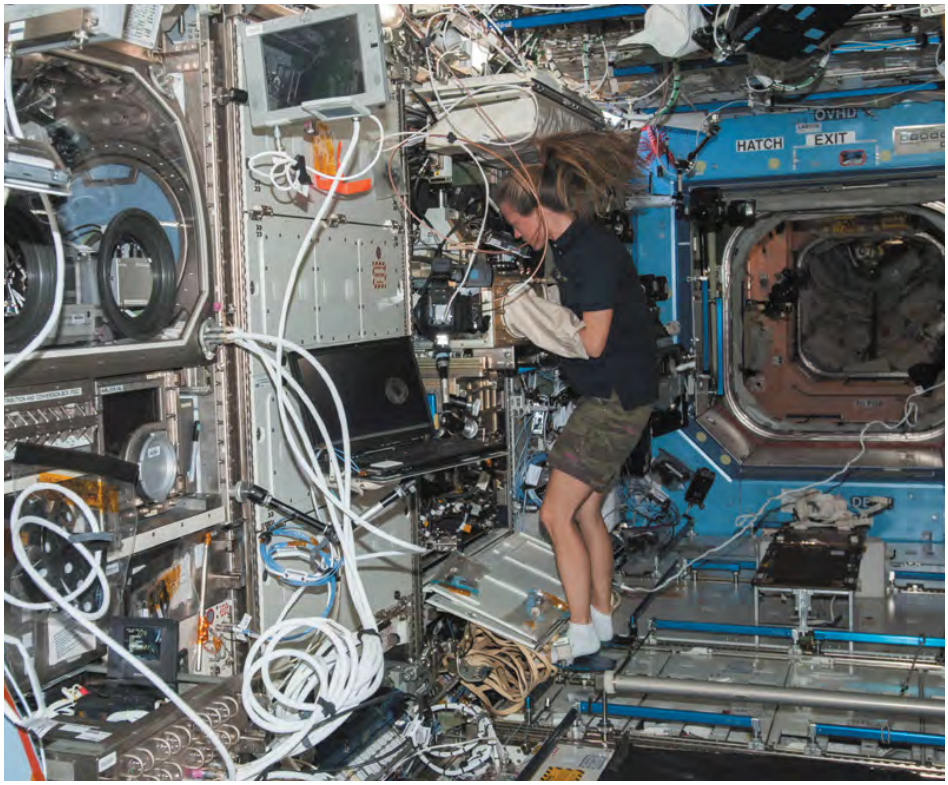
But stem-cell biology has advanced significantly since 2003, and dopaminergic neurons can now be derived from human embryonic stem cells and also from induced pluripotent stem cells — mature cells that have been rewound to an uncommitted stem-cell-like state and that can be coaxed to become a cell type of choice. These potential sources are more desirable than those derived from fetuses, because fetal cells are hard to come by and their biology varies.

Research is under way to ensure that the stem cells develop into the exact type of dopaminergic cell needed to treat Parkinson's and that they become correctly integrated into recipients' brains. But progress has been so fast that clinical trials are already on the horizon. A Japanese trial, using induced pluripotent stem cells, is planned to start in Kyoto within two years; and two trials using human embryonic stem cells are also planned, one to begin within three years in New York and the other in Europe within four to five years.

The Parkinson's Disease Global Force hopes that its joint planning will make comparing outcomes easier. Members will share their protocols for deriving and grafting cells, as well as their clinical criteria for patient selection and follow-up.

They see the TRANSEURO trial as a pathfinder. "We don't know yet which source of cell will turn out to be the best, but right now the fetal cell is the gold standard we need to match," says neurologist Claire Henchcliffe from the Weill Cornell Medical Center in New York, who is coordinating the working group's guidelines on patient assessment and trial design.

The stem-cell approaches have a long way to go before they can rival the promise of fetal cells, says Lund University stem-cell biologist Malin Parmar, a member of the European clinical-trial team. That is because the cells from fetal brains are already on the way to becoming mature dopaminergic cells. "The human body knows very well how to develop each cell type from the embryo," she says. "We haven't learnt all of these secrets yet, but we have learnt some major ones." ■



NASA astronaut Karen Nyberg works on a colloid experiment aboard the International Space Station.

NASA

SPACE

Space-station science ramps up

NASA pushes research agenda in face of Russian resistance.

BY ALEXANDRA WITZE

In January, when the United States proposed extending International Space Station (ISS) operations until 2024, the world was a very different place. That was before Russian military intervention in Ukraine, before US–Russian relations foundered and before Russian deputy prime minister Dmitry Rogozin suggested that US astronauts use a trampoline to get themselves to orbit (see *Nature* http://doi.org/s4f; 2014).

Rogozin also suggested last month that Russia would stop participating in the space-station programme after its scheduled end date of 2020. That statement did not set official government policy, but given Russia's key role in the orbiting outpost it cast a shadow over hopes for the four-year extension.

With the clock ticking, the race is on to conduct as much science as possible in whatever time the space station has left. At a conference next week in Chicago, Illinois, NASA scientists will try to lure researchers who have not worked with near-zero-gravity conditions before. The goal is to get them to propose anything from the usual research agenda — such as protein crystallization and human physiology experiments — to basic biomedical research and Earth-science observations that can take advantage of the high-flying platform before its mission ends (see 'Research push'). "There's never been anything like it," says Julie Robinson, NASA's space-station research chief at the Johnson Space Center in Houston, Texas. "It's like a university, all together with all the disciplines — I don't know if we'll see that again."

More than 1,600 scientists from 69 countries have contributed to experiments carried out on the space station since its first module was launched in 1998. The United States is the largest science user. But over the years, many have questioned the value of the science done in orbit. One main goal is to help humans to endure long-duration spaceflight, but early experiments often failed. For instance, NASA astronauts would spend hours a day exercising on treadmills to slow down muscle wasting and bone loss — to little avail. Force measurements revealed that they were subjecting their bodies to stresses that were not

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Facts About Fetal Tissue Research

From The American Society for Cell Biology

For further information please contact:
Timothy E. Leshan Director of Public Policy

Facts About Fetal Tissue Research

1. What is Fetal Tissue Research?

- Fetal tissue research is research using tissue from non-living human fetuses. "Fetus" is a term that represents the period from eight weeks after conception until birth. Fetal tissue is derived from legal abortions and may be legally used for the purpose of conducting life saving scientific experiments.

- Fetal tissue transplantation research uses fetal tissue to study potential treatment of life treating diseases.

2. Is Fetal Tissue Research Legal?

- Fetal tissue research is legal in the United States. In 1975 the law was clarified to say such research is permitted if "conducted only in accordance with any applicable state or laws regarding such activities (45 C.F.R. 46, Sec. 210).

- In 1993 Congresses passed the National Institutes of Health Revitalization Act (Public Law 103-43), which contained language restricting fetal tissue transplantation research. Prior to 1993, there was a five-year federal moratorium on fetal tissue transplantation research, but through and Executive Order the ban was lifted. The ability to conduct research using fetal tissue for other purposes had not been affected by the ban. The 1993 Revitalization Act amended the Public Health Service Act (42 U.S.C. 289 et seq.) as follows:

  (1) **In General** – The Secretary may conduct or support research on transplantation of human fetal tissue for therapeutic purposes.
  (2) **Source of Tissue** – Human fetal tissue may be used in research carried out under paragraph (1) regardless of whether the tissue is obtained pursuant to a spontaneous or induced abortion or pursuant to a stillbirth.

3. Where Do Scientists Get the Tissue?

- Scientists obtain fetal tissue for research purposes from a variety of sources including, hospitals, nonprofit tissue banks (one of which is funded by the NIH) and in some cases local abortion clinics.

4. Why is Fetal Tissue Research Important?

- Due to their capacity to rapidly divide, grow, and adapt to new environments, fetal cells hold unique promise for medical research into a variety of diseases and medical conditions.
- Researchers use fetal tissue to investigate questions of normal fetal development, and also to understand the potential to use fetal tissue to transplant into other humans to treat disease. Scientists have evidence that leads them to hope that this line of experimentation has great potential for disease treatment and prevention.
- Fetal tissue research has already led to major discoveries in human health and has the potential to continue to benefit mankind. According to the Centers for Disease Control and Prevention, "some vaccines such as rubella and varicella [were] made from human cell-line cultures, and some of these cell lines originated from aborted fetal tissue, obtained from legal abortions in the 1960s. No new fetal tissue is needed to produce cell lines to make these vaccines, now or in the future." These vaccines have effectively eradicated a major source of child morbidity and mental retardation in the U.S.

- Researchers study fetal tissue to learn more about birth defects and diseases. By studying normal and abnormal development in fetal tissue, scientists will learn more about gene activation that may cause metal retardation, Down's Syndrome, SIDS, and defective eye development. By learning more about fetal development, doctors will also be better prepared to conduct fetal surgery as needed. They will also gain new understanding of why some pregnancies are spontaneously aborted.

- The genes responsible for some diseases of later life, such as Alzheimer's, prostate cancer and Type II diabetes, may be activated during fetal development. More research in this area is needed to determine the possible link between fetal development and disease.

- There is hope that fetal tissue transplanted into patients with illnesses such as Parkinson's, diabetes or heart disease may be a valuable treatment. Fetal cells elicit less of an immune response than adult cells and are therefore less susceptible to rejection by the human body. These early fetal cells are not as developed as adult cells and are more able to accommodate to the donor.

  Although the ban on federal funding undoubtedly slowed the progress of such work with regard to Parkinson's disease, cell transplantation is showing great promise as an effective therapy for some Parkinson's patients. Several Parkinson's patients (in the U.S. and abroad) are reported to be off medication and symptom-free as a result of these treatments. The transplantation of fetal cells into the brains of Parkinson's patients has allowed some patients to regain speech, speed of movement, and quality of life.

- There is evidence that the expression of a specific chemical in the fetal thymus may be related to the development of Type I (juvenile) diabetes. Fetal tissue transplantation is being evaluated as a possible treatment.

- Fetal nerve tissue has been used to treat spinal cord injury, holding promise to end certain types of paralysis.

- In 1998 Dr. John Gerhart derived human 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 can develop into cells of other tissue types. This research represents a major breakthrough in stem cell research that may lead to treatments of a variety of devastating diseases.

5. Why Aren't Adult Cells Just as Useful as Fetal Cells?

- Scientists have found fetal cells to be less susceptible to rejection when used to treat diseases. While adult cells are generally more limited in their capacity to proliferate and adapt. For instance, studies are underway to determine if transplanting healthy cardiac cells into patients with heart failure may prove a valuable treatment. One area of research involves the comparison of fetal cell transplants versus adult cell transplants.

6. Why is the Congress Currently Investigating Fetal Tissue Research?

- In 1999, concern was raised by some Members of Congress that providers of fetal tissue were attempting to make a profit from the sale of fetal tissue, described by those who oppose fetal tissue research as "the sale of baby body parts." In response, in 1999 the House passed H. Res. 350, known as the Tancredo Amendment for its sponsor, Rep. Tom Tancredo (R-CO). The Senate defeated a similar measure sponsored by Senator Bob Smith (R-NH) in same year. The Tancredo Amendment calls on the House of Representatives to conduct hearings to investigate the allegations of illegal trafficking of fetal tissue.

7. Is Current Enforcement Adequate?

- Under the current law it is "unlawful for any person to knowingly acquire, receive, or otherwise transfer any human fetal tissue for valuable consideration if the transfer affects interstate commerce." "Valuable consideration" is equivalent to "profit" but does not preclude reasonable payments associated with the transportation, implantation, processing, preservation, quality control or storage of human fetal tissue. This law applies equally to federally funded and non federally funded scientists. Congress is investigating reports of isolated cases where some private providers may be overreaching the lawful limitation. To our knowledge, however, widespread violations of the law is unlikely.

- In 1997 the General Accounting Office issued a report indicating that all federally funded fetal tissue transplant projects were meeting established standards governing informed consent and fetal tissue acquisition, and no complaints regarding fetal tissue research have been lodged with the NIH, the agency charged with the oversight of federally funded research, since the GAO report was issued.

- Legal fetal tissue research funded by the federal government has profound potential to advance human health and prevent immeasurable suffering. Its progress should not be frustrated by a small minority of "bad apples" who may be illegally profiting from the sale of fetal tissue. Instead the law should be enforced and those who violate the law should be prosecuted to its fullest extent.

The American Society for Cell Biology
March 2000

SPECIAL COMMENTARY-ZIKA VIRUS AND PUBLIC HEALTH CONCERNS

Off the Podium: Why Public Health Concerns for Global Spread of Zika Virus Means That Rio de Janeiro's 2016 Olympic Games Must Not Proceed (http://harvardpublichealthr the-podium-why-rios-2016-olympic-games-must-not-proceed/)

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Off the Podium: Why Public Health Concerns for Global Spread of Zika Virus Means That Rio de Janeiro's 2016 Olympic Games Must Not Proceed

Amir Attaran, DPhil, LLB, MS. Faculty of Medicine and Faculty of Law, University of Ottawa

Brazil's Zika problem is inconveniently not ending. The outbreak that began in the country's northeast has reached Rio de Janeiro, where it is flourishing. Clinical studies are also mounting that Zika infection is associated not just with pediatric microcephaly and brain damage, but also adult conditions such as Guillain-Barré syndrome[1] and acute disseminated encephalomyelitis, which are debilitating and sometimes fatal.[2]

Simply put, Zika infection is more dangerous, and Brazil's outbreak more extensive, than scientists reckoned a short time ago. Which leads to a bitter truth: the 2016 Olympic and Paralympic Games must be postponed, moved, or both, as a precautionary concession. There are five reasons.

First, Rio de Janeiro is more affected by Zika than anyone expected, rendering earlier assumptions of safety obsolete. When in January the International Olympic Committee

declared Rio a "safe environment" for the Games, it was speculating, because Brazil's Ministry of Health temporized until February to declare Zika a notifiable disease and begin counting cases.[3] [4] Now with those data finally available, the situation seems not so safe: Rio de Janeiro's suspected Zika cases are the highest of any state in in Brazil (26,000), and its Zika incidence rate is the fourth worst (157 per 100,000).[5] Or in other words: according to the Brazil's official data, Rio is not on the fringes of the outbreak, but inside its heart.

Many have suggested that Zika will follow the pattern of other mosquito-borne diseases and decline during Rio's winter months of July to September. While that is probably true, nobody actually knows because Rio has never experienced a winter with Zika before. If one assumes, reasonably, that Zika will behave like dengue fever, because they are caused by related viruses and transmitted by the same *Aedes aegypti* mosquito, then Zika transmission will ebb but not vanish in Rio's winter, just as dengue did in winters past.

However, nobody knows how deep winter's ebb will be, especially this year, because Rio is undergoing a surprising and unexplained disease surge: in Rio de Janeiro city, dengue cases in the first quarter of 2016 are a shocking six fold higher than a year ago (8,133 cases, compared to 1,285 cases).[6] [7] That vertiginous rise is very worrisome, because it roughly coincides with the biggest military mobilization in Brazil's history, aimed at intensifying mosquito-killing efforts.[8] It would appear that those impressive efforts did not work as well as hoped in Rio, and with the starting baseline of *Aedes*-borne disease so much higher this year than last, it is far from guaranteed that the coming winter's ebb will make a "safe environment" for the Games.

Second, although Zika virus was discovered nearly seventy years ago, the viral strain that recently entered Brazil is clearly new, different, and vastly more dangerous than "old" Zika. Phylogenetic mapping demonstrates that this particular virus arrived in Brazil from French Polynesia in 2013.[9] Although

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the danger went unnoticed in French Polynesia at first, retrospective analyses now show that the risk of microcephaly increased by 23 to 53 fold.[10]

Later studies from Brazil now powerfully argue that the relationship is truly causal.[11] For example, in Rio de Janeiro—where the Games will take place—a very recent study shows that among women with confirmed Zika infections during pregnancy, fully 29% had fetal abnormalities on ultrasound.[12] Further, the Brazilian microcephaly cases have an unusual constellation of congenital defects severer than classical microcephaly, and suggestive of "fetal brain disruption sequence" in which the developing brain and skull collapse while other anatomical features like the scalp skin keep growing.[11]

The effects on the adult nervous system are only beginning to be studied, but the preliminary findings are not good, and suggest that exposure to the virus is linked to Guillain-Barré disease, increasing the odds 60 fold.[1] [13] Science cannot yet explain what makes this new Polynesian/Brazilian viral clade exceptionally neuropathological, so the assumption must be that if it spreads to other places, harm to human health will too. Would that we knew for sure, but we don't, so precaution is called for.

Third, while Brazil's Zika inevitably will spread globally — given enough time, viruses always do — it helps nobody to speed that up.[14] In particular, it cannot possibly help when an estimated 500,000 foreign tourists flock into Rio for the Games, potentially becoming infected, and returning to their homes where both local *Aedes* mosquitoes and sexual transmission can establish new outbreaks.[15] [16]

All it takes is one infected traveler: indeed phylogenetic and molecular clock analyses establish that Brazil's cataclysmic outbreak stems from a single viral introduction event likely between May and December 2013.[9] A few viral introductions of that kind, in a few countries, or maybe continents, would make a full-blown global health disaster. Scientists can disagree on

how much the mass migration of 500,000 foreigners will accelerate the virus's global spread and make the pandemic worse—but none can possibly argue that it will slow it down or make things better.

Fourth, when (not if) the Games speed up Zika's spread, the already-urgent job of inventing new technologies to stop it becomes harder. Basic Zika research is already on the fast track, and with time, the odds are excellent that scientists can develop, test and prove an effective Zika vaccine, antiviral drug, insecticide, or genetically-engineered mosquito. But by spreading the virus faster and farther, the Games steal away the very thing – time – that scientists and public health professionals need to build such defenses.

Fifth, proceeding with the Games violates what the Olympics stand for. The International Olympic Committee writes that "Olympism seeks to create ... social responsibility and respect for universal fundamental ethical principles". But how socially responsible or ethical is it to spread disease? Sports fans who are wealthy enough to visit Rio's Games choose Zika's risks for themselves, but when some of them return home infected, their fellow citizens bear the risk too—meaning that the upside is for the elite, but the downside is for the masses. This equity problem takes on added meaning in poorer, weaker countries like Nigeria, India or Indonesia, which haven't got the resources to fight Zika that Brazil does—and which anyway are proving insufficient. Putting them at risk for Games that are, essentially, bread and circuses seems ethically questionable.

Which leads to a simple question: *But for the Games, would anyone recommend sending an extra half a million visitors into Brazil right now?* Of course not: mass migration into the heart of an outbreak is a public health no-brainer. And given the choice between accelerating a dangerous new disease or not—for it is impossible that Games will slow Zika down—the answer should be a no-brainer for the Olympic organizers too. Putting sentimentality aside, clearly the Rio 2016 Games must not proceed.

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There is precedent for flexibility. Recently, America's baseball leagues rescheduled and moved games out of Puerto Rico because of Zika.[17] Historically, the 1976 Winter Olympics were moved, and the 1994 Winter Olympics broke with the regular schedule. London, Beijing, Athens and Sydney still possess useable Olympic facilities to take over from Rio. Since the IOC decided in 2014 that the Olympics could be shared between countries, sporting events could even be parceled out between them, turning Zika's negative into an unprecedented positive: the first transcontinental, truly Global Olympics.[18]

Any of these alternatives will cost money of course. But unless those with a financial stake in the Games planned poorly, they will have cancellation insurance, legal escape clauses for *force majeure*, and an exit strategy. Nothing of the sort can be said for the world's population whose health is at stake. For while the financial victims can recover their losses or even go bankrupt and rebuild, for the global health victims there is no such thing as going "bankrupt" on a virus or pandemic.

Regrettably, instead of discussing the alternatives, both the International Olympic Committee and the World Health Organization seem to be in deep denial. Asked about Zika, the most senior member of the IOC, Dick Pound, mocked it as "a manufactured crisis" for anyone but pregnant women (manufactured by whom?).[19] With the most recent epidemiological evidence out of Rio, and new clinical studies all but proving that Zika causes microcephaly and, maybe, Guillain-Barré disease, the IOC's sanguine, official statement on Zika and the Games from January 2016 is hopelessly obsolete—that organization must now break its months-long silence.

Even worse is WHO, which has never issued an official statement on Zika and the Olympics. When I pressed WHO about that in April, through a spokesperson it "agreed with" the IOC's obsolete statement, but refused to answer the direct question of whether WHO has confidence in Rio's Games being safe.[20] It is deplorable, incompetent and dangerous that

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WHO, which has both public health expertise and the duty of health protection, is speechlessly deferring to the IOC, which has neither. WHO's hesitancy is reminiscent of its mistakes with Ebola, all over again.

None of this is meant to deny that the Games are a much-loved event. But where is the love for the possible victims of a foreseeable global catastrophe: the damaged or dead adults, and the babies for whom—and mark these coldly clinical words carefully—*fetal brain disruption sequence* is as terrible as it sounds, and extinguishes the hope of a normal life even before it has begun? With stakes like that, bluntly put, these Olympics are no game at all.

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IN this section

NIH dengue vaccine leaps into phase 3 studies
p449

DNA tags speed up drug discovery
p450

FDA approves first mAb biosimilar
p454

Fetal tissue probe unsettles scientific community

On April 20, a special House committee held another hearing in an ongoing investigation on fetal tissue that is casting a pall on the biomedical community.

In the past few months, the subcommittee, called the Investigative Panel on Infant Lives, led by Marsha Blackburn, a Republican from Tennessee, has sent off a total of 15 subpoenas to scientific organizations, along with 40 letters, some of which request the names of researchers, technicians, and all other personnel involved with fetal tissue procurement and research in the past five years. In some cases, the investigative panel also requests copies of all emails exchanged between people involved with fetal tissue research, accounting records, and a wide range of other documents. If the recipients do not comply, they could be held in contempt of Congress.

These and other aggressive tactics have led House Democrats and scientists to call the investigation a smear campaign. They fear that the Panel intends to spook researchers into curbing their studies, to trigger more state laws that halt fetal tissue research, and to cast abortion in an unfavorable light.

However, Mike Reynard, a spokesperson for the Panel, says the requests are not intended to scare, but rather to help the members assess whether fetal tissue research is ethical, crucial, and conducted legally. "The point of the subpoenas is to gather information necessary for our investigators to fully understand exactly what is going on with the transactions between abortion businesses, procurement organizations, and other related entities," he says. "We also want to understand the necessity of the fetal tissue research."

Thus far, the subcommittee has issued subpoenas to, among others, an ethics review board involved with fetal tissue research, two medical supply companies, and the University of New Mexico.

The investigation follows last July's release of doctored videos that claimed to show Planned Parenthood clinics involved in the illegal sale of body parts. Since then, three congressional committees and 12 states have found zero evidence to indicate that Planned Parenthood profits from the sale of fetal tissue.

Larry Landolfi / Photo Researchers, Inc.

The uproar over fetal tissue uses began with action from anti-abortion groups against Planned Parenthood clinics.

In January, a Texas grand jury echoed that finding and instead indicted two people from the anti-abortion organization that produced the videos, the Center for Medical Progress. Nonetheless, Chairman Blackburn authored an op-ed April 6 in the *National Review* headlined "What Happened to 'Safe, Legal and Rare'? Abortion Today is about Profit, Profit, Profit."

"The chair has embarked on a partisan and dangerous witch hunt," said Representative Jan Schakowsky (D-Illinois) at a March 2 hearing of the Panel that focused on the ethics and necessity of fetal tissue research. Speaking at the hearing, Schakowsky recalled the words, "no more baby parts," uttered by the shooter who killed three people and injured nine others at a Planned Parenthood clinic in Colorado Springs, Colorado, in November 2015. The same type of inflammatory language was now being used by the Panel, she noted, in connection with fetal tissue research.

A spokesperson for the Panel says most names will be kept private, but there is no punishment to discourage their being leaked. Because of that possibility, scientists worry they could be targeted by anti-abortion extremists. "We read news of deaths and attacks on abortion clinics, so one has to fear that someone misguided might put something in your mailbox, or do something to your children, and that has really caused a significant amount of anxiety," says Mike McCune, professor of medicine and chief of the Division of Experimental Medicine at the University of California, San Francisco, who studies fetal tissue in order to develop therapies to save infants with lethal congenital disorders and babies infected with HIV *in utero*.

McCune is one of the rare researchers who uses fetal tissue and agreed to speak on the record to *Nature Biotechnology*. Twenty others did not reply or declined to comment. One cancer researcher received hate mail after a conservative media website linked the investigator's name to fetal tissue research. In response, the floors of some researcher's laboratories are now permanently locked and de-identified, constraining the scholarly exchange of students, visitors, and ideas.

When a woman who has already elected to have an abortion decides to anonymously donate fetal tissue, it may go to researchers

directly or to biomedical supply companies that process it—using it to generate cell lines, for example, and then selling those to investigators. These companies include Advanced Bioscience Resources (Alameda, California), StemExpress (Placerville, California), and the Ganogen Research Institute (Redwood City, California). The Panel has contacted these companies. On its website, Ganogen, Inc. writes, "While Ganogen has been subpoenaed by Congress in an act of political intimidation, we remain committed to continuing our research in our quest to save lives."

Because science has advanced over the past decade, the Panel is also asking why fetal tissue has not been replaced with newer tools, such as induced pluripotent stem cells harvested from adults. Fetal tissue cannot be paid for directly, so skeptics wonder whether scientists merely use it because it's cheap. "Are [scientists] acquiring tissue for their own convenience or because it's really needed for life-saving research?" the Panel spokesperson tells *Nature Biotechnology*. He adds that they've heard mixed messages: "Some scientists claim to need it and others say there are alternatives." Indeed, a professor of radiology invited to testify at the Panel's March 2 hearing, radiology researcher Kathleen Schmainda from the Medical College of Wisconsin, argued that fetal tissue research is unethical and unnecessary.

However, Lawrence Goldstein, a neurobiologist at the University of California, San Diego, spoke on behalf of 60,000 life scientists and physicians belonging to the International Society for Stem Cell Research, the American Society for Cell Biology, and the Coalition for Life Sciences at the hearing, where he testified that fetal tissue research may continue to yield life-saving cures.

There is no one cell type best for research because each has specific properties, Goldstein said. Rather, the type of cell used depends on a researcher's goal. For instance, vaccine manufacture often relies on viruses replicating in cells, and certain viruses multiply very well in fetal cells. Teva Pharmaceutical of Petah Tikva, Israel, relies on a fetal cell line named WI-38 to make the adenovirus flu vaccine given to US military personnel. That cell line is also used in the production of measles, rubella, rabies, hepatitis A, and chickenpox vaccines. According to the US National Institutes of Health, cell lines derived from fetal tissue continue to play an essential role in the creation of vaccines for certain diseases, including Ebola.

Goldstein and other researchers who work with fetal tissue say that it is often necessary to study a particular biological question—for example, how the Zika virus infects brain cells—in more than one cell type. If Congress were to shut down the use of fetal tissue cells, Goldstein says, progress toward treatments and cures would be delayed.

A hostile and unstable environment might drive researchers out of fields like infant medicine and pediatric HIV, which advance in part through fetal tissue research.

Still, some speakers at the March 2 hearing insisted the research was wrong, reasoning that one life should not be traded for another. McCune, who uses fetal tissue to figure out how babies with lethal genetic diseases might one day survive by being treated *in utero,* counters that remark by saying that the tissue he uses would otherwise be discarded. He also counters the assertion that fetuses donated after a miscarriage would suffice, because these fetuses often have biological abnormalities that render them inadequate for his studies.

"The hearing falls into the category of trying to muster public opprobrium for the whole practice as a way to close down abortion providers. If there was true interest in having guidelines, they can be found with in a 30-second search on the Internet," says Arthur Caplan, the medical ethicist at New York University Langone Medical Center whose work helped shape the original regulations in 1988.

Researchers who spoke with *Nature Biotechnology* maintain that they go through several steps prior to a study's launch to ensure it is ethical, legal, and makes sense to do. However, it's not clear that these procedures will satisfy the panel. During the hearing, Goldstein told Representative Sean Duffy (R-Wisconsin) that he acquires his fetal tissue from Neuralstem (Germantown, Maryland), and that they have assured him they conduct their business legally. "So that's it?" Duffy asked incredulously. "You haven't taken any further steps?"

Duffy also asked Goldstein some rather inflammatory, open-ended questions, such as, "Do you know how long it takes to carve out a little baby heart, or a little baby lung, or a little baby head?" Goldstein replied that he did not know because he was a researcher with a PhD and not a doctor.

"I don't think there's anything wrong with revisiting ethical debates, but I don't think that's what this is," says R. Alta Charo, a bioethics law professor from the University of Wisconsin–Madison who testified at the hearing. "It seems to be an excuse to milk some value out of the doctored videos so that the general public has the perception that there is something shady in the abortion industry linked to commercial interest." She adds, "That's a real problem if it leads to shutting down research we truly need."

That's already happening. In March, Florida passed legislation to prohibit the donation of aborted tissue. Similar bills that limit or halt research on fetal tissue from abortions have also been introduced in several states, including Indiana, North Dakota, South Dakota, Oklahoma, Ohio, Minnesota, and Wisconsin. And one planned trial on a therapy for wheelchair-using patients with multiple sclerosis has been put on hold due to a sudden freeze on fetal tissue donations. "We may be able to switch to embryonic stem cells in a few years," says an investigator on that trial, Steve Goldman, a neurologist at the University of Rochester Medical Center in Rochester, New York. "But it's a tragedy we cannot try this now. A few years is a big deal to an MS patient who is wheelchair bound—their health rapidly deteriorates at that stage, and they can die."

Even if no one is found guilty in the investigation, a hostile and unstable environment might drive researchers out of fields like infant medicine and pediatric HIV, which advance in part through fetal tissue research. "I can guarantee you that if a young scientist looks down the road and sees a shotgun, they will not gravitate in that direction," McCune says.

Amy Maxmen *Berkeley, California*

The Washington Post

To Your Health

What is Zika? And what are the risks as it spreads?

By Ariana Eunjung Cha and Lena H. Sun February 4

The World Health Organization has designated the Zika virus a public health emergency of international concern, an action it has taken only three times before and which paves the way for the mobilization of more funding and manpower to fight the mosquito-born pathogen spreading "explosively" through the Americas.

On Monday, the Centers for Disease Control and Prevention added four more countries to the list of those pregnant women should try to avoid. They are American Samoa, Costa Rica, Curacao and Nicaragua. The full list can be found here.

The virus is transmitted by the same mosquitoes that carry other tropical viruses such as dengue and yellow fever. Global health officials are alarmed because of its potential link to brain defects in infants as well as a rare syndrome that can lead to paralysis.

Here's what you need to know about Zika:

What is a global public health emergency? The WHO convened a special meeting on Monday to determine whether to declare a global public health emergency like the one for Ebola. What is this and what does this trigger?

Technically known as a Public Health Emergency of International Concern (PHEIC) declaration, it is defined as "an extraordinary event which is determined to constitute a public health risk to other States through the international spread of disease and to potentially require a coordinated international response." In the past it has been used only in the most dire of circumstances.

The last time the WHO took this action was in August 2014 with Ebola and it is typically done when there is a great need for a coordinated international response deemed essential to stopping the spread of a disease. The WHO had done this only twice previously — during the 2009 during the H1N1 influenza epidemic and in May 2014 regarding the reemergence of polio.

The declaration typically comes with a list of global recommendations to nations regarding practical measures such as international travel, trade and border crossings, as well as areas of scientific inquiry to target. The formal declaration was essential to mobilizing resources for previous crises by persuading wealthier countries to send more health workers and supplies to the hardest-hit regions.

I just head about the patient in Dallas who may have contracted Zika through a sexual partner rather than a mosquito bite. How worried should I be about this?

Dallas officials said on Feb. 2 that a person who had not traveled outside the United States appears to have been infected by a sexual partner. The U.S. Centers for Disease Control and Prevention confirmed the person has contracted the virus, but has not explicitly said the transmission was through sex. However, the CDC updated its advisory for pregnant women to reflect this concern. The CDC says that "until more is known," pregnant women should "avoid exposure to semen from someone who has been exposed to Zika virus."

In Britain, health officials said that if a female is at risk of getting pregnant or already pregnant her partner should use a condom if he has been traveling under the following conditions: "for 28 days after his return from an active Zika transmission area if he had no symptoms of unexplained fever and rash" and "for 6 months following recovery if a clinical illness compatible with Zika virus infection or laboratory confirmed Zika virus infection was reported."

What about blood transfusions?

This is a very real concern. Experts say it is theoretically possible to get Zika through blood transfusions from an infected donor, given that they have seen transmission of other related mosquito-borne viruses through the blood. On Feb. 3, health officials in one city in Brazil reported that they believe two people may have

contracted the virus from transfusions, but this has not been confirmed by national authorities, the World Health Organization or other agencies.

Meanwhile, health officials in a growing number of countries are taking precautions to prevent contamination of the blood supply by urging potential donors to delay giving blood for about a month if they have been traveling in Zika-affected regions.

What is Zika?

A summary of the history of the virus from our Health section:

> The virus was discovered in 1947 in a feverish rhesus monkey living in the Zika Forest of Uganda, but until 2007 scientists knew of only 14 human cases of the disease. That year it arrived on the travel-brochure-perfect Yap Island in the southwestern Pacific Ocean. Within a few months, nearly three-quarters of the island's 11,000 or so residents older than 3 had been infected.
>
> At first, those sick with Zika developed fever, joint pains and eye inflammation; then a red, bumplike rash erupted, sometimes followed by painful swelling of hands and feet. Some people vomited. Others were sensitive to light. But the symptoms usually resolved a couple of days later, and no one died.
>
> In 2013, Zika popped up again, this time in Tahiti and other parts of French Polynesia. An estimated 28,000 people (about 11 percent of the population of those islands) felt sick enough with the virus to seek medical care. By 2014 it was showing up in several other South Pacific spots: New Caledonia, east of Australia; the Cook Islands; and, early this year, Easter Island, which marked the official arrival of the disease in the Americas, since that remote island is part of Chile.
>
> Zika showed up in Brazil in May.

What's going on in Brazil?

The country is facing an unprecedented number of Zika virus cases — more than 1 million — as well as an unprecedented number of microcephaly cases that health officials believe are linked. In recent months, Brazil has spent more than $300 million to battle the mosquito, mobilizing hundreds of soldiers in the effort and going door-to-door to try to wipe out places where mosquitoes breed.

According to Washington Post correspondent Dom Phillips, the Brazilian Health Ministry has said 80 percent of those who catch Zika have shown no symptoms. The rest may suffer fever, muscle pain and rashes for a few days, and most people who come down with it recovery quickly.

“We never paid too much attention to this virus,” said Paulo Zanotto, a microbiology professor at the University of Sao Paulo who is coordinating a network of 42 laboratories studying Zika. “I’m really worried because we have no idea of the amount of spread.”

The government estimates that there are between 400,000 and 1.4 million Zika cases in the country, but there has been some confusion about the number of microcephaly cases. At one point, Brazil said there were 4,180 suspected cases. But on Wednesday, the country said that it had looked into 700 of those and that 270 had been confirmed and 462 had been ruled out.

In 2014, Brazil reported only 150 cases, which is a very small number for its population.

What's the scientific basis for the suspected link between Zika and microcephaly?

The World Health Organization and the Centers for Disease Control and Prevention, which is assisting Brazilian authorities in their investigation, have yet to definitively establish a connection between Zika and microcephaly. But the CDC has confirmed the presence of Zika in the bodies of two newborns with microcephaly who died and in the placentas of two women who miscarried children with microcephaly.

On Thursday, Claudio Maierovitch, director of the department of surveillance of communicable diseases at Brazil’s Health Ministry, said the country is investigating 12 confirmed deaths of babies born with microcephaly for potential linkage with Zika virus infection. The country has more than 4,000 suspected cases of microcephaly. He said pregnant women who tested positive for Zika virus have had rash and fever during the first and second trimesters.

What other complications related to Zika should I be worried about?

The CDC is working with Brazilian health officials to investigate a possible link to a growing number of cases of Guillain-Barré syndrome, a rare disease that occurs when your own immune system damages nerve cells. Most people recover fully from it, but others experience long-term nerve damage or paralysis. In rare cases, people have died.

In Brazil, health officials have identified hundreds of cases of Guillain-Barré, a significant increase from last year.

What do we know about the cases in the United States?

Health officials said Zika virus may be the reason for a baby born in Hawaii with microcephaly -- the first such case in the country. The mother is believed to have contracted the disease while living in Brazil last spring. The Associated Press reported that the state's epidemiologist, Sarah Park, said the mother no longer had the virus when she arrived in Hawaii and neither did the boy, so there is no chance a mosquito could have bitten them and spread it.

Florida, Illinois, New Jersey, Texas, Arkansas and other several other states have confirmed that residents who recently traveled to countries where Zika virus has been found in mosquitoes have tested positive for the virus. As of Feb. 4, a total of 51 cases have been reported in 14 states and the District of Columbia. Another 21 have been confirmed to have the virus in Puerto Rico (20) and the U.S. Virgin Islands (1). That brings the total number of cases in the United States to 71. More cases are likely to be reported as residents travel to Zika-affected regions.

How is the virus transmitted?

The primary way this virus is spread happens when a mosquito bites an infected person and then bites someone else. It cannot be transmitted from casual contact person-to-person. Before the report of the Dallas patient who contracted Zika through a sexual partner, there was only one other reported case of sexual transmission.

On Feb. 3, local health authorities in Brazil said two people may have contracted Zika through blood transfusions, the first such cases reported.

The map above shows Zika spreading across the globe. How close is it to us?

Haiti said on Jan. 15 that it had confirmed its first cases of Zika virus in five people in the area of Port-au-Prince, the country's capital. There were cases last year in Panama and Puerto Rico.

Colombian officials said Wednesday that 13,500 people are infected already and that the number could grow rapidly.

"We expect an expansion similar to what we had with the chikungunya virus last year, to finish with between 600,000 to 700,000 cases," Health Minister Alejandro Gaviria told journalists, according to Reuters.

How vulnerable is the United States?

Some infectious disease experts believe it's only a matter of time before mosquitoes with the virus make their way to the United States. They believe Zika is likely to follow a path similar to dengue fever in the United States, with outbreaks beginning in Puerto Rico and Florida and spreading across the Gulf states.

The nation’s Gulf Coast presents an ideal setting for the virus because of its warm climate and the multiple species of mosquitoes there that can transmit the disease -- including A. aegypti, which carries Zika. The region also has another risk factor: poverty. In poorer parts of the South, many residents still live without window screens or air conditioning and in proximity to stagnant water sources that are ideal mosquito breeding grounds.

Yet much of the entire country could be vulnerable. Scientists believe the virus could spread northward due to warming weather.

What can I do to reduce my risk of becoming infected or sick?

The CDC has warned pregnant Americans to try to avoid traveling to certain countries. Its initial list contained 14 countries, but the CDC on Friday added eight more — in South America, the Caribbean and Polynesia — as places where the reach of the virus is growing.

According to the CDC guidance:

> Zika virus can be spread from a pregnant woman to her unborn baby. There have been reports of a serious birth defect of the brain called microcephaly and other poor pregnancy outcomes in babies of mothers who were infected with Zika virus while pregnant. Knowledge of the link between Zika and these outcomes is evolving, but until more is known, CDC recommends special precautions for the following groups:
>
> Women who are pregnant (in any trimester): Consider postponing travel to any area where Zika virus transmission is ongoing. If you must travel to one of these areas, talk to your doctor first and strictly follow steps to prevent mosquito bites during your trip.
>
> Women who are trying to become pregnant: Before you travel, talk to your doctor about your plans to become pregnant and the risk of Zika virus infection. Strictly follow steps to prevent mosquito bites during your trip. Specific areas where Zika virus transmission is ongoing are often difficult to determine and are likely to change over time.

As of Thursday, here are the counties and territories impacted, according to the Pan American Health Organization:

> Brazil, Colombia, El Salvador, French Guiana, Guatemala, Guyana, Haiti, Honduras, Martinique, Mexico, Panama, Paraguay, Saint Martin, Suriname and Venezuela, as well as Puerto Rico.

On Friday, the CDC added eight more countries to the list:

> Barbados, Bolivia, Ecuador, Guadeloupe, Saint Martin, Guyana, Cape Verde, and Samoa.

And this week, the agency also added the U.S Virgin Islands and Dominican Republic to the list.

If you're traveling to one of these countries, here are some tips from the CDC for travelers to prevent getting bitten by mosquitoes:

- Wear long-sleeved shirts and long pants.
- Use insect repellent approved by the Environmental Protection Agency as directed.
- Use products with a higher percentage of the following ingredients: DEET (products include Off!, Cutter, Sawyer and Ultrathon), Picaridin, also known as KBR 3023, Bayrepel, and icaridin (products include Cutter Advanced and Skin So Soft Bug Guard Plus, as well as Autan outside of the United States), Oil of lemon eucalyptus (OLE) or PMD (products include Repel), or IR3535 (products include Skin So Soft Bug Guard Plus Expedition and SkinSmart).

Brady Dennis contributed to this report.

This post has been updated.

Read more:

WHO calls emergency meeting, says Zika virus 'spreading explosively' across Americas

Why the United States is so vulnerable to the alarming spread of Zika virus

For more health news, you can sign up for our weekly newsletter here.

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Public Health Reports First Confirmed Zika Virus Case Acquired Through Sexual Transmission in California

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SACRAMENTO -

California Department of Public Health (CDPH) Director and State Public Health Officer Dr. Karen Smith today announced the first confirmed case of Zika virus acquired in California. This case involves transmission of Zika virus through sexual contact with a Zika infected partner who returned from a country where Zika virus was circulating, not from a mosquito bite. The woman who was infected was not pregnant and had not traveled out of the country. She and her partner have fully recovered.

“This is the first confirmed case in California where Zika virus was transmitted sexually,” said Dr. Smith. “If your partner has traveled to an area where Zika is present, protecting yourself by abstaining from sex or using condoms during sex is the best way to prevent sexual transmission of the Zika virus.”

A man infected with Zika virus can spread it to his sexual partners. It is not known how long after infection a man can spread Zika virus to sexual partners. At this time, there is no evidence that women can transmit Zika virus to their sexual partners.

CDPH recommends that if men have traveled to an area where Zika virus is circulating, they abstain from sex or diligently use condoms with a partner who is pregnant or trying to become pregnant for the duration of the pregnancy. These cautions apply to vaginal, anal or oral sex.

Women who want to get pregnant, whose partner has had exposure to Zika virus, should discuss with their health care provider any potential risk of Zika virus during pregnancy. The virus can spread from a woman to her child during pregnancy and the infection is believed to lead to neurologic complications in the infant, including microcephaly, which is a birth defect in which the baby is born with a smaller-than-normal head due to abnormal brain development.

Most people infected with Zika virus will not develop symptoms. If symptoms do develop, they are usually mild and include fever, rash, joint pain and eye redness. If you have returned from an affected country and you have fever with rash, joint pain, and eye redness within two weeks, or any other symptoms following your return, please contact your medical provider and tell the doctor where you have traveled. While there is no specific treatment for Zika virus disease, the best recommendations are supportive care, rest, fluids and medications for relief of fever.

Zika virus is primarily transmitted to people by mosquitoes known as *Aedes aegypti* (yellow fever mosquito) and *Aedes albopictus* (Asian tiger mosquito), which are the same type of mosquitoes that transmit dengue and chikungunya viruses. These types of mosquitoes have been detected in 12 California counties. To date, there have been 22 travel-associated cases of Zika virus reported in California in 2015-2016. There has been no local mosquito-borne transmission of Zika virus in California.

People who are traveling to areas with known Zika virus risk should take steps to avoid being bitten by mosquitoes, including:

- Use insect repellents containing DEET, picaridin, IR3535, oil of lemon eucalyptus or para-menthane-diol for long-lasting protection. If you use sunscreen and insect repellent, apply the sunscreen first and then the repellent. Pregnant women and women who are breastfeeding should choose an EPA-registered insect repellent and use it according to the product label.
- Wear long-sleeved shirts and long pants.
- Use air conditioning or window/door screens to keep mosquitoes outside. If you are not able to protect yourself from mosquitoes indoors, sleep under a mosquito bed net.
- Help reduce the number of mosquitoes outside by emptying standing water from containers, such as flowerpots or buckets.

For more information on Zika virus disease and other mosquito-borne illnesses, please visit the CDPH Zika virus information Web page.

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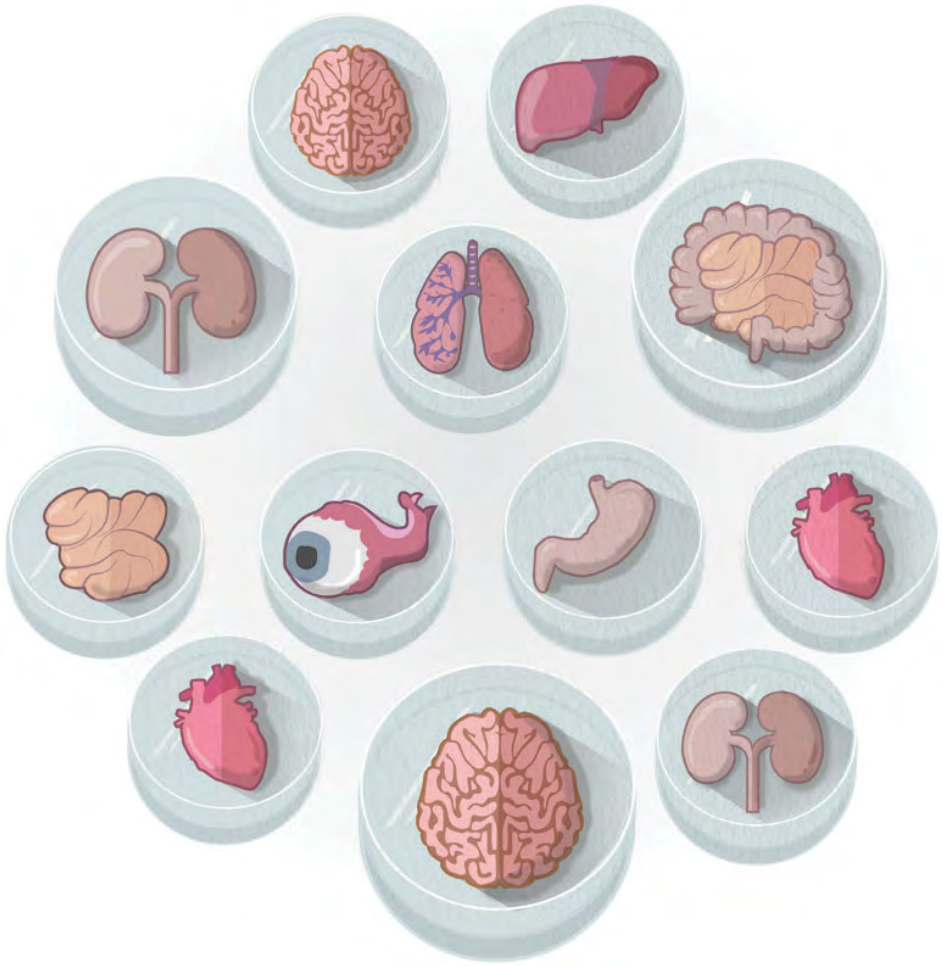

RISE OF THE ORGANOIDS

Biologists are building banks of mini-organs, and learning a lot about human development on the way.

BY CASSANDRA WILLYARD

It was an otherwise normal day in November when Madeline Lancaster realized that she had accidentally grown a brain. For weeks, she had been trying to get human embryonic stem cells to form neural rosettes, clusters of cells that can become many different types of neuron. But for some reason her cells refused to stick to the bottom of the culture plate. Instead they floated, forming strange, milky-looking spheres.

"I didn't really know what they were," says Lancaster, who was then a postdoc at the Institute of Molecular Biotechnology in Vienna. That day in 2011, however, she spotted an odd dot of pigment in one of her spheres. Looking under the microscope, she realized that it was the dark cells of a developing retina, an outgrowth of the developing brain. And when she sliced one of the balls open, she could pick out a variety of neurons. Lancaster realized that the cells had assembled themselves into something unmistakably like an embryonic brain, and she went straight to her adviser, stem-cell biologist Jürgen Knoblich, with the news. "I've got something amazing," she told him. "You've got to see it."

Lancaster and her colleagues were not the first to grow a brain in a dish. In 2008, researchers in Japan reported[1] that they had prompted embryonic stem cells from mice and humans to form layered balls reminiscent of a cerebral cortex. Since then, efforts to grow stem cells into rudimentary organs have taken off. Using carefully timed chemical cues, researchers around the world have produced three-dimensional structures that resemble tissue from the eye, gut, liver, kidney, pancreas, prostate, lung, stomach and breast. These bits of tissue, called organoids because they mimic some of the structure and function of real organs, are furthering knowledge of human development, serving as disease models and drug-screening platforms, and might

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NATURE.COM
To hear a podcast on organoids, go to:
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eventually be used to rescue damaged organs (see 'The organoid bank'). "It's probably the most significant development in the stem-cell field in the last five or six years," says Austin Smith, director of the Wellcome Trust/MRC Stem Cell Institute at the University of Cambridge, UK.

The current crop of organoids isn't perfect. Some lack key cell types; others imitate only the earliest stages of organ development or vary from batch to batch. So researchers are toiling to refine their organoids — to make them more complex, more mature and more reproducible. Still, biologists have been amazed at how little encouragement cells need to self-assemble into elaborate structures. "It doesn't require any super-sophisticated bioengineering," says Knoblich. "We just let the cells do what they want to do, and they make a brain."

GROWING A GUT

This shouldn't come as a major surprise, says molecular biologist Melissa Little at the University of Queensland, Australia. "The embryo itself is incredibly able to self-organize; it doesn't need a template or a map." That has been known since the early 1900s, when embryologists showed that sponges that had been broken up into single cells could reassemble themselves. But such work fell out of fashion, and modern biologists have focused their attention on purifying cells and growing them in culture — often in flat layers that do little to mimic normal human tissue.

Studying these cells to understand how an organ functions is like studying a pile of bricks to understand the function of a house, says Mina Bissell, a cancer researcher at the Lawrence Berkeley National Laboratory in California. "We should just begin to make the house," she says. Bissell's work on cultures of breast cells helped to propagate the idea that cells behave differently in 3D cultures than in conventional flat ones. By the mid-2000s, the idea was catching on. The burst of enthusiasm was fuelled by Yoshiki Sasai, a stem-cell biologist at the RIKEN Center for Developmental Biology in Kobe, Japan, who turned heads when he grew a cerebral cortex[1], followed by a rudimentary optic cup[2] and pituitary gland[3] (see *Nature* **488,** 444–446; 2012).

Just a year after Sasai announced his layered cortex, Hans Clevers, a stem-cell researcher at the Hubrecht Institute in Utrecht, the Netherlands, reported the creation of a mini-gut[4]. The breakthrough stemmed from a discovery in 2007, when Clevers and his colleagues had identified intestinal stem cells in mice. In the body, these cells seemed to have an unlimited capacity to divide and replenish the intestinal lining, and one of Clevers' postdocs, Toshiro Sato, was tasked with culturing them in the lab.

Rather than growing the cells flat, the pair decided to embed them in matrigel, a soft jelly that resembles the extracellular matrix, the mesh of molecules that surrounds cells. "We were just trying things," Clevers says. "We hoped that we would make maybe a sphere or a blob of cells." Several months later, when Clevers put his eye to Sato's microscope, he saw more than blobs. The cells had divided, differentiated into multiple types, and formed hollow spheres that were dotted with knobby protrusions. Inside, the team found structures that resembled the intestine's nutrient-absorbing villi as well as the deep valleys between them called crypts. "The structures, to our total astonishment, looked like real guts," Clevers says. "They were beautiful."

The mini-guts, reported in 2009, may prove to be a powerful tool in personalized medicine. Clevers and his team are using them to study the effectiveness of drugs in people with cystic fibrosis, who have genetic defects that affect ion channels and disrupt the movement of water in and out of the cells lining the lungs and intestine. The researchers take rectal biopsies from people with the disease, use the cells to create personalized gut organoids and then apply a potential drug. If the treatment opens the ion channels, then water can flow inwards and the gut organoids swell up. "It's a black-and-white assay," Clevers says, one that could prove quicker and cheaper than trying drugs in people to see whether they work.

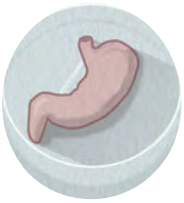
THE ORGANOID BANK

Since the late 2000s, biologists have grown a wide variety of rudimentary organs to understand development and for medical uses.

Organoid	Potential application
Cerebral cortex	Understand brain development, as well as neurodegenerative diseases and other disorders
Intestine	Personalized organoids for identifying patient-tailored drugs
Optic cup	Source of retinal tissue for eye therapies
Pituitary gland	Source of therapeutic cells for endocrine disorders
Kidney	Toxicity testing and a source of tissue for transplantation
Liver	Repair of damaged liver
Pancreas	Treat diabetes and identify drugs for pancreatic cancer
Neural tube	Study nerve development and a source of cell therapies
Stomach	Understand stomach development and model gastric disorders such as ulcers
Prostate	Predict effective drug combinations for prostate cancer
Breast	Understand tumour development
Heart	Study cardiac development and how drugs affect it
Lung	Model for lung development, maturation and disease

He has already used the system to assess whether a drug called Kalydeco (ivacaftor), and 5 other cystic-fibrosis drugs, will work in about 100 patients; at least 2 of them are now taking Kalydeco as a result.

Organoids may also help physicians to choose the best therapies for people with cancer. Earlier this year, Clevers revealed that he had grown a bank of organoids from cells extracted from colorectal tumours[5], and David Tuveson, a cancer researcher at Cold Spring Harbor Laboratory in New York, worked with Clevers to generate pancreas organoids using biopsies taken from people with pancreatic cancer[6]. In both cases, the organoids could be used to find drugs that work best on particular tumours. "What patients are looking for is a logical approach to their cancer," Tuveson says. "I'm very excited about what we're learning."



THE SMALL-SCALE STOMACH

That excitement is shared by developmental biologist James Wells, who last year reported that he and his team had created an organoid that resembled part of a human stomach[7].

Wells started with a different raw material to Clevers, whose organoids arise from adult stem cells that can generate only a limited number of cell types. Wells, who is at the Cincinnati Children's Hospital Medical Center in Ohio, and his colleagues craft organoids from embryonic stem cells, which have the ability to become almost any type of cell. As a result, they have been able to create mini-organs that are more complex.

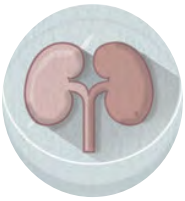
A decade ago, Wells and his colleagues began trying to coax human embryonic stem cells to form intestinal cells. When the team manipulated two key signalling pathways, the layer of cells produced tiny round buds. Wells noticed that these 'spheroids' mimicked sections of the primitive gut tube, which forms four weeks after conception. This was thrilling, because he realized that he now had a starting point from which to develop a variety of organoids. "Every organ from your mouth down to your anus — oesophagus, lungs, trachea, stomach, pancreas, liver, intestine, bladder — all of them come from this very primitive tube," he says.

Wells and his colleagues mined the literature and their own experience to determine what chemical cues might send these gut tubes down the developmental path toward a specific organ. Using this strategy, in 2011 the team developed its first human organoid[8], an intestine about the size of a sesame seed. But growing a stomach was a bigger challenge. In humans, the organ has two key areas: the fundus at the

top, which churns out acid, and the antrum towards the base, which produces many key digestive hormones — and the signalling pathways that lead to one versus the other were unknown. What is more, "the human stomach is different from the stomachs of most animals that we use in the lab", so there is no good animal model, says Kyle McCracken, a former graduate student of Wells and now a medical student at the centre.

The researchers went for a trial-and-error approach: they made some educated guesses and painstakingly tested different combinations of growth factors. Eventually, the effort paid off. In a 2014 paper[7], Wells and his team revealed that they had created organoids that resembled the antrum. Using these as a model system, the team says that it has figured out the chemical trigger that prompts the development of a fundus. Now the researchers are working to answer other basic questions about stomach development and physiology, such as which factors regulate acid secretion, and they are trying to generate other mini-organs from their primitive gut tubes.

This newfound ability to examine human development excites Daniel St Johnston, a developmental geneticist at the University of Cambridge's Gurdon Institute. "You can actually watch how the cells organize themselves to make complicated structures," he says — something that is impossible in a human embryo. But most organoids are still single tissues, which limits what developmental biologists can learn, he says. "There are certain questions you can't really address because they depend upon the physiology of the whole organism."



THE BABY KIDNEY

Melissa Little has spent more than a decade marvelling at the complexity of the kidney. "It has, in an adult, probably 25–30 different cell types, each doing different jobs," she says. Tubular structures called nephrons filter fluid from the blood and produce urine. The surrounding space, called the interstitium, holds an intricate network of blood vessels and the plumbing that carries urine away.

In 2010, Little and her colleagues started trying to turn embryonic stem cells into a progenitor cell that gives rise to nephrons. For three years, they tried various combinations and timings of growth factors. "It really took a lot of mucking around to make progress," she says. But finally, in 2013, the team landed on just the right mixture. Little had been aiming to produce just the progenitor cells. But when she looked in the dish she saw two cell types spontaneously patterning themselves as they would in an embryo. "There was a moment of, 'Oh wow. Isn't that amazing'," she says.

This organoid resembles an embryonic kidney rather than an adult one: it has a mix of nephron progenitors and the cells that give rise to urine-collecting ducts[9]. "If you want to get them to mature further, that's where the challenge really lies," Little says. So her team has been working to grow a more-sophisticated version — with blood vessels and interstitium. The hope then is to transplant the mini-organs into mice to see if they will mature and produce urine. "I'm pretty excited about what we can build," Little says.

Because the kidney plays a key part in drug metabolism and excretion, Little thinks that her mini-kidneys could be useful for testing drug candidates for toxicity before they reach clinical trials. And researchers say that other human organoids, such as heart and liver, could similarly be used to screen drug candidates for toxic effects — offering a better read-out on the response of an organ than is possible with standard tissue culture or animal testing.

But Michael Shen, a stem-cell researcher at Columbia University in New York who has created a prostate organoid, is sceptical that these model systems could completely replace lab animals. Animals can show how a therapy affects the immune system, for example, something that organoid systems cannot currently do. "You want to be able to validate your experimental findings in an *in vivo* system," he says. "I view that as a rigorous test."

LITTLE LIVERS

Takanori Takebe was inspired to grow a liver after a chilling spell in New York. While working in the organ-transplantation division at Columbia University in 2010, Takebe saw people die from liver failure owing to a lack of organs. "That was a sad situation," he says. When he looked into tissue engineering, he thought that the usual methods — seeding cells onto an artificial scaffold — seemed destined to fail. Part of the problem, he says, is that adult liver cells are very difficult to grow. "We cannot maintain it in culture for even a couple of hours."

Takebe, who took up a research position at Yokohama City University in Japan, decided to work on induced pluripotent stem (iPS) cells, adult cells that have been reprogrammed to behave like embryonic stem cells. He coaxed human iPS cells into forming liver-cell precursors, or hepatoblasts. In the embryo, hepatoblasts rely on a complex symphony of signals from other nearby cells to mature, and Takebe suspected that these support cells would also be necessary to develop a liver in a dish. He and his colleagues mixed hepatoblasts with such cells — called mesenchymal and endothelial cells — and it worked. The team managed to create 'liver buds', structures no bigger than a lentil that resemble the liver of a six-week-old human embryo[10]. The researchers went on to find that, unlike mature liver cells, such structures can survive in culture for as long as two months.

A liver bud is still a far cry from an entire liver — a hefty, multi-lobed organ composed of tens of billions of hepatocytes. But Takebe hopes that if he can infuse many thousands of buds into a failing organ, he might be able to rescue enough of its function to make a transplant unnecessary. The process seems to work in mice. When Takebe and his group transplanted a dozen of the buds into mouse abdomens, they saw dramatic effects. Within two days, the buds had connected up with the mouse's blood supply, and the cells went on to develop into mature liver cells that were able to make liver-specific proteins and to metabolize drugs. To mimic liver failure, the team wiped out the animals' natural liver function with a toxic drug. After a month, most of the control mice had died, but most of those that received liver bud transplants had survived.

Takebe and his team hope to start human trials in four years. "We will target the children that critically need a liver transplant," he says. He and his colleagues are currently working to make the liver buds smaller and produce them in huge quantities that they can infuse through the large portal vein that feeds the liver. Takebe thinks that the timeline is "doable". But Smith says that the process seems rushed, and that the basic biology of these organs needs to be well understood before they are used in the clinic. "It's like running before you can walk," he says.

Biologists know that their mini-organs are still a crude mimic of their life-sized counterparts. But that gives them something to aim for, says Anthony Atala, director of the Wake Forest Institute for Regenerative Medicine in Winston-Salem, North Carolina. "The long-term goal is that you will be able to replicate more and more of the functionality of a human organ." Already, the field has brought together developmental biologists, stem-cell biologists and clinical scientists. Now the aim is to build more-elaborate organs — ones that are larger and that integrate more cell types.

And Wells says that even today's rudimentary organoids are facilitating discoveries that would have been difficult to make in an animal model, in which the molecular signals are hard to manipulate. "In a Petri dish it's easy," he says. "We have chemicals and proteins that we can just dump onto these cells." ■

Cassandra Willyard *is a science writer based in Madison, Wisconsin.*

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3. Suga, H. *et al. Nature* **480,** 57–62 (2011).
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A Polio-Free U.S. Thanks to Vaccine Efforts

Thanks to effective vaccine, the United States has been polio-free since 1979. But poliovirus is still a threat in some countries. Be part of the success story and get your child vaccinated on schedule.

Polio, or poliomyelitis, is a crippling and potentially deadly infectious disease. It is caused by the poliovirus. The virus spreads from person to person and can invade an infected person's brain and spinal cord, causing paralysis (can't move parts of the body).

Thanks to the polio vaccine, dedicated health care professionals, and parents who vaccinate their children on schedule, polio has been eliminated in this country for more than 30 years.

It is crucial to maintain the success rate of U.S. vaccination efforts since the disease still exists in some parts of the world. People most at risk are those who never had polio vaccine, those who never received all the recommended vaccine doses, and those traveling to areas that could put them at risk for getting polio (http://wwwnc.cdc.gov/travel/notices).

EPI
POLIO GLOBAL ERADICATION INITIATIVE

Polio: the fewest cases in the fewest places in the world. Learn more about efforts to vaccinate every child and make the world polio-free (http://www.cdc.gov/polio/).

The Childhood Polio Vaccination Schedule

For best protection, children should get four doses of polio vaccine. This vaccine is given as a shot in the arm or leg and is extremely safe. Ideally, your child should receive a dose at ages

- 2 months,
- 4 months, and
- 6 through 18 months,
- then a booster dose at age 4 through 6 years.

Inactivated polio vaccine (IPV) may sometimes be given in the same shot with other vaccines (in other words, in a combination vaccine), so discuss this option with your child's doctor. Getting the recommended doses of the polio vaccine is an extremely important part of keeping the United States polio-free.

For information about adults who may not have received sufficient vaccine protection, see the adult polio vaccination schedule. (http://www.cdc.gov/vaccines/vpd-vac/polio/vacc-in-short.htm)

Paying for Vaccine

Most health insurance plans cover the cost of vaccines. However, you may want to check with your insurance provider before going to the doctor. If you don't have health insurance, or if your insurance doesn't cover vaccines for your child, the Vaccines for Children Program (http://www.cdc.gov/features/vfcprogram/index.html) may be able to help. This program helps families of eligible children who might not otherwise have access to vaccines. To find out if your child is eligible, (http://www.cdc.gov/vaccines/programs/vfc/parents/qa-detailed.html) visit the VFC website (http://www.cdc.gov/features/vfcprogram/) or ask your child's doctor. You can also contact your state VFC coordinator (http://www.cdc.gov/vaccines/programs/vfc/contacts-state.html).

Even if you were previously vaccinated, you may need a onetime booster shot before you travel anywhere that could put you at risk for getting polio.

Traveling to Another Country?

Polio has been eliminated from most of the world, but the disease still exists in a few countries in Asia and Africa. Even if you were previously vaccinated, you may need a one-time booster shot before you travel anywhere that could put you at risk for getting polio. A booster is an additional dose of vaccine to ensure the original vaccine series remains effective.

Visit CDC's Travelers' Health website (http://wwwnc.cdc.gov/travel/notices) for timely travel health information.

Make sure you get your travel vaccination(s) well before your departure date to ensure complete protection. See your health care professional for more information.

Polio Once Caused Widespread Panic

In the late 1940s to the early 1950s, polio outbreaks in the United States increased in frequency and size; polio crippled an average of more than 35,000 people in the United States each year. It was one of the most feared diseases of the twentieth century; parents were frightened to let their children go outside, especially in the summer when the virus seemed to peak. Travel and commerce between affected cities were sometimes restricted. Public health officials imposed quarantines (used to separate and restrict the movement of well people who may have been exposed to a contagious disease to see if they become ill) on homes and towns where polio cases were diagnosed.

More Information

- Polio Vaccination (http://www.cdc.gov/vaccines/vpd-vac/polio/default.htm)
- History of Polio Timeline (http://www.historyofvaccines.org/content/timelines/polio)
- Whatever Happened to Polio? (http://americanhistory.si.edu/polio)
- March of Dimes (http://www.marchofdimes.com/)
- Global Polio Eradication Initiative (http://www.polioeradication.org/)
- Polio (http://www.cdc.gov/polio)

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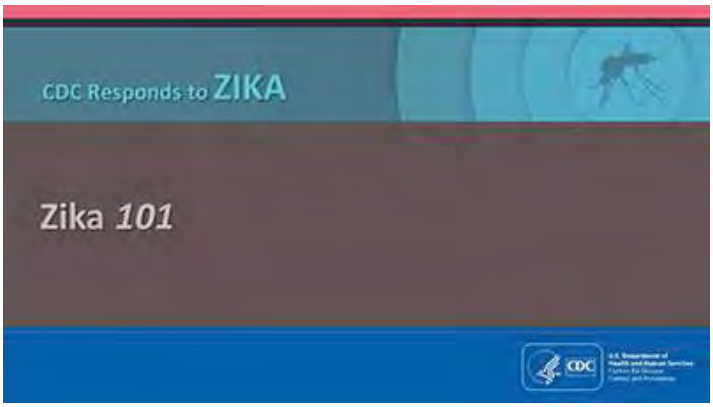
About Zika Virus Disease

Zika 101 Presentation



- English [PPT - 3.7 MB]
- Spanish [PPT - 3.7 MB] (http://espanol.cdc.gov/zika/comm-resources/zika101slides.pptx)

Zika: The Basics of the Virus and How to Protect Against It

- English [PDF - 2 pages]

Zika virus disease (Zika) is a disease caused by the Zika virus, which is spread to people primarily through the bite of an infected *Aedes* species mosquito. The most common symptoms of Zika are fever, rash, joint pain, and conjunctivitis (red eyes). The illness is usually mild with symptoms lasting for several days to a week after being bitten by an infected mosquito. People usually don't get sick enough to go to the hospital, and they very rarely die of Zika. For this reason, many people might not realize they have been infected. However, Zika virus infection during pregnancy can cause a serious birth defect called microcephaly, as well as other severe fetal brain defects. Once a person has been infected, he or she is likely to be protected from future infections.

Zika virus was first discovered in 1947 and is named after the Zika Forest in Uganda. In 1952, the first human cases of Zika were detected and since then, outbreaks of Zika have been reported in tropical Africa, Southeast Asia, and the Pacific Islands. Zika outbreaks have probably occurred in many locations. Before 2007, at least 14 cases of Zika had been documented, although other cases were likely to have occurred and were not reported. Because the symptoms of Zika are similar to those of many other diseases, many cases may not have been recognized.

In May 2015, the Pan American Health Organization (PAHO) issued an alert regarding the first confirmed Zika virus infection in Brazil. On February 1, 2016, the World Health Organization (WHO) declared Zika virus a Public Health Emergency of International Concern (PHEIC). Local transmission has been reported in many other countries and territories. Zika virus will likely continue to spread to new areas.

Specific areas where Zika is spreading are often difficult to determine and are likely to change over time. If traveling, please visit the CDC Travelers' Health site (http://wwwnc.cdc.gov/travel/page/zika-travel-information) for the most updated travel information.

File Formats Help:

How do I view different file formats (PDF, DOC, PPT, MPEG) on this site? (http://www.cdc.gov/Other/plugins/)

(http://www.cdc.gov/Other/plugins/#pdf) (http://www.cdc.gov/Other/plugins/#ppt)

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Content source: Centers for Disease Control and Prevention (http://www.cdc.gov/)

National Center for Emerging and Zoonotic Infectious Diseases (NCEZID) (http://www.cdc.gov/ncezid)

Division of Vector-Borne Diseases (DVBD) (http://www.cdc.gov/ncezid/dvbd/index.html)

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Pregnancy and Rubella

Rubella is very dangerous for a pregnant woman and her developing baby. Anyone who is not vaccinated against rubella is at risk of getting the disease. Although rubella was declared eliminated from the U.S. in 2004, cases can occur when unvaccinated people are exposed to infected people, mostly through international travel. Women should make sure they are protected from rubella before they get pregnant.

Infection with rubella virus causes the most severe damage when the mother is infected early in pregnancy, especially in the first 12 weeks (first trimester). Since 2012, six babies with CRS have been reported in the United States.

Congenital Rubella Syndrome (CRS)

Congenital rubella syndrome (CRS) is a condition that occurs in a developing baby in the womb whose mother is infected with the rubella virus. Pregnant women who contract rubella are at risk for miscarriage or stillbirth, and their developing babies are at risk for severe birth defects with devastating, lifelong consequences. CRS can affect almost everything in the developing baby's body.

The most common birth defects from CRS can include:

- Deafness
- Cataracts
- Heart defects
- Intellectual disabilities
- Liver and spleen damage
- Low birth weight
- Skin rash at birth

Less common complications from CRS can include:

- Glaucoma

- Brain damage
- Thyroid and other hormone problems
- Inflammation of the lungs

Although specific symptoms can be treated, there is no cure for CRS. Since there is no cure, it is important for women to get vaccinated before they get pregnant.

Top of Page

Vaccine Recommendations

Women who are planning to become pregnant should check with their doctor to make sure they are vaccinated before they get pregnant.

Because MMR vaccine is an attenuated (weakened) live virus vaccine, pregnant women who are not vaccinated should wait to get MMR vaccine until after they have given birth.

Adult women of childbearing age should avoid getting pregnant for at least four weeks after receiving MMR vaccine.

Pregnant women should NOT get MMR vaccine.

If you get rubella or are exposed to rubella while you're pregnant, contact your doctor immediately.

Top of Page

Related Pages

March of Dimes – Rubella and Pregnancy (http://intranet.cdc.gov/http:/www.marchofdimes.org/complications/rubella-and-pregnancy.aspx)

Page last reviewed: March 31, 2016
Page last updated: March 31, 2016
Content source: National Center for Immunization and Respiratory Diseases (NCIRD) (http://www.cdc.gov/ncird/index.html), Division of Viral Diseases (http://www.cdc.gov/ncird/dvd.html)

Rubella: Make Sure Your Child Gets Vaccinated

Language: English

Rubella is a contagious disease caused by a virus. For some people—especially pregnant women and their unborn babies—rubella can be serious. Make sure you and your child are protected from rubella by getting vaccinated on schedule.

Most people who get rubella usually have a mild illness, with symptoms that can include a low-grade fever, sore throat, and a rash that starts on the face and spreads to the rest of the body. Some people may also have a headache, pink eye, and general discomfort before the rash appears.

Rubella is dangerous for pregnant women and unborn babies

The most serious complication from rubella infection is the harm it can cause a pregnant woman's unborn baby. If an unvaccinated pregnant woman gets infected with rubella virus she can have a miscarriage, or her baby can die just after birth. Also, she can pass the virus to her unborn baby who can develop serious birth defects such as—

- heart problems,
- loss of hearing and eyesight,
- intellectual disability, and
- liver or spleen damage.

Serious birth defects are more common if a woman is infected early in her pregnancy, especially in the first trimester.

Children should be vaccinated on schedule to protect them from rubella infection and to prevent them from spreading rubella to a pregnant woman and her unborn baby.

Protect your child, and others, with rubella vaccine

The best way to protect your child from rubella is to get him or her vaccinated on schedule. Children should be vaccinated against rubella to protect them from infection and to prevent them from spreading rubella to a pregnant woman and her unborn baby, as well those who cannot get vaccinated because they have a health condition or are too young.

Rubella vaccine is usually given as part of a combination vaccine called MMR, which protects against three diseases: measles, mumps, and rubella. MMR vaccine is safe and effective and has been widely used in the United States for more than 30 years.

Children should get 2 doses of MMR vaccine:

- the first dose at 12 through 15 months of age and
- the second dose at 4 through 6 years of age, before entering school.

Your child's doctor may also offer the MMRV vaccine, which protects against four diseases: measles, mumps, rubella, and varicella (chickenpox).

Talk to your child's healthcare professional for help deciding which vaccine to use.

Paying for rubella vaccine

Most health insurance plans cover the cost of vaccines. However, you may want to check with your insurance provider before going to the doctor. Learn how to pay for vaccines.

If you don't have health insurance or if your insurance does not cover vaccines for your child, the Vaccines for Children (VFC) Program may be able to help. This program helps families of eligible children who might not otherwise have access to vaccines. To learn more, visit the VFC website or ask your child's doctor. You can also contact your state VFC coordinator.

Planning a pregnancy? Make sure you're protected against rubella.

If you are planning to get pregnant, make sure you are first protected against rubella, because if you are infected during pregnancy, this disease can be very dangerous to your unborn

baby. If you're unsure whether you're immune to rubella, or think you might be pregnant, discuss with your doctor.

- Fact Sheet on Rubella and the Vaccine to Prevent it [408 KB]
- Rubella Vaccination
- Vaccine Information Statement in English and MMRV
- Vaccine Information Statements in other languages: MMR and MMRV
- Adult Immunization Schedule (anyone over 18 years old)
- Recommended Immunizations for Children from Birth through 6 Years Old [722 KB]

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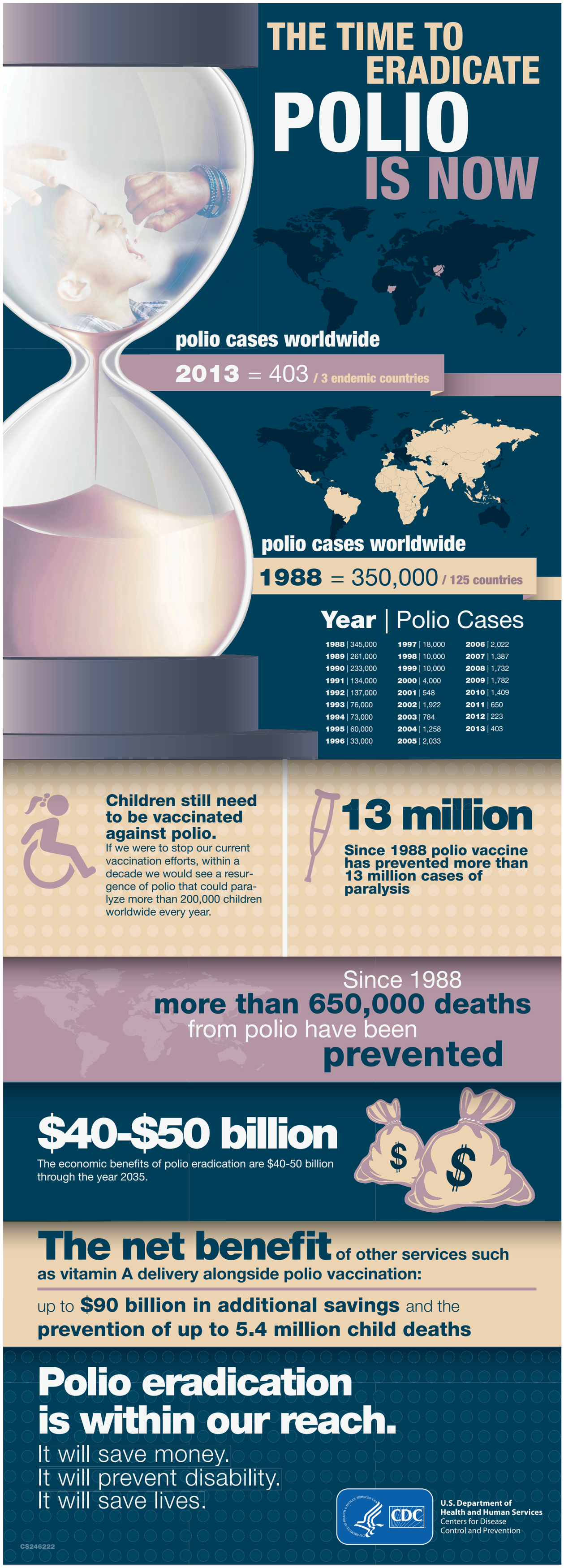
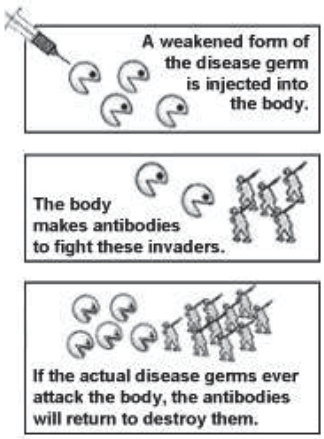

THE TIME TO ERADICATE POLIO IS NOW
polio cases worldwide
2013 = 403 / 3 endemic countries
polio cases worldwide
1988 = 350,000 / 125 countries
Year | Polio Cases
1988 | 345,000
1989 | 261,000
1990 | 233,000
1991 | 134,000
1992 | 137,000
1993 | 76,000
1994 | 73,000
1995 | 60,000
1996 | 33,000
1997 | 18,000
1998 | 10,000
1999 | 10,000
2000 | 4,000
2001 | 548
2002 | 1,922
2003 | 784
2004 | 1,258
2005 | 2,033
2006 | 2,022
2007 | 1,387
2008 | 1,732
2009 | 1,782
2010 | 1,409
2011 | 650
2012 | 223
2013 | 403
Children still need to be vaccinated against polio.
If we were to stop our current vaccination efforts, within a decade we would see a resurgence of polio that could paralyze more than 200,000 children worldwide every year.
13 million
Since 1988 polio vaccine has prevented more than 13 million cases of paralysis
Since 1988
more than 650,000 deaths
from polio have been
prevented
$40-$50 billion
The economic benefits of polio eradication are $40-50 billion through the year 2035.
The net benefit of other services such as vitamin A delivery alongside polio vaccination:
up to $90 billion in additional savings and the
prevention of up to 5.4 million child deaths
Polio eradication is within our reach.
It will save money.
It will prevent disability.
It will save lives.
CS246222
U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

Why Are Childhood Vaccines So Important?



It is always better to prevent a disease than to treat it after it occurs.

Diseases that used to be common in this country and around the world, including polio, measles, diphtheria, pertussis (whooping cough), rubella (German measles), mumps, tetanus, rotavirus and *Haemophilus influenzae* type b (Hib) can now be prevented by vaccination. Thanks to a vaccine, one of the most terrible diseases in history – smallpox – no longer exists outside the laboratory. Over the years vaccines have prevented countless cases of disease and saved millions of lives.

Immunity Protects us From Disease

Immunity is the body's way of preventing disease. Children are born with an immune system composed of cells, glands, organs, and fluids located throughout the body. The immune system recognizes germs that enter the body as "foreign invaders" (called *antigens*) and produces proteins called *antibodies* to fight them.

The first time a child is infected with a specific antigen (say measles virus), the immune system produces antibodies designed to fight it. This takes time . . . usually the immune system can't work fast enough to prevent the antigen from causing disease, so the child still gets sick. However, the immune system "remembers" that antigen. If it ever enters the body again, even after many years, the immune system can produce antibodies fast enough to keep it from causing disease a second time. This protection is called immunity.

It would be nice if there were a way to give children immunity to a disease without their having to get sick first.

In fact there is:

Vaccines contain the same antigens (or parts of antigens) that cause diseases. For example, measles vaccine contains measles virus. But the antigens in vaccines are either killed, or weakened to the point that they don't cause disease. However, they *are* strong enough to make the immune system produce antibodies that lead to immunity. In other words, *a vaccine is a safer substitute for a child's*

first exposure to a disease. The child gets protection without having to get sick. Through vaccination, children can develop immunity without suffering from the actual diseases that vaccines prevent.

Top of Page

More Facts

- Newborn babies are immune to many diseases because they have antibodies they got from their mothers. However, this immunity goes away during the first year of life.
- If an unvaccinated child is exposed to a disease germ, the child's body may not be strong enough to fight the disease. Before vaccines, many children died from diseases that vaccines now prevent, such as whooping cough, measles, and polio. Those same germs exist today, but because babies are protected by vaccines, we don't see these diseases nearly as often.
- Immunizing individual children also helps to protect the health of our community, especially those people who cannot be immunized (children who are too young to be vaccinated, or those who can't receive certain vaccines for medical reasons), and the small proportion of people who don't respond to a particular vaccine.
- Vaccine-preventable diseases have a costly impact, resulting in doctor's visits, hospitalizations, and premature deaths. Sick children can also cause parents to lose time from work.

Top of Page

Related Pages

Why Immunize?
Vaccines: A Safe Choice
Parents Guide to Immunizations
For Parents: How Vaccines Prevent Diseases

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Content source: National Center for Immunization and Respiratory Diseases (http://www.cdc.gov/ncird/)

Fetal Tissue Research: Frequently Asked Questions

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CRS REPORT
Prepared for Members and
Committees of Congress

Contents

Contacts

This report provides answers to frequently asked questions concerning the regulation and use of fetal tissue in research, including a description of what constitutes fetal tissue research, uses of fetal tissue for medical purposes, and how such tissue is acquired, along with rules and regulations governing the use and acquisition of fetal tissue.

What is fetal tissue?

Fetal tissue is any tissue or organ obtained from a fetus, which is the product of conception (egg and sperm) from the end of the eighth week of pregnancy onward. Prior to the ninth week, the product of conception is called an embryo.

What is fetal tissue research?

Researchers use fetal tissue to produce cell cultures, also called cell lines, which can be maintained in a laboratory environment for very long periods of time, in some cases indefinitely. Cultured cells mimic many of the properties that they have in a living body, and therefore can be used as a model for researchers studying basic biological processes. Research involving fetuses and fetal tissue has been conducted in the United States since the 1930s, and the National Institutes of Health (NIH) has been supporting research using fetal tissue since the 1950s.[1] NIH spent $76 million on human fetal tissue research in FY2014, and will spend an estimated $76 million in FY2015 and $77 million in FY2016.[2]

What are the uses of fetal tissue in medicine and medical research?

Fetal tissue has been used "to identify and test the efficacy of vaccines and to examine the toxicity of drugs used by pregnant women. Vaccines for polio, measles, rubella and Rh disease were developed through the use of fetal tissue or cell lines derived from fetal tissue."[3] Human fetal tissue is used to study normal human development in order to gain insight into birth defects and other developmental diseases. Fetal tissue has been used in studies of genetic disease in the early stages of development, including organ formation.

[1] Patricia Donovan, "Funding Restrictions on Fetal Research: The Implications for Science and Health," *Family Planning Perspectives*, vol. 22, no. 5 (September/October 1990), pp. 224-231; and, Dorothy E. Vawter and Arthur Caplan, "Strange Brew: The Politics and Ethics of Fetal Tissue Transplantation Research in the United States," *Journal of Laboratory Clinical Medicine*, vol. 120, no. 1 (July 1992), pp. 30-34.

[2] At http://report.nih.gov/categorical_spending.aspx, putting "human fetal tissue" in the search box reveals the dollar amount spent or estimated by NIH for FY2011- FY2016. Clicking on the dollar amount for FY2011-FY2014 reveals the number of projects as well as details on each research project using human fetal tissue.

[3] Donovan, "Funding Restrictions on Fetal Research," p. 227.

What is human fetal tissue transplantation research?

Since the late 1920s, researchers in several countries, including the United States, "have grafted fetal liver, nerve, thymus and pancreas tissue into children and adults in efforts to reverse various neurological disorders, spinal cord injuries, diabetes, immune deficiencies, cancers and life-threatening blood diseases."[4] Perhaps the most widely known application in the field of human fetal tissue transplantation has been the treatment of Parkinson's disease. The first such attempt, using the transplantation of human fetal brain cells, "took place in 1987 at Lund University in Sweden where the technique was pioneered."[5] Although controversial at the time, the approach "produced such striking results in some cases that by 1997 about 200 patients around the world had received the treatment."[6] However, because many patients did not benefit from the treatment, and it was unclear why this was the case, an international moratorium was imposed in 2003 on such replacement-therapy trials.[7]

In 2006, a retrospective analysis conducted by the original seven teams that had performed the transplant experiments "worked out that the procedure tended to be most effective in patients who were relatively young and whose disease was at an early stage."[8] In addition, "those who benefited the most had at least 100,000 dopamine-producing cells of fetal origin integrated into their brains. Cells from at least three fetuses are needed to achieve these numbers."[9] As a result, a new trial—called TRANSEURO, funded by the European Union—is being launched using dopamine-producing cells from fetal brains.[10] The trial was scheduled to begin in July 2014 and expects to enroll 150 patients in the United Kingdom, Sweden, France, and Germany.[11]

Similar trials involving the implementation of various types of stem cells into individuals with Parkinson's disease are scheduled to begin in 2016 in Kyoto, Japan (using induced pluripotent stem cells); 2017 in New York; and 2018/2019 in Europe (both using human embryonic stem cells).[12] According to one source, many such human embryonic stem cell (ESC) lines "have now been generated that are well characterized and quality controlled and this includes two human ESC-based sources that have already been approved by the U.S. FDA for early stage clinical trials in humans."[13]

[4] Donovan, "Funding Restrictions on Fetal Research," p. 227; and, Vawter and Caplan, "Strange Brew," p. 30.

[5] Allison Abbott, "Fetal-cell revival for Parkinson's," *Nature*, vol. 510 (June 12, 2014), pp. 195-196.

[6] Constance Holden, "Fetal cells again?," *Science*, vol. 326 (October 16, 2009), pp. 358-359.

[7] Abbott, "Fetal-cell revival for Parkinson's," p. 195.

[8] Ibid.

[9] Ibid.

[10] Ibid., p. 196.

[11] Ibid. For further information about the trial, see http://www.transeuro.org.uk/.

[12] Abbott, "Fetal-cell revival for Parkinson's," p. 196.

[13] Janelle Drouin-Ouellet and Roger A. Barker, "Stem cell therapies for Parkinson's disease: are trials just around the corner?," *Regenerative Medicine*, vol. 9, no. 5 (2014), pp. 553-555.

How is fetal tissue acquired for research?

Fetal tissue used in research is obtained from elective abortions. Under certain rare circumstances, fetal tissue may also be obtained from a miscarriage, also called a spontaneous abortion, or following the removal of an ectopic pregnancy, which occurs when an embryo has implanted outside the uterus. Because the timing or recognition of a spontaneous abortion or ectopic pregnancy is unpredictable, and both conditions may result in a serious health emergency for the woman, the fetal tissue collected under these circumstances is often not suitable for research purposes.

According to a Government Accountability Office (GAO) report published in October 2000, most biomedical researchers at that time obtained human fetal tissue from a "central tissue supplier"; three identified as receiving NIH funding included the Birth Defects Laboratory at the University of Washington, the Brain and Tissue Banks for Developmental Disorders at the University of Maryland, and the University of Miami School of Medicine/Children's Hospital of Orange County.[14] According to a 1992 journal article, NIH had funded such a center for collecting fetal tissue for many years.[15] Another source of human fetal tissue mentioned in the GAO report was "private, nonprofit central tissue supply organizations that did not directly receive federal funds."[16] Those identified by GAO in 2000 were Advanced Bioscience Resources, Inc. (Alameda, CA), and the Albert Einstein College of Medicine Human Tissue Repository (New York, NY). Alternatively, some researchers obtained fetal tissue directly from an academic medical center hospital or a health clinic.[17]

A recent media article states that "many researchers buy tissue from two small California companies," StemExpress, in Placerville, and Advanced Bioscience Resources Inc. (ABR), in Alameda, "a nonprofit that has 12 employees and recent sales of about $1.4 million."[18] According to the article, fetal tissue accounted for about 10% of StemExpress's business and the tissue "has been used in studies of leukemia, Hodgkin's lymphoma and Parkinson's disease."[19]

Can fetal tissue be sold for research purposes?

Under the NIH Revitalization Act of 1993, it is "unlawful for any person to knowingly acquire, receive, or otherwise transfer any human fetal tissue for valuable consideration if the transfer affects interstate commerce."[20] While this provision prohibits the sale or purchase of fetal tissue itself, the term *valuable consideration* "does not include reasonable payments associated with the

[14] U.S. General Accounting Office, *Human Fetal Tissue: Acquisition for Federally Funded Biomedical Research*, GAO-01-65R, October 4, 2000, p. 4.

[15] Vawter and Caplan, "Strange Brew," p. 30.

[16] U.S. General Accounting Office, *Human Fetal Tissue: Acquisition for Federally Funded Biomedical Research*, GAO-01-65R, October 4, 2000, p. 5.

[17] U.S. General Accounting Office, *Human Fetal Tissue: Acquisition for Federally Funded Biomedical Research*, GAO-01-65R, October 4, 2000, pp. 4-5.

[18] Denise Grady and Nicholas St. Fleur, "Shadowy Trade in Fetal Tissue," *The New York Times*, July 28, 2015, pp. D1, D3.

[19] Ibid.

[20] PHS Act §498B; 42 U.S.C. §289g-2(a).

transportation, implantation, processing, preservation, quality control, or storage of human fetal tissue."[21] Thus, tissue companies may charge researchers to recover the costs associated with these types of activities.

Persons violating these provisions shall be subject to fines, imprisonment for not more than 10 years, or both.[22] Violations involving the payment of valuable consideration shall result in fines reflecting not less than twice the amount of the valuable consideration received.[23]

According to the founder of StemExpress, the fetal cells are difficult to isolate and involve "expensive processes that take millions of dollars of equipment. Just to attempt to do some of these isolations can cost us thousands of dollars, and it may not even work."[24] As an illustration of just how expensive, "a vial containing five million frozen fetal liver CD133+ stem cells can cost more than $24,000 ... and an overnight shipment to Germany, for example, can cost thousands of dollars."[25] Another supplier of fetal tissue, ABR, charged "$300 a specimen for tissue from a second-trimester fetus, and $515 if the fetus was first-trimester," according to a 2013 price sheet.[26]

Who investigates the illegal sale of fetal tissue?

On the federal level, the Department of Justice, and more specifically the Federal Bureau of Investigation (FBI), would open investigations into individuals and entities suspected of violating federal law with respect to the illegal sale, or trafficking, of human fetal tissue and other organs. As noted earlier, federal law prohibits the sale or purchase of human fetal tissue in interstate commerce.[27] In 2000, the FBI reportedly investigated a Kansas clinic affiliated with Planned Parenthood for allegedly selling—and profiting from the sale of—fetal tissue; ultimately, no laws were found to have been broken.[28]

What federal regulations govern the collection and use of fetal tissue for research?

Federal law permits the Department of Health and Human Services (HHS) to fund *research on new therapies that involve the transplantation of human fetal tissue* using tissue derived from an elective or spontaneous abortion, or from a stillbirth.[29] However, human fetal tissue may be used for such purposes only if the following conditions are met:

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[21] PHS Act §498B; 42 U.S.C. §289g-2(e)(3).

[22] 42 U.S.C. §289g-2(c)(1).

[23] 42 U.S.C. §289g-2(c)(2).

[24] Grady and St. Fleur, "Shadowy Trade in Fetal Tissue," p. D3.

[25] Ibid. See also a StemExpress price list at http://stemexpress.com/product-category/fetal-liver/.

[26] Ibid.

[27] PHS Act §498B; 42 U.S.C. §289g-2(a).

[28] Sandhya Somashekhar and Danielle Paquette, "Undercover video shows Planned Parenthood Official Discussing Fetal Organs Used for Research," *The Washington Post*, July 14, 2015.

[29] PHS Act §498A(a); 42 U.S.C. §289g–1(a).

- The woman must provide her written consent that she is donating the fetal tissue for research, that the donation is being made without any restrictions on who may receive the tissue, and that she has not been informed of the identity of any such recipients.[30]
- The attending physician must declare in writing that, in the case of an induced abortion (1) the woman's consent for the abortion was obtained prior to requesting or obtaining consent to donate the fetal tissue for research; (2) the timing, method, or procedures used to terminate the pregnancy were not altered in order to obtain the tissue; and (3) the abortion was performed in accordance with applicable state law. In addition, the attending physician must declare that the tissue has been donated with the woman's consent and that the woman has been fully informed of the physician's interest, if any, in the research, and of any medical or privacy risks associated with the tissue donation.[31]
- The principal researcher must declare in writing that (1) he or she is aware that the tissue is human fetal tissue that may have been obtained from an elective or spontaneous abortion, or a stillbirth, and that it was donated for the purposes of research; and (2) prior to obtaining the informed consent of a research subject to be a recipient of the transplanted tissue (see discussion of Common Rule, below), he or she will provide the same information about the fetal tissue to the research subject and get written acknowledgement of receipt of such information.[32]

In addition to the above statutory requirements, fetal tissue research that involves human subjects is subject to the Common Rule.[33] Under the Common Rule, research protocols must be approved by an Institutional Review Board (IRB) to ensure that the rights and welfare of the research subjects are protected.[34]

The Common Rule lists several criteria for IRB approval, including the requirement that researchers obtain the informed consent of their research subjects.[35] In addition, it sets out the types of information that must be provided to prospective research subjects during the informed consent process, including an explanation of the purpose of the research, a description of the research procedures, and a description of the risks and benefits of the research.[36] An IRB may decide to waive the informed consent requirement if it determines that (1) the research poses no more than minimal risk to the subjects, (2) the waiver will not adversely affect the rights and welfare of the subjects, and (3) the research is not practicable without a waiver.[37]

If the human fetal tissue to be used in the research is identifiable, such that information associated with the material links it to one or more living individuals (which often may be the case), then

[30] PHS Act §498A(b)(1); 42 U.S.C. §289g–1(b)(1).

[31] PHS Act §498A(b)(2); 42 U.S.C. §289g–1(b)(2).

[32] PHS Act §498A(c); 42 U.S.C. §289g–1(c).

[33] The Common Rule is the informal name given to core federal regulations governing the protection of human subjects in research supported or conducted by the federal government. The regulations were first promulgated by HHS at 45 C.F.R. Part 46, Subpart A.

[34] 45 C.F.R. §46.109.

[35] 45 C.F.R. §46.111(a)(4).

[36] 45 C.F.R. §46.116(a).

[37] 45 C.F.R. §46.116(d).

those individuals also become research subjects under the Common Rule.[38] Thus, an IRB may have to review the protocol for collecting and testing the human fetal tissue, and the woman who is donating the tissue may have to provide informed consent (unless waived by the IRB).

The researchers must also obtain prior approval from the Food and Drug Administration (FDA) by filing an Investigational New Drug (IND) application if the research is testing a new diagnostic or therapeutic intervention that the researchers hope will receive FDA marketing approval. One of the IND requirements is that the researchers obtain IRB approval.

Importantly, if the purpose of the human fetal tissue research is simply to acquire new biomedical knowledge, and it is not being conducted under an IND or involving human research subjects, then the research is not subject to the Common Rule or FDA regulation.

Finally, the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule applies if the researchers want access to medical information about the woman from whose fetus the fetal tissue was obtained. Under the Privacy Rule, an individual's medical information may not be used or disclosed for research without the individual's written authorization unless an IRB (or equivalent Privacy Board) waives the authorization based on certain specified criteria.[39]

What federal regulations govern the clinical use of fetal tissue?

Currently, fetal tissue is not being used in any clinical applications involving transplantation. Any such therapeutic use of human fetal tissue that received approval from the FDA would be regulated under the agency's Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) regulations.[40] An HCT/P is an article "containing or consisting of human cells and tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient."[41] HCT/Ps include bone, ligament, skin, dura mater, heart valves, cornea, hematopoietic stem/progenitor cells derived from peripheral and cord blood, and semen or other reproductive tissue.[42]

FDA regulates HCT/Ps primarily under its general authority to control the spread of communicable diseases.[43] The HCT/P regulations are focused on (1) preventing the use of contaminated cells and tissues with the potential for transmitting infectious diseases, (2) preventing the improper handling or processing of cells and tissues that might contaminate or damage them, and (3) ensuring the clinical safety and effectiveness of cells and tissues.

[38] 45 C.F.R. §46.206.

[39] 45 C.F.R. §164.512(i).

[40] 21 C.F.R. Part 1271.

[41] 21 C.F.R. §1271.3.

[42] Ibid. HCT/Ps do not include vascularized human organs for transplantation, which are regulated by the Health Resources and Services Administration (HRSA). Nor do they include plasma and blood or derivative products regulated by FDA under 21 C.F.R. Parts 606, 607, 630, and 640.

[43] PHS Act §361; 42 U.S.C. §264.

The regulations require establishments that recover, handle, store, and distribute HCT/Ps for clinical purposes to register with FDA and submit a list of their products.[44] The regulations also establish eligibility criteria for donors of HCT/Ps, including donor screening and testing.[45] Finally, the regulations include a set of good tissue practices (GTPs) that govern the methods, facilities, and controls used to deal with HCT/Ps.[46] The GTPs address personnel, procedures, environmental control and monitoring, equipment, supplies and reagents, recovery, processing and process controls, storage, shipment and distribution, records, tracking, and complaints.

Is the system for collecting non-fetal organs and tissue different from that for fetal tissue?

The federal government has established policies and a system for procuring organs that are separate from policies for the acquisition of fetal tissue. Organs are procured (or acquired) from living persons or cadavers. An organ is "[a] human kidney, liver, heart, lung, pancreas, or intestine (including the esophagus, stomach, small or large intestine, or any portion of the gastrointestinal tract), or vascularized composite allograft." The National Organ Transplant Act (NOTA of 1984; P.L. 98-507) created the Organ Procurement and Transplantation Network (OPTN), which is the federally supported system for organ sharing in the United States. The Health Resources and Services Administration (HRSA) oversees organ procurement by way of the OPTN's operations.

Does the Department of Veterans Affairs (VA) allow the use of human fetal tissue in research conducted by VA researchers?

No. The Veterans Health Administration (VHA) states that "research in which the focus is either a fetus, or human fetal tissue, in-utero or ex-utero (or uses human fetal tissue), cannot be conducted by VA [researchers] while on official duty, at VA facilities, or at VA-approved off-site facilities."[47] Additionally, the use of stem cells are governed by the policy set by NIH for recipients of NIH research funding.

Does the Department of Defense use fetal tissue in medical research?

No. The Department of Defense medical research programs are not using fetal tissue in medical research at this time. However, there is not a blanket ban on the use of such tissue. Under

[44] 21 C.F.R. Part 1271, Subpart B.

[45] 21 C.F.R. Part 1271, Subpart C.

[46] 21 C.F.R. Part 1271, Subpart D.

[47] Department of Veterans Affairs, Veterans Health Administration, "Requirements for the Protection of Human Subjects in Research," VHA Handbook 1200.05, November 12, 2014.

Department of Defense Instruction 3216.02, entitled Protection of Human Subjects and Adherence to Ethical Standards in DOD-Supported Research, any "research involving human subjects using fetal tissue shall comply with sections 289g–289g-2" of title 42, United States Code.[48]

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[48] http://www.dtic.mil/whs/directives/corres/pdf/321602p.pdf.

The Washington Post
Wonkblog

'We lose money doing this': Tiny company caught in abortion debate takes on Congress

By Danielle Paquette May 27

PLACERVILLE, CALIF. — StemExpress, a tiny biomedical company in this foothill town east of Sacramento, has emerged at the heart of the contentious national debate over abortion and the scientific use of human fetal tissue. FBI agents say its floor-to-ceiling windows are security hazards, a potential line of sight for snipers. The backdrop of pine trees and hills provides cover, employees say, to strangers who crouch with cameras.

Inside, Melanie Rose, a laboratory technician, knows anyone could be watching. One recent May morning, she opened a foam box with fetal tissue packed in ice — a donation for medical research.

Rose, who is working toward a master's degree in stem cell treatment, is one of 24 employees here thrust into view after antiabortion activists released a series of videos last year.

The videos shed light on an uncomfortable aspect of a little-known industry. They targeted Planned Parenthood, which provides abortions and, for a time, StemExpress paid a nominal fee to obtain the fetal tissue. The tissue, which is in limited supply, is a vital component in stem cell research — a great hope for medical breakthroughs. StemExpress collects the tissue and extracts the stem cells for researchers

worldwide. Most of it is from adult sources — drawn from blood and bone marrow — but a small amount is from fetal tissue.

That work, with fetal tissue, has catapulted the small biotech firm out from under the radar. It is now the target of loiterers, protesters and death threats and the subject of a congressional inquiry.

At the heart of the issue is whether the work is done for profit. The exchange of fetal tissue for research is legal, so long as neither party makes money in the deal.

House Republicans and antiabortion advocates assert that firms such as StemExpress do profit illegally and that that profit fuels a demand for abortions.

StemExpress chief executive Cate Dyer says profit is not a factor.

"We lose money doing this," Dyer said about working with fetal tissue. "We don't have to do this, and we won't stop doing this."

The consequences of this supercharged debate transcend one firm. Scientists and doctors across the country say the political turmoil on Capitol Hill has stalled lifesaving work and imperiled progress toward, among other treatments, a Zika virus vaccine.

"We want to accelerate lifesaving research," Dyer said. "That's what it's all about. That is my passion."

Dyer once worked as an emergency medical technician at Santa Barbara Cottage Hospital's trauma center. Watching people die every day at the Southern California facility, she said, inspired her to search for ways to prevent death. She started the company in 2010 with $9,000 in savings. In 2015, StemExpress said it posted roughly $5 million in revenue.

Her company's innovation, as she describes it, is isolating the stem cells from donor tissue from the clinic, which extends their lifespan for research. Otherwise, she said, a researcher in New York who wanted an adult liver in California would lose a substantial number of its usable cells during the cross-country flight.

Before the videos came out, Dyer said, StemExpress had never had so much as a threat. Hundreds have since hit the StemExpress inbox. She said a recent message was typical of what they'd received: "We know that you use aborted fetuses in your 'research.' Repent now before it is too late."

Dyer said the company provides the samples to researchers at a financial loss to expedite the creation of medicines and vaccines — and that fetal tissue represents less than 1 percent of the business.

"I want to be able to focus on saving people's lives," Dyer said, "and instead I have to deal with death threats."

"Sometimes," she said, "people cut the letters out of magazines and send us messages."

A fateful dinner meeting

David Daleiden, an activist who leads an outfit he calls the Center for Medical Progress, secretly shot the videos. He started looking into StemExpress after seeing a Craigslist posting for a contract job to collect tissue from a women's health clinics.

StemExpress is a business, and that's clear from the list of products and bioservices on its website. He found it disturbing.

"The big problem, when we talk about the harvesting and sale of fetal tissue from abortion, is you're creating a market," he said. "You're introducing this extra new level of demand for abortion."

The video shows a dinner meeting with Dyer last May at an upscale restaurant in El Dorado Hills, Calif. Daleiden and his colleague posed as biotech business owners who wanted to partner with StemExpress.

Daleiden asked for details about StemExpress's interest in fetal tissue, where it comes from, how it's procured, issues with shipping it and the growing demand for it. Daleiden also asked about StemExpress's relationship with Planned Parenthood.

Dyer's description of Planned Parenthood as a "high-volume institution" later drew scrutiny from House Republicans.

The conversation, which Dyer says lasted about two hours, was edited down to less than 10 minutes. Any talk of money, she said, was taken out of context in the editing. She says that her business grew quickly because of the research community's high demand for adult tissue and blood, and that's what she was referring to when profit was discussed.

The company's records indicate that roughly 1 percent of the tissue StemExpress collects is fetal. StemExpress typically gave Planned Parenthood $55 per sample, paying mostly for use of its rooms, storage and staffers.

Last year, a StemExpress catalog advertised a vial of two million "fresh" stem cells from a fetal liver for $1,932, and $1,840 for the same amount "cryopreserved," or frozen. Company records show they charge researchers a flat fee of $595 for each sample of fetal tissue, which costs an average $732 to prepare. In addition to compensating staffers who collect the tissue, the company pays for mileage, shipping, packaging, lab equipment, screening the sample for diseases and general upkeep.

In 2015, revenue from the transfer of fetal tissue to researchers totaled roughly $26,000. The cost of preparing the tissue, the company said, was about $33,000 — resulting in a $7,000 financial loss.

Congressional demands

The House Energy Committee's Select Investigative Panel on Infant Lives has demanded that StemExpress and other biomedical players hand over thousands of pages of financial records and the names of their employees, issuing 36 subpoenas since March.

Its mission, according to its website, is to compile information about abortion providers and the biotech companies who "sell baby body parts." The members plan to send their findings to Congress at the end of the year. On Tuesday, 180 of 188 House Democrats urged Speaker Paul D. Ryan (R-Wis.) to dissolve the panel, accusing it of harassment and McCarthyism.

Medical authorities have warned lawmakers that stigmatizing fetal tissue research could jeopardize public health. In March, the Association of American Medical Colleges — a group that includes the American Congress of Obstetricians and Gynecologists, Harvard University, and the Stanford University School of Medicine — sent a letter to congressional investigators.

"From therapies for end-stage breast cancer, diabetes and Parkinson's disease to a promising vaccine for Ebola," they said, "vital medical research depends on continued use of fetal tissue under current laws and regulations."

Allowing people to donate the tissue for research, the authors stressed, is not linked to an increase in abortions, which have declined in the United States as birth control grows more accessible.

Researchers say the toll is material. During the investigation, one lab, Novogenix Laboratories in Los Angeles, has gone out of business. Dyer said the subpoenas and travel to Washington have halted her business's expansion.

After the videos came out, she said, the supply of fetal tissue quickly dwindled. The company recorded 76 samples in 2013, 72 in 2014 and 39 in 2015. Now, on average, it gets four samples a month.

StemExpress says it has provided more than 2,000 pages of documents to Congress, including five years of banking records.

Rep. Marsha Blackburn (R-Tenn.), the chair of the House panel who describes herself as "pro-life," said she wants to see further proof — a precise breakdown of each expense that goes into procuring and purifying fetal tissue — that StemExpress does not turn a profit. Company estimates about the cost of procuring tissue, she said, are not enough. The panel has issued a subpoena to StemExpress's bank.

Rep. Jan Schakowsky (Ill.), the panel's ranking Democrat, said StemExpress has been cooperative.

"This is really dangerous stuff," she said, "and it seems to me that the real goal of this so-called investigation — I prefer the term witch hunt — is they're hellbent on putting them out of business."

Dyer said she has strived to respond to the panel's requests for evidence but has resisted demands to hand over employees' names, fearing it would threaten their security. Blackburn has said that getting employees' names is necessary for investigators to set up interviews and that the names will not be made public.

Dyer's security fears are not unfounded. In November, about four months after Daleiden released the first undercover video of Planned Parenthood officials, Robert L. Dear Jr. killed three people and wounded nine at a Planned Parenthood clinic in Colorado. He later told authorities, "No more baby parts."

The next month, Scott Orton, a 57-year-old Washington state resident, was arrested after he blogged about killing StemExpress employees and, specifically, Dyer.

"She will have to face the souls of the babies she's bought and sold when she arrives on the other side," he wrote, according to an FBI affidavit. "I'm sending her there early."

Chilling effects on research

Those kinds of threats and the growing political pressure have chilled stem cell research at laboratories across the country.

Steven Goldman, a neurologist at the University of Rochester Medical Center in New York, said the outrage — and anxiety over becoming a target of it — has delayed his research on multiple sclerosis.

In 2012, Goldman's team received a $12.1 million grant from the Empire State Stem Cell Board to develop a cure. The team extracted stem cells from fetal tissue — collected from abortions performed at local hospitals — to see whether they could regenerate myelin, the insulating sheath around nerve fibers, in mouse brains.

It worked, Goldman said. He and his colleagues planned to start clinical trials on late-stage multiple sclerosis patients this year. Since Daleiden's first video, however, the researchers' supply of fetal tissue dried up.

"Hospitals seemed less willing" to donate, Goldman said. "We'd never had significant rejections by patients, and all of the sudden they were turning down consent forms."

Goldman has pushed his multiple sclerosis research schedule back to 2019.

"This kind of delay," he said, "results in the additional deaths of people who could have been rescued."

Although the National Institutes of Health has expanded funding for fetal tissue research in recent years — federal grant money for the work jumped from $67 million in 2013 to $84 million in 2016 — scientists who receive the money say the projects have become harder to complete.

Progress has stalled at Stanford University, for example, which received more than $1.3 million in the funding in 2015.

For four years, Steven Sloan, a PhD student in neuroscience, has studied fetal tissue to better understand brain development and the types of cells that might contribute to disorders such as autism.

In 2014 and 2015, the school, a client of StemExpress and local hospitals, received tissue within a week of requesting a sample. But as the congressional investigation heated up, Sloan said, the scientists started waiting longer than a month. "All of a sudden," he said, "getting tissue was like pulling teeth."

Sloan, who graduates this month and plans to pursue a medical degree, said he probably will stick with adult tissue in future research.

"The backlash," he said, "makes you think twice about proceeding with this kind of work."

Other institutions have received more direct political pressure. Following demands from Rep. Doug Lamborn (R-Colo.), Colorado State University, a former client of StemExpress, stopped ordering fetal tissue for a project to cure HIV/AIDS. The university decided to "seek alternatives to aborted fetal tissue sources," spokesman Mike Hooker said.

As summer — and mosquito season — approaches, Rita Driggers says, her research is particularly urgent. The medical director of the Maternal-Fetal Medicine Program at Washington's Sibley Memorial Hospital said doctors need such tissue to defeat the Zika virus. Her study, published in the New England Journal of Medicine, suggests that Zika lingers in pregnant women long after symptoms fade.

A patient of Driggers's had returned from Mexico, Guatemala and Belize with Zika and learned her baby's brain wasn't developing. When she terminated the pregnancy, she asked whether the tissue could be studied. "She wanted her misfortune to benefit other people," Driggers said.

Even if all goes well, Driggers said, a Zika vaccine is at least two years away.

"If researchers are threatened, it's going to make us think twice about continuing research," she said, adding that her former boss has received death threats for her stem cell work. "Ultimately, the patients that could benefit from the research won't."

At the StemExpress lab, Dyer has hired armed guards, installed security cameras and put her staff through active-shooter training.

Rose, the 27-year-old lab technician, wears a silver Saint Christopher pendant for protection.

She cried when protesters first surrounded StemExpress, waving Bibles and photos of fetuses. Now she tries to make eye contact through the windows. To smile.

When Rose sets to work, she breaks the tissue apart, then soaks it in enzymes and counts the number of stem cells on a grid under a microscope. She pours the cells into two-milliliter vials, which are stored in liquid nitrogen tanks until they are shipped to a researcher at a university or major health institution.

"This tissue," she said, "would be thrown away if we didn't send it to researchers who are truly trying to save lives. I want them to see what I'm doing. That something good can come of it."

This story has been updated.

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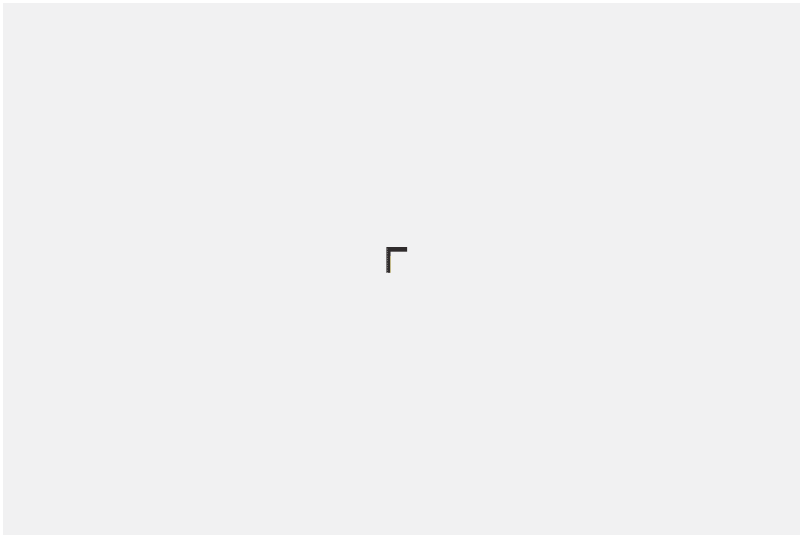
Danielle Paquette is a reporter covering the intersection of people and policy. She's from Indianapolis and previously worked for the Tampa Bay Times. Follow @dpaqreport

NATIONAL GEOGRAPHIC
http://news.nationalgeographic.com/2016/01/160128-zika-virus-birth-defects-brian-damage-history-science.html

Why Zika Is This Year's Scary Virus

It is "spreading explosively" in the Americas and may be the next public health emergency.



Young people shy away from a municipal worker who is spraying insecticide to kill mosquitoes that might carry the Zika virus in Recife, Brazil. On Thursday, the World Health Organization announced that it will form an emergency committee to combat the virus.

PHOTOGRAPH BY FELIPE DANA, ASSOCIATED PRESS

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By **David Quammen**

PUBLISHED JANUARY 28, 2016

Scary new viruses emerge abruptly in our modern world, provoking stark headlines and demands for bold government action—but in most cases the causes are complex and have developed, unnoticed, over years or decades. That's true again for Zika, a virus unknown to most people until recent days, and now suddenly the subject of somber warnings from the Centers for Disease Control and Prevention and the World Health Organization, which announced on Thursday that the virus is "spreading explosively." The alarm stems from an epidemic of birth defects in Brazil, which may be linked with Zika virus infection of mothers during pregnancy. Amid this furor, it's worth distinguishing fact from supposition and placing the Zika phenomenon in a broader context.

This virus was first isolated in Uganda in 1947, within a small enclave called Zika Forest, near the west shore of Lake Victoria, where researchers from the Rockefeller Foundation were studying yellow fever. Ironically, the earliest known victim of Zika virus infection in Africa was an Asian macaque—a rhesus monkey, set out in a cage in a treetop as bait for the mosquitoes that carry yellow fever virus. Instead of that virus, its blood yielded this new thing, dubbed Zika. The virus had never been seen before, but it had probably lurked chronically in African monkeys, or some other native reservoir, for millennia. The same virus later turned up, in the same forest, within mosquitoes of the *Aedes* genus, and those mosquitoes are now identified as vectors of Zika, transmitting the virus from host to host when they bite.

Eventually it was found infecting people, too, not just in Africa but also in Asia—from Senegal to Cambodia, in fact, a wide range throughout which *Aedes* mosquitoes reside. The symptoms, such as headache, fever, a rash, bloodshot eyes, were generally mild. Then, in 2007, Zika virus caused more than a hundred cases on Yap, a tiny island in the southwestern Pacific, having somehow gotten there from the Asian mainland. *Aedes* mosquitoes were present on Yap and passed the virus from one victim to another. But no one suffered badly enough to be hospitalized. Six years later, Zika emerged more dramatically in French Polynesia, sending an estimated 28,000 people (11 percent of the population) into medical care. Among 72 patients with severe neurological symptoms, 40 contracted Guillain-Barré syndrome, a dangerous autoimmune dysfunction, sometimes triggered by infection. That was the first signal that Zika virus infection could be dire.

The second signal came in April of last year, with a spate of Zika virus infections diagnosed in northeastern Brazil—a new location for the virus, on the South American mainland, and with a huge population of susceptible humans now within reach. Worse news came in October: a drastic increase in cases of microcephaly (smallness of head, linked to incomplete brain development) among infants born to mothers in the northeast. Amniotic fluid from at least two of those mothers contained evidence for the presence of Zika virus, suggesting (but not proving) the link between Zika and microcephaly. As the numbers rose further and anxiety grew, the WHO and the CDC issued warnings, and the WHO called a meeting for February 1, to consider proclaiming Zika a public health emergency. Alas, as we saw during the Ebola events of 2014, such a declaration doesn't necessarily trigger a coordinated and efficacious international response.

Mother Solange Ferreira bathes her son Jose Wesley in Poco Fundo, Brazil. Jose has microcephaly, a condition suspected to be caused by the Zika virus.
PHOTOGRAPH BY FELIPE DANA, ASSOCIATED PRESS

This is a story of biogeography as well as medicine and public health, and of the consequences of human travel and transport. How did Zika virus get to Brazil? Possibly it traveled in the blood of athletes—when competitors from French

Polynesia and other Pacific islands came to Rio de Janeiro, in August 2014, for the Va'a World Sprint Championship in outrigger canoeing. (Some commentators have wondered whether the 2014 World Cup in soccer brought Zika to Brazil, but that extravaganza included no teams from Pacific islands.) Still, bringing the virus was one thing; spreading it was another.

Vectors were necessary, for transmitting it from human to human. One competent mosquito (*Aedes aegypti*, commonly called the yellow fever mosquito) is an African creature that probably hitchhiked to the Americas on sailing ships at the time of the slave trade. Another, known as the Asian tiger mosquito (*Aedes albopictus*), arrived more recently, reaching not just South and Central America but also the southern United States, probably by way of egg-laden water amid shipments of used tires from Asia. If those mosquitoes hadn't been transplanted by human activity, decades and centuries before Zika virus, then the virus itself couldn't have taken hold here between the Pacific and Atlantic oceans.

What next? Urgent concern for all pregnant women, or women who may become pregnant, of course, not just in Brazil but throughout all the warmer zones of this hemisphere, wherever *Aedes* mosquitoes are present. The WHO has cautioned that Zika is likely to spread throughout the Americas, except for Canada and Chile. Additional cases of Zika virus infection have already occurred in Colombia, Venezuela, El Salvador, Mexico, and other South and Central American countries, and several of those countries, including El Salvador, Jamaica, and Colombia, have already advised women to delay pregnancy.

Zika infections carried by travelers have been brought back to Minnesota, New York, Hawaii (where a microcephalic baby was born), and other states in the U.S. The question about such cases, in the U.S. or elsewhere, is: Will infected people infect *Aedes* mosquitoes, who will infect other people? It's big question, given that the Asian tiger mosquito is now also present across southern Europe, including much of Italy, and both the tiger mosquito and the yellow fever mosquito inhabit most Asian cities. By one account, more than half the humans on Earth live within areas infested by *Aedes* mosquitoes. Public health officials will need to be vigilant in reducing the opportunities—in the form of standing water near human habitations—for those mosquitoes to lay eggs that mature to adulthood. They will need also to be sensitive to social realities: You can't simply tell poor, disempowered women without access to birth control means, "Don't get pregnant."

Bottom line: This is not something that is merely happening to us, a cosmic misfortune, a one-off event over which we must get up on our hind legs and howl at our governments for insufficient diligence. It is, on the contrary, a result of things we do as a modern society—traveling, transporting people and things speedily around the globe, having babies to the point where there are more than seven billion of us on this planet, so that we now represent an irresistible resource for any virus that can adapt to preying upon us—and it's part of a longer, broader pattern. In 2012, MERS coronavirus emerged from Saudi Arabia, stirring our concerns. In 2014 it was Ebola, blazing out of West Africa in search of a larger host base. Next year it will be virus X, and the year after, virus Y. This year it is Zika.

Octopuses: Masters of Disguise and Agile Hunters

1 / 10

Peerless Beauty This iconic Hubble image of the spiral galaxy NGC 1300 is suffused with detail—bright blue young stars, the dust lanes spiraling around the bright nucleus, distant galaxies shining through.

NASA, ESA, AND THE HUBBLE HERITAGE TEAM (STSCI/AURA). ACKNOWLEDGMENT: P. KNEZEK (WIYN)

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Nidhi Chabra May 17, 2016

Yes It Is Scary :'(

Also Read Related Article To **#ZikaVirus "10 Things You Need To Know About The Zika Virus"** - **http://www.beauty360expo.com/10-things-you-need-to-know-about-the-zika-virus/**

b. mills Feb 9, 2016

And so the US Congress is out to destroy Planned Parenthood, which would at least offer those poor, disenfranchised women accessible BIRTH CONTROL--access to therapeutic abortions would be nice, too, but PREVENTION would be much nicer, of course. As to the comment about evolution, I presume the author is from a state or school district where science education is particularly lacking (perhaps because the teaching of evolution is banned?) Lamrakianism--the notion that a single trait developed in one individual's lifetime constitutes a mutation that is then passed down through the species--is nonsense. The Soviets, in espousing that idea, set their natural sciences back quite a bit, until they finally chucked the idea.To say the least, we need better science education on a public level, not just for a few fortunate souls.

charles Pickerell Feb 3, 2016

Apart from the increased movement of people etc which obviously allows this to spread faster, are there any other known or hypothesised ecological reasons for this relatively recent increase in cases?

Muriel Strand Jan 31, 2016

evolution happens...

JUNIETTE FIFIELD Jan 30, 2016

Now this is a random thought sparked by this article; If this Zika virus is causing a widely known birth defect that creates a small head, however, no loss of thought and physical function control; Wouldn't it really be considered the process of human evolution to a degree of extent? If you were to think about all the medical drugs we take and the effect they create genetically all we do is improve the genetic code throughout generations to sustain and bond with our DNA or it seems any way. I'm not going as far as saying that all genetic codes will be able to sustain or mutate a virus or such, however, we as humans evolved from something that evolved from something that withheld its own against a virus that could kill it, by thus transforming itself into mutated organisms.

Susan Dowman-Nevling Feb 9, 2016

@JUNIETTE FIFIELD This is not a defect simply causing a small head. It also causes incomplete brain development, often early death, inability to walk, inability to perform self care, often very short stature.it is a devastating birth defect that causes severe inability to learn or function. If it is a mutation that would not help the human race. It would be the end of it.

Shana Garrett Jan 30, 2016

We already do collaborative studies all over the world, all of the time, and on pathogens most people have never even heard about. Research takes more than a couple days. It can take many years...which is why there is no cure for cancer or vaccine for HIV (yet). Funding is the number 1 issue clogging the works. In the US, most funding for medical research comes from the federal government in the form of NIH grants. Every time congress votes to cut funding or reject an increase in funding for research, the process gets slower. Big Pharma doesn't make vaccines. They don't even do vaccine research and development, because they are not money making items individually (vaccinations are price controlled so that they can be mass distributed) and a Big Pharma would rather sell the drugs that treat the symptoms when people get ill than sell something that will prevent widespread disease. This isn't merely cynical speculation, I am a molecular biologist, who has worked in vaccine research at the federal and university levels for 20 years!

Caroline Green Jan 28, 2016

I have read that this is not as fatal as Ebola but I agree with the former reader's view, more scientists should pay their attention to this issue. And try to find an efficient way.

-Caroline

http://www.creativebiomart.net/blog

Carter Fox Jr. Jan 28, 2016

Why can't scientists, communicate with each other, to the extent of, the Biologists, share with the Chemist, so the Chemist can find strengths and weaknesses, and share this information with Big Pharma, and find a way to immunize folks from these disorders, "Before They Get To The Epidemic Stage"?

Mihajlo Filipovic Feb 9, 2016

@Carter Fox Jr.

Because they don't want it.

See here for some real scare: **http://thefreethoughtproject.com/experience-purchase-zika-virus-online/**

Susan Dowman-Nevling Feb 9, 2016

@Mihajlo Filipovic @Carter Fox Jr.

So very untrue. Trashjournalism.

HEALTH

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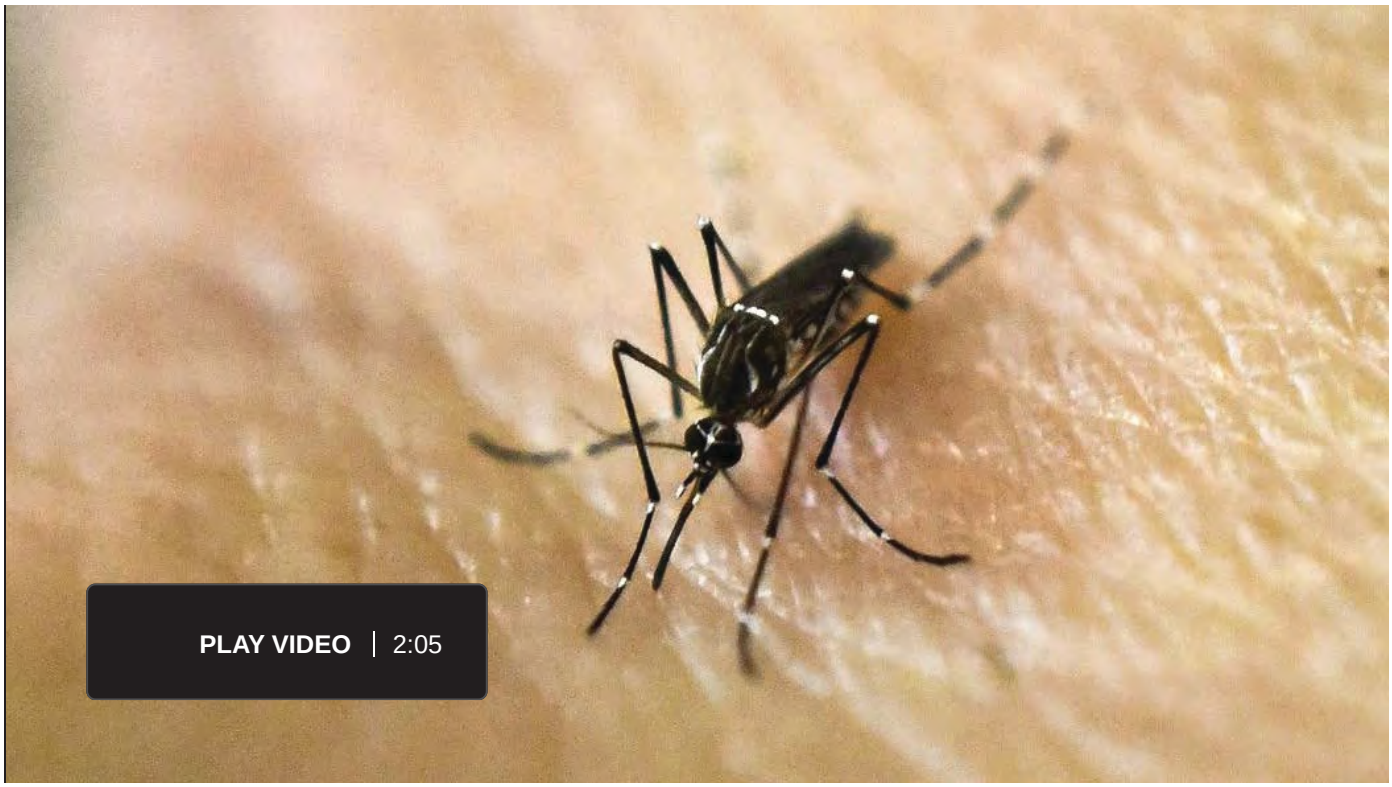
Short Answers to Hard Questions About Zika Virus

By DONALD G. McNEIL Jr., CATHERINE SAINT LOUIS and NICHOLAS ST. FLEUR UPDATED March 18, 2016 | RELATED ARTICLE



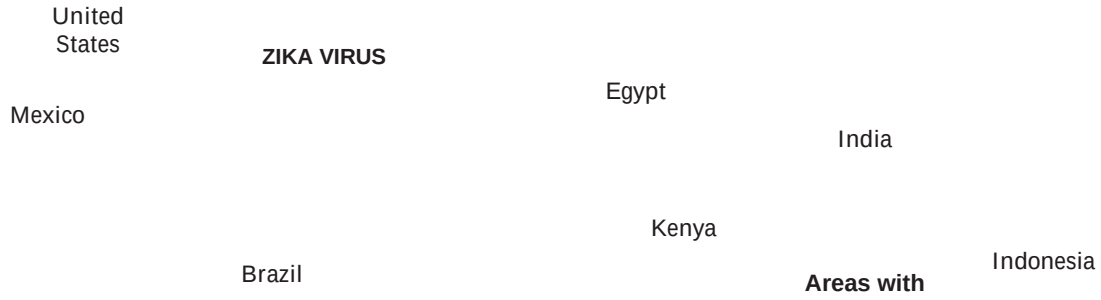
The World Health Organization has declared the Zika virus an international public health emergency, prompted by growing concern that it could cause birth defects. As many as four million people could be infected by the end of the year.

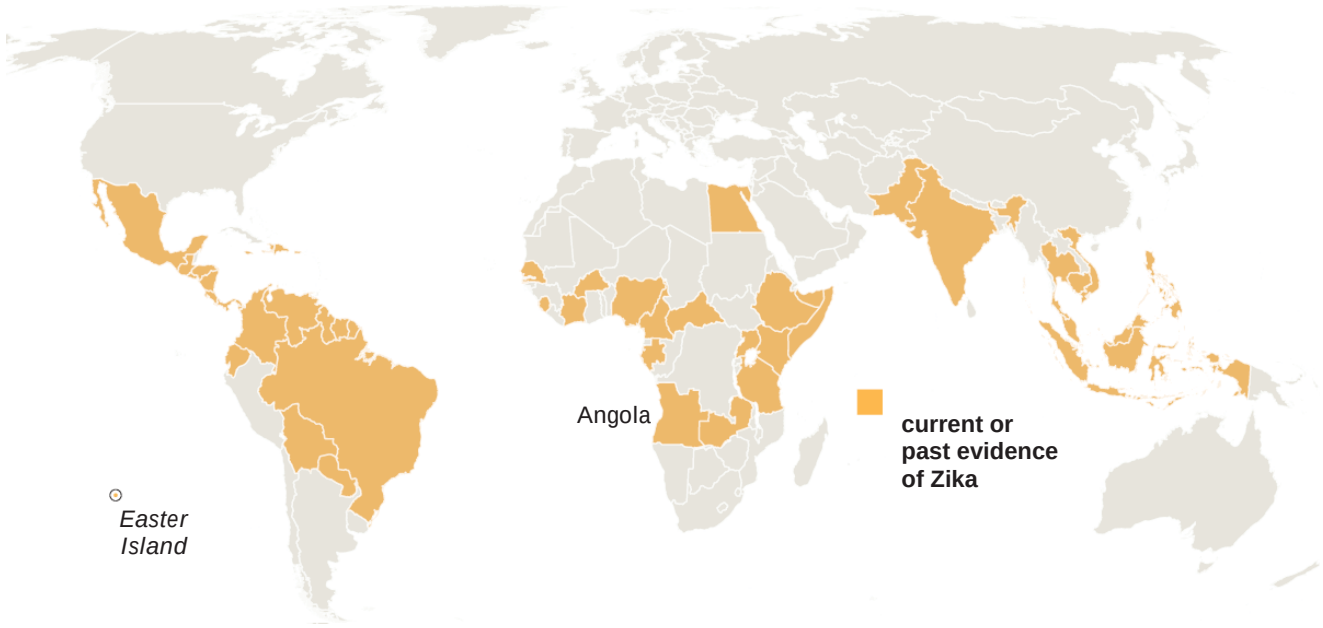
Officials at the Centers for Disease Control and Prevention have urged pregnant women against travel to more than thirty countries, mostly in the Caribbean and Latin America, where the outbreak is growing. Some pregnant women who have been to these regions should be tested for the infection, the agency has said.

The infection appears to be linked to the development of unusually small heads and brain damage in newborns – called microcephaly – as well as other neurological defects. In adults, the virus is linked to

a form of temporary paralysis.

Here are some answers and advice about the outbreak.





By The New York Times | Sources: Centers for Disease Control and Prevention; Pan American Health Organization

1. What is the Zika virus?

A tropical infection new to the Western Hemisphere.

The Zika virus is a mosquito-transmitted infection related to dengue, yellow fever and West Nile virus. Although it was discovered in the Zika forest in Uganda in 1947 and is common in Africa and Asia, it did not begin spreading widely in the Western Hemisphere until May, when an outbreak occurred in Brazil.

Until now, almost no one on this side of the world had been infected. Few people here have immune defenses against the virus, so it is spreading rapidly. Millions of people in tropical regions of the Americas may now have been infected.

Yet for most, the infection causes no symptoms and leads to no lasting harm. Scientific concern is focused on women who become infected while pregnant and those who develop a temporary form of paralysis after exposure to the virus.

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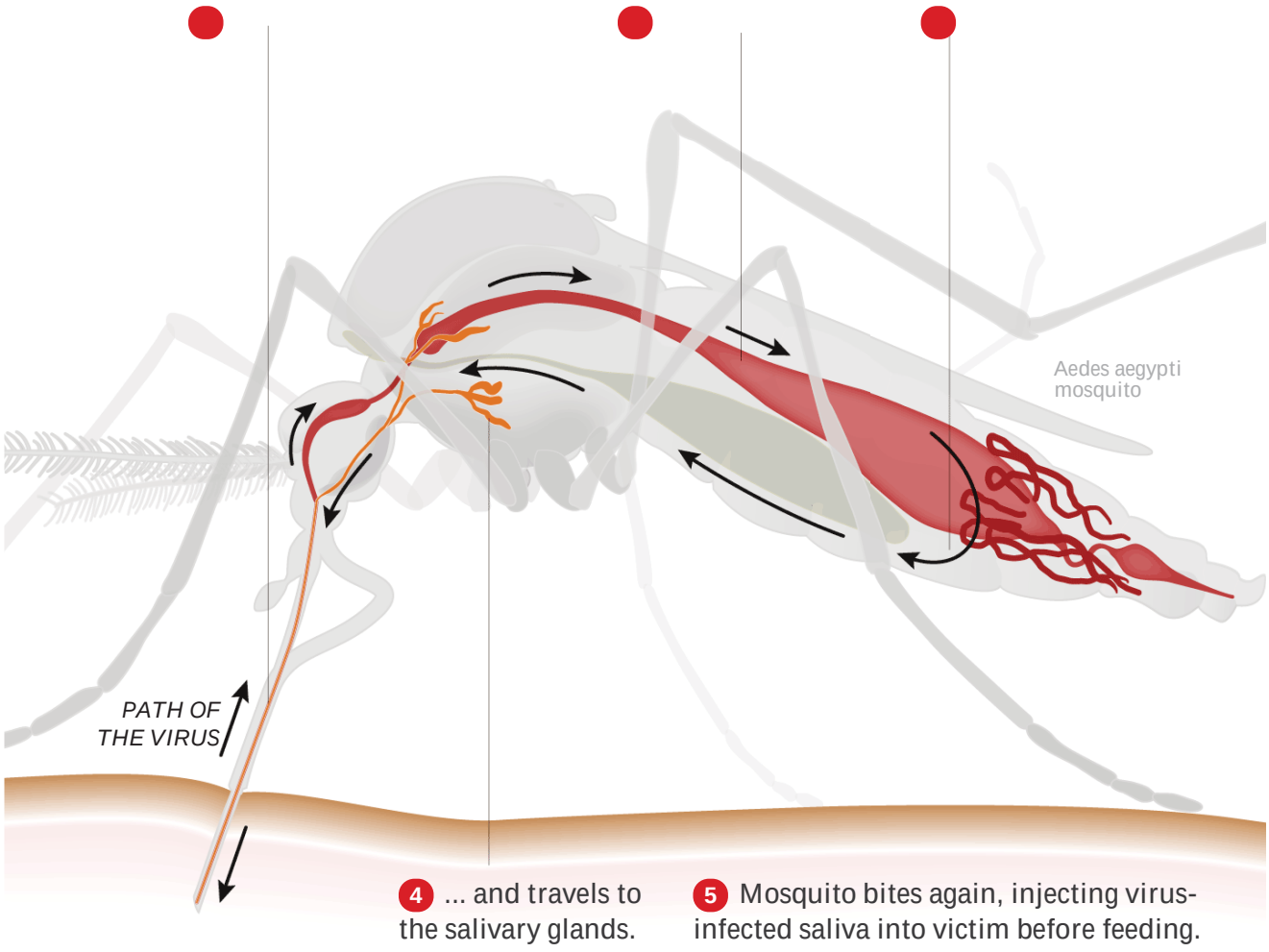
1 Mosquito feeds on virus-infected blood.

2 Infected blood travels to the midgut.

3 Virus enters the circulatory system ...

How mosquitoes spread Zika



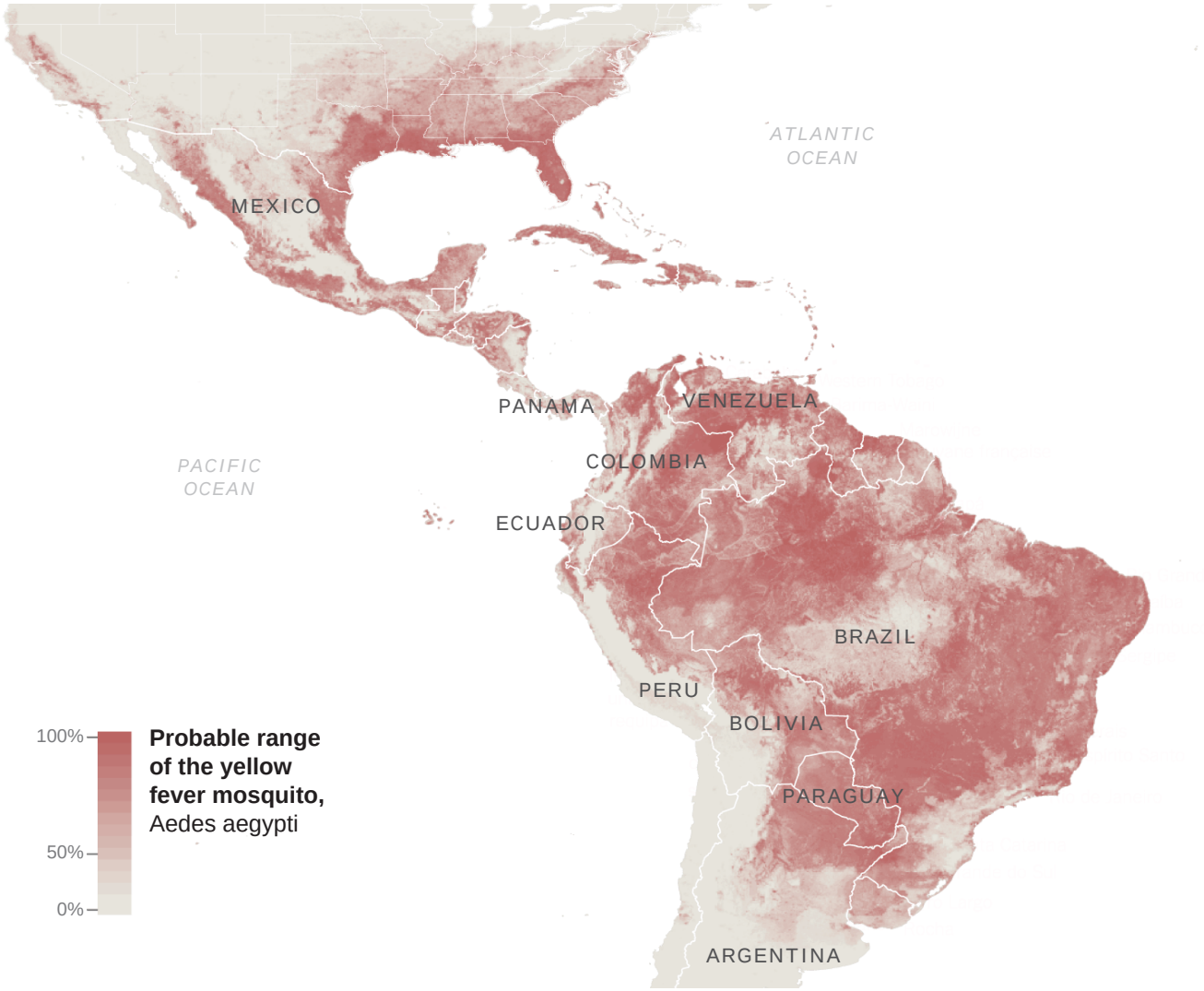
By Sarah Almukhtar and Mika Gröndahl | Sources: Dr. W. Augustine Dunn; Oxitec; The Anatomical Life of the Mosquito, R. E. Snodgrass

2. How does a mosquito transmit Zika?

The virus moves from its gut to its salivary glands.

Only female mosquitoes bite people: they need blood to lay eggs. They pick up the virus in the blood. It travels from their gut through their circulatory system to their salivary glands and is injected into its next human victim. Mosquito saliva contains proteins that keeps blood from clotting. When a mosquito bites, it first injects saliva so its prey's blood does not clog its strawlike proboscis.

UNITED STATES



By The New York Times | Source: Moritz U. G. Kraemer et al., eLife Sciences; Simon Hay, University of Oxford

3. What areas is Zika likely to reach?

Wherever certain mosquitoes go.

Zika is spread by mosquitoes of the Aedes genus, which can breed in a pool of water as small as a bottle cap and usually bite during the day. The aggressive yellow fever mosquito, Aedes aegypti, has spread most Zika cases, but that mosquito is common in the United States only in Florida, along the Gulf Coast, and in Hawaii – although it has been found as far north as Washington, D.C., in hot weather.

The Asian tiger mosquito, Aedes albopictus, is also known to transmit the virus, but it is not clear how efficiently. That mosquito ranges as far north as New York and Chicago in summer.

4. Can the Zika virus be sexually transmitted?

Yes.

Experts believe that the vast majority of Zika infections are transmitted by mosquitoes, not sex.

As of early March, however, more than a more than a dozen instances of transmission through sex have been reported in four countries.

In each case in which details were released, the virus was transmitted by a man who had visited a region where the infection circulates to a woman who had not.

Live virus has been found in semen more than two months after symptoms of infection disappeared. Scientists believe the prostate or testes can serve as a reservoir, sheltering the Zika virus from the immune system. In some cases, the men with infections had blood in their semen.

Health authorities now recommend that women who are pregnant or trying to become pregnant avoid contact with semen from men who have visited areas where the Zika virus is transmitted. Women who are pregnant should have sex only with partners using a condom, or abstain, until they give birth – whether they are engaging in vaginal, anal or oral sex.

There are still many unknowns.

Can a woman pass the virus to a man through sex? Can it be passed through anal, oral or other forms of sexual contact?
Does a man have to have blood in his semen to be infectious? Is he infectious before the blood appears?
If there is no blood, must he have had symptoms of Zika infection, like fever and rash, to be contagious? How long does a man remain infectious?

---

5. How might Zika cause brain damage in infants?

Experts aren't yet certain.

The possibility that the Zika virus causes microcephaly – unusually small heads and often damaged brains – emerged in October when doctors in northern Brazil noticed a surge in babies with the condition.

Several reports now have shown that the virus can cross the placenta and attack fetal nerve cells, including some that develop into the brain.

Studies to prove whether the virus was to blame for microcephaly are expected to take until June, but

evidence continues to mount. The virus is now considered “guilty until proven innocent,” one World Health Organization official said.

Normally, microcephaly occurs in about 1 in 5,000 to 1 in 10,000 of all births. Scientists analyzing outbreaks of the Zika virus in French Polynesia and northeast Brazil have estimated that the incidence rose to nearly 1 in 100 births nine months after those outbreaks peaked.

By The New York Times | Source: Brazil’s Ministry of Health

6. What is microcephaly?

An usually small head, often accompanied by brain damage.

Babies with microcephaly have unusually small heads. In roughly 15 percent of cases, a small head is just a small head, and there is no effect on the infant, according to Dr. Constantine Stratakis, a pediatric geneticist and a scientific director at the National Institute of Child Health and Human Development.

But in the remainder of cases, the infant's brain may not have developed properly during pregnancy or may have stopped growing in the first years of life. These children may develop a range of problems, like developmental delays, intellectual deficits or hearing loss.

The consequences can vary widely. Pinpointing an underlying cause helps clinicians to advise parents about their newborn's prognosis.

Genetic abnormalities are a common cause. Microcephaly can also be caused by infections of the fetus, including German measles (also known as rubella), toxoplasmosis (a disease caused by a parasite found in undercooked contaminated meat and cat feces) and cytomegalovirus.

Microcephaly may also result if a pregnant woman consumes alcohol, is severely malnourished or has diabetes. If the defect occurs in a child's first years, it may be a result of a brain injury during labor.

There is no treatment for an unusually small head.

"There is no way to fix the problem, just therapies to deal with the downstream consequences," said Dr. Hannah M. Tully, a neurologist at Seattle Children's Hospital who specializes in brain malformations.

By The New York Times | Sources: Centers for Disease Control and Prevention; Pan American Health Organization

7. What places should pregnant women avoid?

More than 30 countries and territories, mostly in the Americas and South Pacific.

World health authorities expect the outbreak to eventually reach every place in the Americas where the Aedes aegypti mosquito has previously spread the dengue virus. That includes everywhere from South Florida and the Gulf Coast to northern Argentina and Chile. Hawaii will be affected as well; some Pacific Islands are now having outbreaks.

Even within those countries, according to the C.D.C., pregnant women can safely visit areas at altitudes above 6,500 feet because mosquitoes are not normally found there. The latest C.D.C. updates are here.

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8. How do I know if I've been infected? Is there a

test?

It's often a silent infection and hard to diagnose.

Until recently, Zika was not considered a major threat because its symptoms are relatively mild. Only one of five people infected with the virus develop symptoms, which can include fever, rash, joint pain and red eyes. Those infected usually do not have to be hospitalized.

There is no widely available test for Zika. Because it is closely related to dengue and yellow fever, it may cross-react with antibody tests for those viruses. To detect the virus, a blood or tissue sample from the first week in the infection must be sent to an advanced laboratory so the virus can be detected through sophisticated molecular testing.

9. I'm pregnant and live in or recently visited a country with Zika virus. What do I do?

Pregnant women should get blood tests and ultrasound scans.

The C.D.C. has updated its guidelines several times.

As of early March, all pregnant women who have visited areas with active Zika transmission should have a blood test for the virus, whether or not they have symptoms.

All pregnant women who live in those areas, such as Puerto Rico or American Samoa, should be tested at least twice during their pregnancies, whether or not they have symptoms.

Testing for the virus is highly accurate in the first week after symptoms appear. After that, diagnostic tests must rely on antibodies, and false positives are possible if a woman has been infected with related viruses, like dengue and yellow fever, or has been vaccinated against them.

More complex testing can lower the false-positive rate, but not eliminate it.

In addition, all pregnant women who may have been exposed should have at least one ultrasound looking for evidence of fetal microcephaly or calcifications, indicating that the fetal skull is hardening too early.

If tests show that a woman is infected, she should have ultrasounds at regular intervals.

Unfortunately, ultrasounds usually cannot detect microcephaly before the end of the second trimester.

The current guidelines are here.

They may be updated again.

---

10. I'm of childbearing age, but not pregnant and not planning to get pregnant. Should I go to an affected country?

Only if you use birth control consistently.

Half of pregnancies are unintended. If you want to visit a country where Zika transmission has been reported, Dr. Laura E. Riley, a specialist who works with high-risk pregnancies and infectious disease at Massachusetts General Hospital, advises strict use of birth control to ensure you don't become pregnant.

Women who become unexpectedly pregnant while traveling or shortly afterward will have to deal with blood tests, regular ultrasounds and a great deal of anxiety.

"Why would you ever sign yourself up for that?" Dr. Riley said. "There's enough in life to worry about. I wouldn't add that to my list."

---

11. I'm pregnant now, but wasn't when I visited one of the affected countries. What's the risk?

Very low.

With rare exceptions, the virus does not appear to linger in women, and those who recover from the infection are immune.

“Our understanding thus far is that the risk is very, very low if you were in that place prior to conception,” Dr. Laura E. Riley of Massachusetts General Hospital said.

“I wouldn’t be worried about if you conceived after you got back to the U.S.”

12. If I live in an area where the virus is circulating, should I delay becoming pregnant?

That may be wise, some officials say.

Health officials in five countries — Brazil, Colombia, Ecuador, El Salvador and Haiti — and Puerto Rico have suggested that women delay pregnancy temporarily. Obstetricians in some countries are privately giving patients the same advice, saying the risk of fetal damage during an epidemic’s peak is too great.

Once infected residents have recovered and have become immune, these officials argue, the epidemic will fade and women can safely become pregnant again. Also, many companies are working on Zika vaccines, and delaying pregnancy will buy time for them to arrive.

The Centers for Disease Control and Prevention recently recommended that women who have had symptoms of the virus or tested positive for it should wait at least eight weeks after their symptoms first appeared before trying to get pregnant.

Officials recommended that men who had symptoms should wait six months before having unprotected sex. The virus has been known to live longer in semen. Symptoms can include rashes and sore joints.

Gleyse Kelly da Silva holding her daughter, Maria Giovanna, who was born with microcephaly in Recife, Brazil. The birth defect has been linked to the Zika virus. Felipe Dana/Associated Press

13. Does it matter when in her pregnancy a woman is infected with the Zika virus?

Anytime during pregnancy may be dangerous.

Originally, doctors in Brazil believed that infections in the first trimester were the most dangerous, because mothers who gave birth to babies with microcephaly were usually infected then.

A later study found that some mothers infected late in pregnancy also had disastrous outcomes, including the sudden deaths of infants in the womb.

Some experts who have studied the long-term consequences of rubella – another virus that attacks fetuses – say they believe that children who survive a Zika infection without microcephaly nonetheless may suffer serious consequences, including blindness and deafness at birth, learning and behavior difficulties in childhood, and perhaps even mental disabilities later in life.

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14. Should infants be tested?

Other birth defects may be linked to the virus.

Federal health officials say that newborns should be tested for infection with the Zika virus if their mothers have visited or lived in any country experiencing an outbreak and if the mothers' own tests are positive or inconclusive.

The reason, officials said in interviews, is that infection with the virus could be linked to defects in vision and hearing, among other abnormalities, even if the child does not suffer microcephaly. The other defects may require further assessments and testing.

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15. I'm a man and have returned from a place where the Zika virus is spreading. How long until I can be sure that I won't infect a sexual partner?

Err on the side of caution.

Whether or not you have had symptoms, you should do everything you can to avoid infecting a woman who may be pregnant or is trying to become pregnant, because the consequences for the baby may be disastrous.

To do that, you must avoid vaginal, anal and oral sex for the length of the pregnancy — or use condoms every time.

It is not known how long the Zika virus can survive in semen, but live virus has been found in men more than two months after infection. The testes are somewhat shielded from the immune system, so

it may take longer for the body to eliminate an infection there.

The Centers for Disease Control and Prevention recently recommended that men and women who have traveled to Zika-infected areas, but had no active signs of the disease, wait eight weeks before trying to get pregnant “in order to minimize risk.”

Men who have had symptoms of Zika infection, on the other hand, should wait six months before having unprotected sex, officials said. Symptoms can include rashes and sore joints.

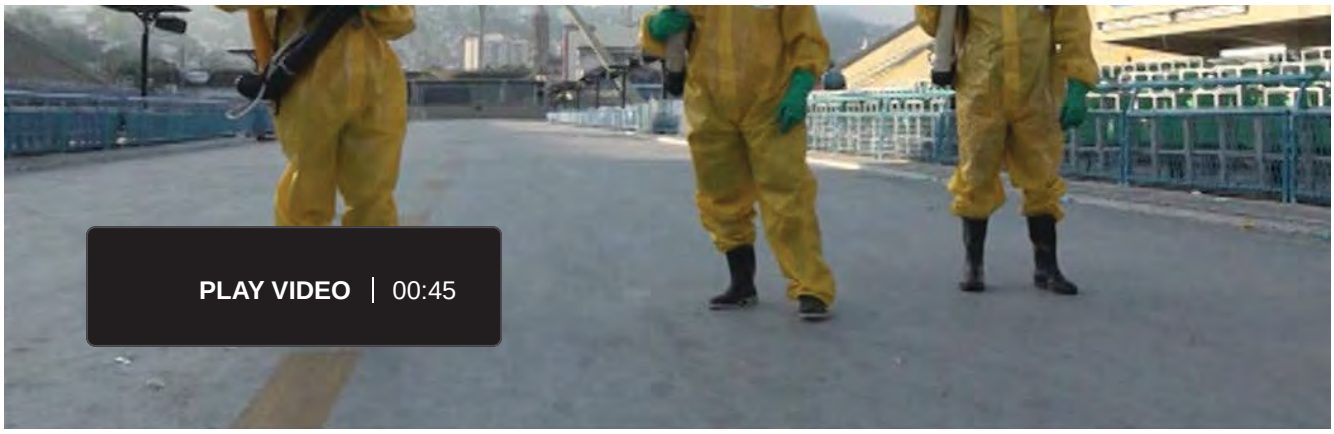
It is not known whether men must develop symptoms to be infectious, or whether men must have blood in their semen to be infectious.

It is not known whether a gay man can infect a male partner through sex, but it is theoretically possible, doctors say.

16. Is there a treatment?

No.

The C.D.C. does not recommend a particular antiviral medication for people infected with the Zika virus. The symptoms are mild – when they appear at all – and usually require only rest, nourishment and other supportive care.



Health workers sprayed insecticide in the Sambadrome in Rio de Janeiro as part of a campaign to combat mosquitoes, which transmit the Zika virus.

17. Is there a vaccine? How should people protect themselves?

Protection is difficult in mosquito-infested regions.

There is no vaccine against the Zika virus. Efforts to make one have just begun, and creating and testing a vaccine normally takes years and costs hundreds of millions of dollars.

Because it is impossible to completely prevent mosquito bites, the C.D.C. has advised pregnant women to avoid going to regions where the virus is being transmitted, and has advised women thinking of becoming pregnant to consult doctors before going.

Travelers to these countries are advised to avoid or minimize mosquito bites by staying in screened or air-conditioned rooms or sleeping under mosquito nets; wearing insect repellent at all times; and wearing long pants, long sleeves, shoes and hats.

How Zika Spread Around the World


Before 2007
Nigeria
Pakistan
Uganda
Indonesia
Costa Rica
2007-2014
Thailand
Yap (Micronesia)
Gabon
French Polynesia
Easter Island
2015-2016
Mexico
Cape Verde
Maldives
Brazil
Fiji

By Jasmine Lee | Source: World Health Organization

18. If the Zika virus has been in Africa and Asia for decades, why wasn't a link to microcephaly detected earlier?

It may be that the virus had never struck such a large population without immunity.

Microcephaly is rare, and it has many other causes, including infection of the fetus with rubella (German measles), cytomegalovirus or toxoplasmosis; poisoning of the fetus by alcohol, mercury or radiation; or severe maternal malnutrition and diabetes. It is also caused by several gene mutations, including Down syndrome.

Until recently, health officials paid little attention to the Zika virus. It circulated in the same regions as dengue and chikungunya, and compared with those two painful infections – nicknamed "break-bone fever" and "bending-up fever" – Zika was usually mild.

The virus is thought to have reached Asia from Africa at least 50 years ago. While it may have caused spikes in microcephaly as it first spread, there was no testing to pin down which of many possible causes was to blame.

In 2007, a Southeast Asian strain of the Zika virus began leapfrogging the South Pacific, sparking rapid outbreaks on islands where no one had immunity to it. Because island populations are small, rare side effects did not occur often enough to be noticed. But in 2013, during an outbreak in French Polynesia, which has 270,000 residents, doctors confirmed 42 cases of Guillain-Barrê syndrome, which can cause paralysis. That was about eight times the normal number and the first hint that the Zika virus can attack the nervous system, which includes the brain.

Zika was first confirmed in Brazil – a country of 200 million – last May, and it spread rapidly. The first alarms about microcephaly were raised in October, when doctors in the northeastern state of Pernambuco reported a surge in babies born with it. Pernambuco has nine million people and 129,000 annual births. In a typical year, nine are microcephalic infants.

By November 2015, when Brazil declared a health emergency, Pernambuco had had 646 such births.

---

19. Has a Zika outbreak outside Brazil ever been linked to microcephaly?

Officials in French Polynesia have suspicions about an outbreak two years ago.

French Polynesia is the only area outside Brazil to be affected by a Zika outbreak in which public health officials have identified an increase in the number of fetuses and babies with unusually small heads. There is “very high suspicion” of a link between the Zika virus and microcephaly in French Polynesia, said Dr. Didier Musso, an infectious disease specialist at the archipelago’s Institut Louis Malardé – though he said additional research was needed.

In November, French Polynesian officials took another look at an outbreak of the Zika virus that lasted from October 2013 to April 2014. They reported finding an unusual increase – from around one case annually to 17 cases in 2014-15 – of unborn babies developing “central nervous system malformations,” a classification that includes microcephaly.

There were no investigations at the time to determine whether the mothers were infected with the Zika virus during pregnancy. Four of the mothers were tested later, and the results indicated they may have been infected. Additional research is underway, Dr. Musso said.

HISTORICAL PERSPECTIVE

Polio and Nobel Prizes: Looking Back 50 Years

Erling Norrby, MD, PhD,[1] and Stanley B. Prusiner, MD[2]

In 1954, John Enders, Thomas Weller, and Frederick Robbins were awarded the Nobel Prize in Physiology or Medicine "for their discovery of the ability of poliomyelitis viruses to grow in cultures of various types of tissue."[53,70] This discovery provided for the first time opportunities to produce both inactivated and live polio vaccines. By searching previously sealed Nobel Committee archives, we were able to review the deliberations that led to the award. It appears that Sven Gard, who was Professor of Virus Research at the Karolinska Institute and an adjunct member of the Nobel Committee at the time, played a major role in the events leading to the awarding of the Prize. It appears that Gard persuaded the College of Teachers at the Institute to decide not to follow the recommendation by their Nobel Committee to give the Prize to Vincent du Vigneaud. Another peculiar feature of the 1954 Prize is that Weller and Robbins were included based on only two nominations submitted for the first time that year. In his speech at the Nobel Prize ceremony, Gard mentioned the importance of the discovery for the future production of vaccines, but emphasized the implications of this work for growing many different, medically important viruses. We can only speculate on why later nominations highlighting the contributions of scientists such as Jonas Salk, Hilary Koprowski, and Albert Sabin in the development of poliovirus vaccines have not been recognized by a Nobel Prize.

Ann Neurol 2007;61:385–395

Polioviruses are small enteric RNA viruses that on rare occasions spread to the central nervous system (CNS) and cause disease. Replication of the virus in anterior horn cells of the spinal cord can result in paralysis. In the 1950s, both inactivated and live polio vaccines were developed to prevent paralytic disease. Three vaccines for types 1, 2, and 3 polioviruses had to be developed to create effective immunity.

Although polio has been largely eradicated using primarily live vaccines, it persists in some parts of the world. The goal of global polio eradication, like that achieved for smallpox in 1978, remains elusive. Target dates have been moved back repeatedly. Still, most public health officials retain their belief that it is possible to eradicate polio from our planet using a combination of inactivated and live poliovirus vaccines. In fact, the type 2 strain of the virus has been eradicated. The World Health Organization, assisted by a number of nongovernmental organizations, is now aiming at eliminating the last reservoirs of poliovirus types 1 and 3. Presently, wild viruses of these types remain endemic in four countries. From these areas, they can spread to reinfect people living in countries that were previously declared to be polio-free.

The global campaign of immunization against poliomyelitis was made possible by two vaccines: (1) an inactivated virus preparation developed by Jonas Salk, Julius Youngner, and their colleagues[1–3]; and (2) live, attenuated virus preparations developed initially by Hilary Koprowski, Herald Cox, and their coworkers,[4–6] and later by Albert Sabin and his colleagues.[7] These vaccines dramatically changed the lives of millions of children in developed countries where polio vaccination was initially introduced. Examples of the extraordinary effectiveness of the vaccines are illustrated by the decline in poliomyelitis cases in the United States and Sweden (Fig 1).

By any measure, the eradication of polio must be considered a milestone in the annals of medicine. That said, it is reasonable to ask why the successful development of both inactivated and live polio vaccines was not celebrated by a Nobel Prize. First, it can be argued that Alfred Nobel would have thought such work, which improved the lives of so many, would be most appropriate for the award that bears his name. Second, one may ask why the Nobel Prize was awarded to Enders, Weller, and Robbins in the fall of 1954 just when the first clinical trial of the Salk vaccine was being completed. Why didn't the Nobel Committee wait to view the outcome of a mass immunization program encompassing nearly 650,000 children that was announced in the spring of 1955[8]?

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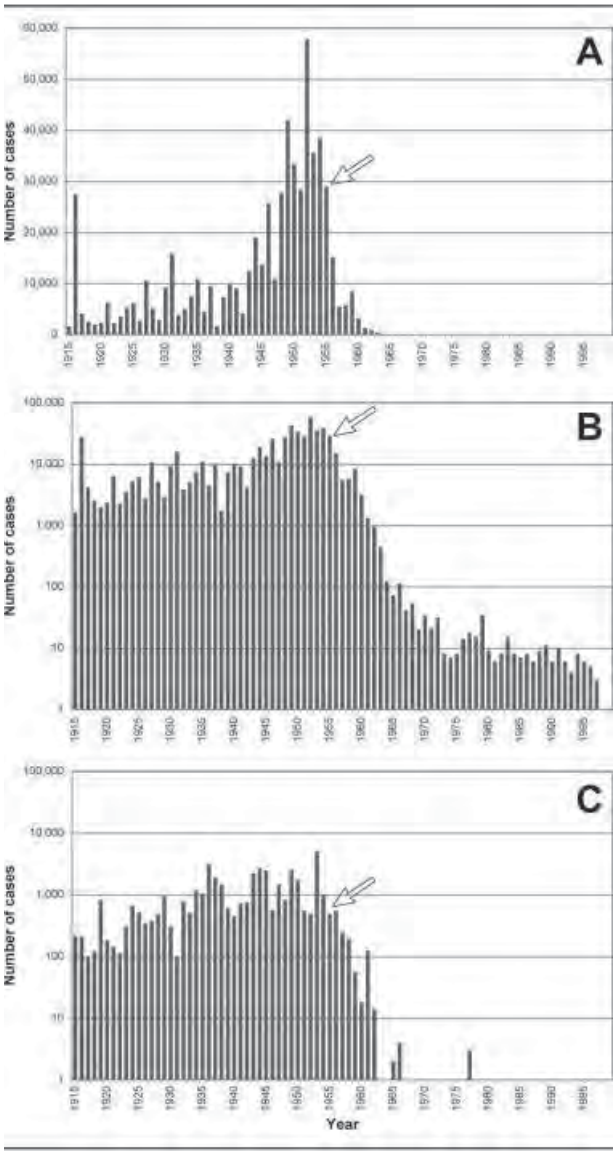

Fig 1. Epidemiology of annual number of polio infections in the United States (A, B) and Sweden (C) between years 1915 and 1999. Polio disappeared from the United States and Sweden after the introduction of inactivated vaccines (arrows). *Data are shown in arithmetic (A) and logarithmic (B, C) scale. Note that Sweden eradicated polio by use of only inactivated vaccine, whereas the United States, like most other countries, switched to the live vaccine in 1963. The incidence of polio cases in the United States until 1999, when the inactivated vaccine began to be used again, is due to disease associated with the live vaccine and to imported cases. (Data were provided by Margareta Bottiger, Michael Katz, and Post-Polio Health International.)*

Because the Nobel Archives are open to scholarly investigations 50 years after the awarding of a Prize, we decided to investigate the circumstances surrounding the award of the 1954 Nobel Prize in the hope of answering the questions posed above. After reviewing some of the salient features of polio infections, we describe our findings, which seemed to shed light on this epic saga in the history of medicine.

Polio Epidemics in the Twentieth Century

The poliovirus appears to have infrequently caused CNS disease in humans before the nineteenth century, although atrophied limbs in young people were recorded in ancient Egypt.[9] Presumably, nonsymptomatic enteric infections of the poliovirus in young children were so common that these conferred widespread immunity. These young individuals suffered no CNS dysfunction because they were presumably protected by maternal antibodies. As hygiene improved and public sanitation measures were implemented, the age at which children developed their own antibodies increased. Because maternal antibodies to poliovirus in children disappear between the ages of 1 and 2 years, an increasing population of susceptible children emerged. These young people had not acquired immunity to polioviruses through inapparent enteric infections as infants when they were still protected by their mother's anti-polio antibodies.[10] Gradually a nonimmune population of older children and young adults emerged, and when exposed to polioviruses, many of them experienced development of paralytic polio.

The first well-described outbreaks of polio were registered among children in Scandinavia. Heine, a German orthopaedist, gave the first complete clinical description of the disease in 1840, and Medin, a Swedish pediatrician, reported the first epidemics.[9] The disease originally known as Heine–Medin disease and later, infantile paralysis or poliomyelitis, is today generally referred to as polio. The number of outbreaks grew with time, and they began to spread to other geographic areas.

During the first half of the twentieth century, the incidence of polio increased and epidemics in the summer months became commonplace in many industrialized countries (see Fig 1). Year after year, the epidemics killed children and left many more crippled. The disease created anxiety, horror, and political unrest. In the United States, efforts to deal with the recurrent polio epidemics were spearheaded by Franklin Roosevelt, who himself was crippled by polio in 1921, and by Roosevelt's associate Basil O'Connor. When Roosevelt was elected President of the United States in 1932, he was in a position to acquire and dedicate enormous resources to a national campaign against polio. Roosevelt and O'Connor created the National Foundation for Infantile Paralysis and raised immense funds through annual campaigns called the "March of Dimes" that were used to care for polio victims and support vaccine research. Today, the National Foundation supports research on birth defects.

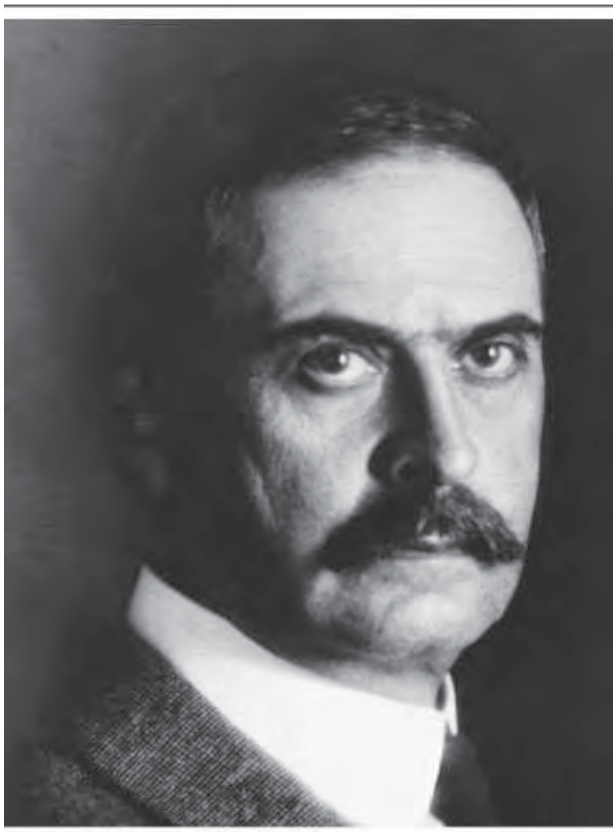

Fig 2. Karl Landsteiner. (Courtesy of the National Library of Medicine.)

Initial Attempts to Produce a Vaccine

In 1908, Karl Landsteiner (Fig 2) demonstrated the viral origin of poliomyelitis when he transmitted the disease to monkeys using a filtered preparation of macerated CNS tissue obtained from individuals who had died of polio.[11] Landsteiner later discovered human blood groups, for which he was awarded the Nobel Prize in 1930. The filterable agent causing poliomyelitis was difficult to study because there were no simple procedures for growing the virus in the laboratory. Experiments had to be performed with tissues harvested from infected monkeys.

By using inactivated virus from the brains of polio-infected animals, it was possible to demonstrate that effective immunity could be induced in monkeys.[9] It was also possible to demonstrate, by rather cumbersome but important experiments with monkeys, that three different types of polioviruses are distinctly antigenic. This meant that not one, but three different vaccines had to be developed for polioviruses types 1, 2, and 3. In addition, the idea of preparing enough vaccine for massive immunizations was unattractive for two reasons: First, the number of monkeys needed would be enormously expensive; and second, nonpoliovirus antigens might evoke a harmful encephalitic response.[9]

In the 1930s and 1940s, several attempts to develop a polio vaccine resulted in abysmal failures.[9] The failures sensitized the medical community to the disastrous results that an ineffective vaccine could bring.

By the mid 1930s, transmission of the Lansing type 2 strain of poliovirus from humans to mice was reported.[12] A few years later, transmission of the Lansing strain from monkeys to cotton rats was described.[13,14] But these results were not pursued until the late 1940s when Hilary Koprowski and coworkers, using the poliovirus attenuated in the brains of cotton rats, produced an experimental live virus vaccine and, thus, initiated the modern era of polio vaccinology. In 1950, Koprowski orally vaccinated himself, his technician, and later, a group of children with an extract prepared from the brains of cotton rats.[4] A critical breakthrough in vaccine development occurred when it was described that polioviruses could be grown in nonnervous tissue.[15–18] This discovery resulted in the award of the 1954 Nobel Prize in Physiology or Medicine to John Enders, Thomas Weller, and Frederick Robbins. In 1956, Koprowski switched from vaccines prepared from attenuated poliovirus strains propagated in rodent brain to those grown in cultured monkey kidney cells.[19,20]

Early Deliberations

Because the Nobel Archives up to and including 1956 were open when we performed the research described here, we were able to look back 50 years at the deliberations that led to the 1954 Prize and at some subsequent discussions. Nominees for a Nobel Prize are evaluated at three levels: (1) short notes for relatively weak candidates, (2) preliminary reviews of a few pages for stronger candidates, and (3) exhaustive analyses for the strongest candidates. Generally, a preliminary review precedes a detailed analysis. In addition to these documents, we found a record of the concluding meeting of the enlarged Nobel Committee (the nominal five-member committee with adjunct members chosen annually). This record is a decision and not a discussion document; it presents a list of the major candidates, provides comments on their Prize-worthiness, and gives the proposal for the Prize recipients. Nowhere in the archives could we find the opinions of the individual committee members with respect to particular nominees.

John Enders was first nominated for a Nobel Prize by Dr L. P. Gebhardt in 1952, for his discovery that polioviruses could be propagated in cultures of nonnervous tissues. Only Enders was named; he was considered such a strong candidate that an exhaustive review was made. In a document of more than 20 typewritten pages, Dr Sven Gard, Professor of Virology at the Karolinska Institute, described the background for this discovery and the dramatic changes in poliovi-

rus research that it had brought in the past 3 years. The practical consequences of Ender's discovery were also highlighted in this review, much of which is summarized below.

Before the discovery by the Enders' group, many attempts had been made to grow polioviruses in tissue cultures. Forty years earlier, Simon Flexner had reported his attempts to grow polioviruses in tissue culture. Based on observations in infected monkeys, Flexner and his colleagues[21,22] concluded that poliovirus replication occurred exclusively in neural tissue or cells. Two decades later, Albert Sabin and Peter Olitsky[23] reinvestigated the growth of poliovirus in tissue culture using the neurotropic monkey-adapted MV strain provided by Flexner. They interpreted their data as confirming Flexner's earlier findings.

Gard commented on the misconception that polioviruses could not be grown in tissue cultures when he wrote:

> Sabin's and Olitsky's work was viewed for some 15 years to come as the last word on in vitro replication of poliomyelitis virus. It was concluded on the basis of their data that virus, not only in vivo, but also in vitro displays a pronounced species specificity and an extreme neurotropism.

The widely held perception that poliovirus replication was confined to nervous system tissue was overthrown by the pioneering work of John Enders, Thomas Weller, and Frederick Robbins (Fig 3).[15–18] In 1954, the College of Teachers of the Karolinska Institute decided to award the Nobel Prize to Enders, Weller, and Robbins "for their discovery of the ability of poliomyelitis viruses to grow in cultures of various types of tissue."[53,70]

Fig 3. The discovery of John Enders (right), Thomas Weller (left), and Frederick Robbins (center), shown at the Nobel Prize ceremony, revolutionized poliovirus research. (Reprinted by permission of the Harvard Medical Library in the Francis A. Countway Library.)

Enders, Viruses, and Cultured Cells

Enders had a long-standing interest in growing viruses in tissue cultures. In 1940, he engaged a medical student, Thomas Weller, for a tutorial research project. Together with another researcher, Dr Alto Feller, they managed to obtain substantial replication of vaccinia virus in chicken embryo tissue maintained in a roller tube culture system.[24] Weller left to serve in the armed forces in World War II and did not return to Enders's laboratory until 1946.

About a year after Weller's return, Dr Fredrick Robbins, a medical school classmate, joined him in Enders's laboratory. Enders asked Robbins to review the available tissue culture techniques for their use in the propagation of viruses and assigned him the task of growing viruses from children with infant diarrhea.[25] Meanwhile, Enders tried to cultivate the measles virus in tissue culture, and Weller, the chickenpox virus. In addition to measles and chickenpox viruses, Enders and his colleagues examined the ability of other viruses to grow in tissue cultures. In 1949, Weller and Enders published a manuscript on the successful cultivation of mumps and influenza viruses in suspended cell cultures with the production of hemagglutinin.[26] By the early 1950s, they successfully cultivated a half-dozen human viruses in a series of pioneering studies.[27,28]

Although the main focus of the laboratory was not to grow polioviruses, a series of experiments, performed between March and June 1948, demonstrated the robust growth of polioviruses in tissue culture. In his attempts to isolate varicella virus, Weller used tissues obtained from aborted human embryos. Some unused cultures that had been established for another set of experiments were inoculated with the cotton rat–adapted Lansing strain of poliovirus. Although no growth of varicella virus was recorded in some cultures, poliovirus grew spectacularly. Using bioassays in rats, Weller documented extremely high titers of poliovirus in these cultures.

The reasons for the inoculation of poliovirus into tissue cultures, and who took the initiative, are unclear. In a retrospective, Weller[29] states that he initiated the poliovirus experiments, but according to Robbins,[25,30] the idea for these studies came from Enders.

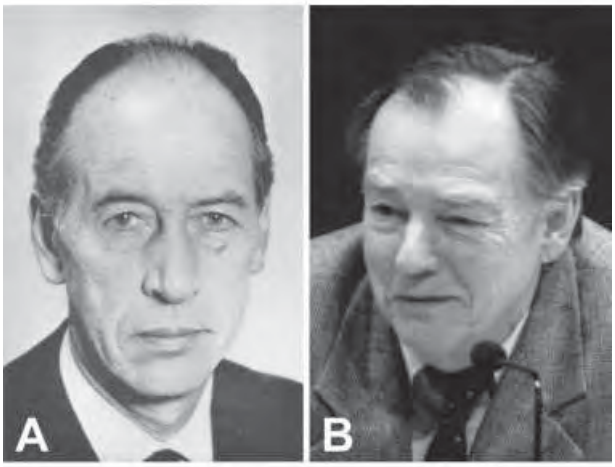

Fig 4. Swedish polio pioneers (A) Sven Gard and (B) Erik Lycke. (Photos were kindly provided by Samuel Katz and Erik Lycke.)

Sven Gard and His Role

Discussions about awarding a Nobel Prize for the growth of polioviruses in cultured cells evolved over 3 years, from 1952 to 1954. As a prominent researcher in the field of polio and polio-related viruses, Sven Gard (Fig 4) was unusually well qualified to lead such discussions. Whether he was so opinionated that he should have recused himself from such important deliberations is unclear; certainly, his encyclopedic knowledge of polioviruses must have been considered by many to be a great asset.

Sven Gard was the teacher and predecessor of the chair of virology at the Karolinska Institute for one of us (E.N.); the other (S.B.P.) never met him. Gard's early work in which he determined the dose of a polio-like virus in mice by measuring the length of the incubation time[31] was well known to one of us (S.B.P.) because the same approach was used 40 years later in the discovery of the prion.[32–34]

Gard was a physician who was fascinated by microbial diseases. He appears to have developed an interest in polio through contacts with Carl Kling. That polio might be a waterborne disease, which is spread by sewage-contaminated drinking water, was proposed by Kling.[9]

In 1939, Gard worked at the Rockefeller Institute as a visiting scientist in Max Theiler's laboratory. The Nobel Committee was seasoned with respect to the importance of viral vaccines. Theiler received the 1951 Nobel Prize "for his discoveries concerning yellow fever and how to combat it." Theiler's achievement was to produce an effective and safe live vaccine against yellow fever by passaging the virus in mice. Gard did not become involved in Theiler's yellow fever studies, but collaborated instead on investigations of a murine, polio-like virus known as the Theiler virus.[35,36] Gard also participated in epidemiological studies of human polioviruses in the United States.

In 1940, Gard returned to Sweden to pursue his interest in polio and polio-like viruses under the guidance of professors The Svedberg and Arne Tiselius at Uppsala University. Svedberg received the Nobel Prize in Chemistry in 1926 and Tiselius was awarded the Prize in Chemistry in 1948. By 1943, Gard completed his PhD thesis on the purification of the murine polio-like virus from the brains of tens of thousands of mice by use of physicochemical methods available at the time.[37]

In the mid-1950s, Gard and his collaborator Erik Lycke (see Fig 4) pioneered an understanding of the kinetics of formalin inactivation of poliovirus. Salk had argued that the inactivation was linear,[3,38] that is, that the log of remaining virus activity was a linear function of the time of treatment with formaldehyde, but Gard and Lycke showed that inactivation did not proceed according to a simple first-order reaction, indicating that the interactions between the virus and formaldehyde were more complicated.[39–42] This finding indicated that it was not possible to estimate the length of the formaldehyde treatment merely by extrapolation from a linear inactivation curve. These considerations appear to have been quite pertinent in explaining the tragic "Cutter incident" in the United States in 1955, in which more than 200 cases of polio occurred in children receiving one of the early batches of the inactivated vaccine, as well as in their families and community contacts.[43–47] At a symposium in London in 1957, Gard presented an empirical formula fitting the available experimental data.[48] Gard and Lycke published a thorough analysis of calculations using Gard's formula and applied these to the results of both Swedish and German studies.[41] The work of Gard, Lycke, and their colleagues led to the introduction of modified conditions for the production of an inactivated polio vaccine in Sweden.[49,50] The positive experiences of the modified, inactivated vaccine led to the decision in Sweden not to use the live vaccine; the eradication of polio in Sweden was achieved solely with inactivated preparations.[51,52]

Nomination of Enders in 1952

As mentioned above, one Nobel Prize nomination was submitted in 1952 for Enders alone. In his analysis of Enders's work for the Nobel Committee in 1952, Gard pointed out that the dogma of strict neurotropism of the poliovirus was beginning to be questioned by the late 1940s. After high levels of poliovirus were found in human feces, investigators began to question how so many virions could be produced by nerve endings in the intestinal mucosa.[53] A more likely explanation was that polioviruses replicated in nonneural tissues, an interpretation that Enders appeared to embrace. More-

over, Enders encouraged Robbins to pursue additional experiments on the growth of poliovirus in tissue culture once the initial results were obtained.[15–18] The last paragraph of their *Science* article[15] references the dogma of poliovirus neurotropism in light of their new findings. It reads:

> It would seem, from the experiments described above, that the multiplication of the Lansing strain of poliomyelitis virus in the tissues derived from arm or leg, since these do not contain intact neurons, has occurred either in peripheral nerve processes or in cells not of nervous origin.

Gard emphasized in his evaluation that Enders and collaborators did not invent any new tissue culture technique. In spite of this, they were successful in propagating poliovirus where other investigators had failed. At least two explanations might account for this difference in the results. First, choosing the Lansing poliovirus strain may have been critical. Sabin and Olitsky had used the MV strain of poliovirus in their attempts to propagate the virus in tissue cultures.[23] The MV strain is a highly neurotropic virus that Flexner established during 20 consecutive passages in monkey brain and is likely to have a reduced capacity for growth in nonnervous cells.[54,55] The Lansing strain used by Enders, Weller, and Robbins was also neurotropic, but passage in this case had occurred in cotton rats.[13,14] Whether repeated passage through monkeys versus rats is the correct explanation for this difference in growth properties is unclear. Second, the Enders group allowed a longer time for the virus to grow in cultures. Sabin and Olitsky split their cultures every third day according to the conventions of the time, whereas the Enders group kept the cultures for weeks with repeated changes of the culture media to renew the nutrients.

In 1952, Gard came to the conclusion that the growth of poliovirus in nonnervous tissue was worthy of a Nobel Prize, but he "refrains at present from formulating an opinion on whether a Nobel Prize in this field should be given to Enders alone." The Nobel Committee agreed that Enders's contribution was worthy of a Nobel Prize, but the Prize that year was awarded to Selman Waksman "for his discovery of streptomycin, the first antibiotic effective against tuberculosis." It is notable that antibiotics, such as penicillin and streptomycin, greatly facilitated the isolation of viruses in tissue cultures by suppressing bacterial contamination.

Nominations of Enders and Collaborators in 1953 and 1954

In 1953, Enders was again nominated for the Nobel Prize; this time by Drs J. H. Means and John H. Dingle. No further analysis of Enders was made that year, and the Nobel Committee did not mention him in their summary report. Curiously, Gard was not an adjunct member of the Committee in 1953, but he is said to have visited Enders's laboratory in Boston in October 1953 (T. Weller, personal communication). Whether the impressions that he gained during this visit influenced his interpretation of the relative contributions of Enders, Weller, and Robbins remains unknown. This contact between Gard and the Enders laboratory at Children's Hospital in Boston is potentially the source of the widely circulated, but unsubstantiated, story that Enders contacted the Nobel Committee stating that he would refuse to accept the Nobel Prize unless his two young collaborators were included.[56] This story has been widely circulated and one of us (S.B.P.) remembers learning about Enders's attempt to influence the Nobel Committee in a medical school lecture at the University of Pennsylvania. We have been unable to find any correspondence between Enders and the Nobel Committee, much less a letter stating the conditions under which he would be willing to accept the Nobel Prize. In this context, it should be added that Enders accepted both the Passano and Lasker awards alone before the award of the Nobel Prize.

In 1954, nine nominations of Enders, several of them relatively exhaustive, were submitted for a Nobel Prize. Some of these came from prominent scientists in the field of virology: J. R. Paul, C. H. Andrewes, and F. M. Burnet. Later, Burnet shared the Nobel Prize with Peter Medawar in 1960 for their "discovery of immunological tolerance". Only two of the nine nominations of Enders included Weller and Robbins. These two nominations came from less authoritative researchers in the field: P. L. Lence from Ljubljana, Yugoslavia, and Dr G. Bruynoghe from Louvain, Belgium. Bruynoghe's proposal also listed other nominees, including G. K. Hirst, D. Horstmann, and D. Bodian. Lence, in his nomination, refers to "the production of a non-toxic polio vaccine." In his letter, he first refers to the successful growth of polioviruses in nonnervous tissue by "Enders et al." Lence states, "By this discovery, the main hurdle to production of a vaccine was passed." He then cites as follow-up information on the cultivation by Cox[57,58] of poliovirus in chicken embryo cells and the first attempts to produce a vaccine by Koprowski and colleagues[4] and the work of "Youngster [Youngner] et al." Lence concludes by recommending that Enders, Weller, and Robbins should receive the Nobel Prize. The names of Bruynoghe and Lence are not known to Erik Lycke (personal communication), a close collaborator of Gard in the early 1950s, and hence probably not to Gard himself at the time. They may have been microbiologists, but they were unlikely to have been virologists. Because their nominations were accepted, they must have been affiliated with an academic institution that was invited

to make proposals by the Nobel Committee of Physiology or Medicine.[59] What would have happened in 1954 if their nominations had not been submitted remains uncertain.

The Nobel archives demonstrate that, in 1954, Sven Gard wrote another review of the developments in the field, but this one was only five typewritten pages in length. In the beginning of this review, he wrote: "It seemed likely to me that both Weller and Robbins had taken active part in the planning and execution of the experiments." He emphasized the rapid development of the field, with possibilities for providing laboratory support to clinical diagnoses and epidemiological surveillance, as well as for production of large quantities of virus for vaccine purposes. He clearly notes:

> In preliminary experiments with many thousand individuals, Salk has demonstrated that formalin-inactivated virus can produce a considerable serological immunity. At present, field trials are performed on a large scale to assess the protective efficacy of the Salk vaccine. It was tested in a total of 650,000 children in the U.S.A., 25,000 in Canada and 20,000 in Finland, out of which about 1/3 have received an inactivated control preparation. The results of these trials are not expected to become available until the beginning of next year.

Gard concludes his evaluation with an extraordinarily enthusiastic assessment:

> It is not an exaggeration to state that the discovery by Enders' group is the most important in the whole history of virology.…The discovery has had a revolutionary effect on the discipline of virology.

In the last paragraph of his analysis, Gard reiterates the Prize-worthiness of the discovery and concludes:

> Since the time when I submitted my previous evaluation I have come to the firm conviction that no one of the three members of the group can be said to have contributed more than any of the others to provide a solution to the problem. If it would be decided to award the discovery with a Nobel Prize, which I consider to be highly motivated, I would propose that the Prize should be given jointly to Enders, Weller and Robbins.

Interestingly, the names are given in the above order, and included as so in the Nobel Foundation Directory, and not in alphabetical order as listed below.

The Decision

The conclusion of the enlarged Nobel Committee in the document sent to the College of Teachers on September 28, 1954, reads:

> The Nobel Committee decided to propose that the 1954 Nobel Prize in Physiology or Medicine should be given to Vincent du Vigneaud for his discovery of the structure of vasopressin and oxytocin, confirmed by the synthesis of these hormones. Professors Gard and Hellström were of the opinion that the Prize instead should be given to John Franklin Enders, Frederick C. Robbins and Thomas H. Weller jointly for their discovery of the capacity of poliomyelitis virus to grow in different tissue cultures from primates.

Expression of dissenting views in the final proposal from the Committee is a relatively uncommon phenomenon. Generally, the Committee attempts to make a unanimous recommendation. During the ensuing debate by the College of Teachers, apparently Gard and Hellström managed to swing the opinion of the majority in favor of Enders, Weller, and Robbins, so that they became recipients of the 1954 Prize (see Fig 3). This was neither an isolated nor precedent-setting situation; other historical examples exist in which the Nobel Assembly of the Karolinska Institute did not follow the recommendation of its Nobel Committee.

Secrecy surrounding the selection of Nobel Prize awardees is generally well maintained,[60] but in 1954, the recommendation of the Nobel Committee of the Karolinska Institute was leaked to a US newspaper.[61] *The New York Times,* but not the main Stockholm newspaper of the day, reported "Up to the time of voting, the College (of the Stockholm Royal Karolinska Institute) was more or less decided between the selected trio (Enders, Weller, and Robbins) and another American, Professor Vincent du Vigneaud, age 53, of Cornell and New York."[61] Du Vigneaud must have been very disappointed when he learned of his failed candidacy. However, he was compensated the following year when he received the Nobel Prize in Chemistry. In the fall of 1955, both the Chemistry Nobel Committee of the Royal Swedish Academy of Sciences and the Nobel Committee at the Karolinska Institute recommended Hugo Theorell for a Nobel Prize. Theorell, who was a professor at the Karolinska Institute, was awarded the Prize in Physiology or Medicine and du Vigneaud the Prize in Chemistry. Parenthetically, Theorell was a victim of polio and used a cane to walk.

Polio Research and Vaccine Production

Before Enders and his colleagues left the field of poliovirus propagation and vaccine production, they demonstrated that the neurovirulence of poliovirus could be attenuated by repeated passage in tissue culture.[62] Enders later used the same approach with the measles virus to generate the attenuated strain that remains in use today as a vaccine.[63]

The ability to grow poliovirus to high titers in tissue cultures set the stage for development of effective, safe vaccines. Following the lead of Enders and coworkers, Salk and his collaborators showed that monkey kidneys provided a useful substrate for large-scale production of poliovirus and for preparation of a formalin-inactivated vaccine.[1,2,64] In this work, Julius Youngner, who was a

member of the Salk group, introduced an important technical improvement when he, like Dulbecco and Vogt,[65] resurrected the method of trypsinizing tissue fragments initially used at the Rockefeller Institute.[66] Monolayer cell cultures were established using the trypsin technique and became the standard for most future work.[67,68] By reading cytopathic effects, a term introduced by Enders and his colleagues, numerous medically important viruses were identified during the 1950s and early 1960s.

The growth of poliovirus in tissue culture facilitated both the isolation of attenuated strains that were suitable for live vaccines and the large-scale production of these attenuated viruses that enabled mass vaccination programs. Studies with tissue culture–grown, attenuated poliovirus begun around 1953, but the vaccines were not recommended for general use until 1961. Parallel studies of competing live vaccines were undertaken by Koprowski,[19,20] Cox and colleagues,[5] and Sabin.[7,69] Eventually, the three vaccine strains that Sabin developed became the live vaccine of choice because they were thought to give the lowest frequency of vaccine-associated cases of polio.

Under the aegis of the National Foundation for Infantile Paralysis in the United States, the inactivated vaccine that Salk developed came into general use after a successful initial trial in 1954, which led to a dramatic reduction in the occurrence of polio cases (see Fig 1).[8] Despite this success, the Salk vaccine was replaced by the Sabin live vaccine in 1961; the latter vaccine was easier to administer and presumably had an improved capacity to induce herd immunity because of the spread of attenuated virus from vaccinated individuals. Eventually, after decades of use, the Sabin live vaccine was replaced in 1999 by the Salk inactivated vaccine that had been used originally. Because reversion of the attenuated polioviruses to wild-type occurs in vaccinees at a low rate, use of the Sabin vaccine is no longer recommended in countries where polio has been almost eradicated.

Why Not Wait for Results from the First Vaccine Trials?

Although the discovery of Enders, Weller, and Robbins was critical to polio research, virology, and future vaccine development, it is reasonable to question why the College of Teachers of the Karolinska Institute awarded the Nobel Prize in Physiology or Medicine to Enders, Weller, and Robbins in the fall of 1954. Why did they not want to wait to learn the results of one large and two smaller polio vaccine trials that had been started in the spring of that year? After all, the critical deliberations took place about 4 months after all the children in these vaccine trials had been immunized.

Not surprisingly, Jonas Salk was nominated for the first time in 1955 for the Nobel Prize in Physiology or Medicine. At the time of nomination, the results of the large field trial, mentioned in Gard's 1954 evaluation of Enders and collaborators, were still pending.[8] The rigorous analysis offered by Thomas Francis on April 12, 1955, showed the Salk vaccine was clearly protective. The incidence of polio among the almost 200,000 children who had received the vaccine was reduced at least 50% with no adverse side effects reported after vaccination. In response to Salk's nomination by Drs A. J. Carlson and H. A. Rusk, Sven Gard wrote what appears to be a rather ambiguous formulation in a preliminary evaluation submitted on April 13, 1955:

> It appears to me that the problem (of polio vaccine production) is of such an importance from a practical medical viewpoint that a more comprehensive review is motivated. However, it is hardly possible to take a conclusive position for the moment. The results of the field trials that last year were conducted in U.S.A., Canada and Finland to a major extent have an influence on the standpoint to be taken. The results of these trials have now been compiled, but the complete report will not be available for some time to come. Under these conditions I *still* [our italics] consider that I should propose that the work is subjected to an exhaustive analysis.

However, the Committee did not initiate any further analysis that year.

In response to three nominations of Salk the next year by Leslie A. Osborn, Karl T. Neubuerger, and A. Sarpyener, Gard prepared another preliminary analysis consisting of eight typewritten pages. Gard described the first animal immunizations in 1910, studies of six different procedures for inactivation of polioviruses, the failed immunizations in the 1930s by Kolmer and Brodie, as well as Flexner's view that inactivated poliovirus is not immunogenic. Next, Gard comments on studies showing three distinct poliovirus strains, each of which requires a separate vaccine.

On this background, Gard analyzes Salk's contributions. He describes Salk's faulty interpretation of inactivation studies that were used to define conditions for the manufacture of polio vaccines. Gard argues that Salk's rigid attitude and incorrect recommendations were responsible for the Cutter incident. He concludes:

> Salk's most important contribution is according to my opinion that he definitely demonstrated that serological immunity and protective effects [against the disease, authors' comment] can be obtained by use of a formalin inactivated poliovirus vaccine. This is in principle nothing new and furthermore Salk has not in the development of his methods introduced anything that is principally new, but only exploited discoveries made by others. It has not been possible to reproduce some of his experimental results in other laboratories [the presumed linear rate of virus inactivation for one thing, our comment] and it seems now reasonably well secured that some of his working hypotheses are in fact incorrect. It cannot be excluded that

> some of the accidents that occurred in connection with the mass immunizations in the U.S. in 1955 result directly from the practical application of such incorrect hypotheses. According to my opinion Salk has not demonstrated the cautiousness that one would expect to be applied in this context. It is my view, based on these conclusions, that Salk's publications on the poliomyelitis vaccine cannot be considered as Prize worthy.

In the late 1960s, an initiative emerged from Rune Grubb, the Professor of Bacteriology at Lund University in Sweden, to nominate Salk, Sabin, and Koprowski for the Nobel Prize (E. Lycke, personal communication). Among the long list of names, numerous Swedish microbiologists signed the petition. In this initiative, Gard was included as a fourth nominee. The nomination cited Salk and Gard for the development of the inactivated vaccine, as well as Sabin and Koprowski for the attenuation of poliovirus strains and development live polio vaccines. After wide discussions, the nomination was signed by professors of virology, bacteriology, and immunology from many universities in Sweden. It is likely that professors from other Scandinavian countries also signed the nomination. When the nomination came to Gard's attention, without a moment's hesitation, he made it clear that he would not accept any nomination. He justified his refusal by referring to the Nobel statutes that the Prize was to be given for achievements of primary nature and not for applications of work derived from the accomplishments of those already awarded the Prize. Certainly, the long road to eradicating polio through the use of inactivated and live vaccines is undoubtedly filled with remarkable contributions to science, some of which are of a "primary nature," But Gard's decision was firm and the nomination was never submitted to the Nobel Committee. The nomination of four scientists, when Nobel's will clearly states a maximum of three awardees, was flawed from its inception.

So we return to the question of why the College of Teachers late in the fall of 1954 chose to support a minority opinion of the Nobel Committee and awarded the Nobel Prize in Physiology or Medicine to Enders, Weller, and Robbins. We can only speculate what prompted the College of Teachers to adopt the opinion of Gard and Hellström. As the most knowledgeable person on the subject of polioviruses in Sweden at this time, Gard was in a position to speak authoritatively. His evaluation for the Nobel Committee shows the admiration that he had for the discovery of the Enders group when he described their work as "the most important in the whole history of virology." Such hyperbole might best be understood within the context of Gard's presentation speech at the Nobel Prize award ceremony on December 10, 1954. In the final segment of his comments addressed to Enders, Weller, and Robbins, Gard states: "By giving the virologists a practical method for the isolation and study of viruses you relieved them of a handicap, burdening them from the birth of their science and placed them for the first time on an even footing with other microbe hunters."[70]

Fig 5. Polio vaccine pioneers (A) Herald Cox, (B) Hilary Koprowski, (C) Albert Sabin, (D) Jonas Salk, and (E) Julius Youngner. (Photos were kindly provided by Indiana State University, Samuel Katz, Hilary Koprowski, and Julius Younger.)

Unquestionably, Gard understood the importance of their discovery for future vaccine production, but for him, their work had much wider implications. Clearly, Enders, Weller, and Robbins laid the foundation for the accomplishments of many virologists in the 1950s and early 1960s. During that period, the majority of medically important human viruses were identified by examination of cytopathic effects in tissue cultures.

We conclude that Gard's admiration for the work of the Enders's group prompted him to push for the award of the 1954 Nobel Prize, and that his persuasive personality greatly influenced the College of Teachers. Gard's caustic analysis of Jonas Salk's nomination in 1956 suggests that any future nominations of the vaccine pioneer (Fig 5) were doomed. Certainly, it is reasonable to assume that until 1972, when Gard retired, no nomination of Salk was ever considered seriously by the Nobel Committee.

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FINAL VOTE RESULTS FOR ROLL CALL 147

(Democrats in roman; Republicans in *italic*; Independents underlined)

H R 2507 YEA-AND-NAY 28-May-1992 2:16 PM
QUESTION: On Agreeing to the Conference Report
BILL TITLE: NATIONAL INSTITUTES OF HEALTH REVITALIZATION AMENDMENTS OF 1992

	YEAS	NAYS	PRES	NV
DEMOCRATIC	216	32		19
REPUBLICAN	43	116		7
INDEPENDENT	1			
TOTALS	**260**	**148**		**26**

---- YEAS 260 ---

Abercrombie	*Gradison*	Owens
Ackerman	*Green*	Owens (UT)
Anderson	Guarini	Pallone
Andrews (ME)	Hall (TX)	Panetta
Andrews	Hamilton	Pastor
Andrews (TX)	Harris	Patterson
Annunzio	Hayes (IL)	Payne (NJ)
Applegate	Hefner	Payne (VA)
Aspin	*Henry*	Pease
Atkins	Hertel	Perkins
AuCoin	Hoagland	Peterson (FL)
Bacchus (FL)	*Hobson*	Peterson (MN)
Beilenson	Hochbrueckner	Pickett
Bentley	Horn	Pickle
Berman	*Horton*	*Porter*
Bevill	*Houghton*	Price (NC)
Bilbray	Hoyer	*Pursell*
Blackwell	Hubbard	Rangel
Boehlert	Huckaby	*Ravenel*
Bonior	Hughes	Reed
Borski	Jacobs	Richardson
Boucher	Jefferson	*Ridge*
Brewster	Jenkins	*Riggs*
Brooks	*Johnson (CT)*	Rose
Browder	Johnson (SD)	Rostenkowski
Brown (CA)	Johnston	*Roukema*
Bryant (TX)	Jones (GA)	Rowland
Bustamante	Jones (NC)	Roybal
Byron	Jontz	Russo

Cardin	Kaptur	Sabo
Carper	Kennedy (MA)	Sanders
Carr	Kennelly	Sangmeister
Chandler	Kildee	Savage
Chapman	Kleczka	Sawyer
Clay	*Klug*	Scheuer
Clement	*Kolbe*	Schumer
Coleman (MO)	Kopetski	Serrano
Coleman	Kostmayer	Sharp
Collins (IL)	Lancaster	*Shaw*
Condit	Lantos	*Shays*
Conyers	LaRocco	*Shuster*
Cooper	Laughlin	Sikorski
Cox (IL)	*Leach*	Sisisky
Coyne	Lehman	Skaggs
Cramer	Lehman (FL)	*Skeen*
Darden	Levin	Slattery
DeFazio	*Lewis (CA)*	Slaughter
DeLauro	*Lewis (FL)*	Smith (FL)
Dellums	Lewis (GA)	Smith (IA)
Derrick	Lipinski	*Smith (TX)*
Dicks	Lloyd	*Snowe*
Dingell	Long	Solarz
Dooley	Lowey	Spratt
Dorgan (ND)	*Machtley*	Staggers
Downey	Markey	Stark
Durbin	Martinez	Stokes
Dwyer	Matsui	Studds
Early	Mavroules	Swett
Eckart	McCloskey	Swift
Edwards (CA)	McCurdy	Synar
Edwards	McDermott	Tallon
Engel	McHugh	Tanner
English (OK)	McMillen (MD)	*Thomas*
Erdreich	McNulty	Thomas (GA)
Espy	*Meyers*	Torres
Evans	Mfume	Torricelli
Fascell	Miller (CA)	Towns
Fawell	*Miller (WA)*	Traficant
Feighan	Mineta	Unsoeld
Flake	Moakley	*Upton*
Foglietta	*Molinari*	Valentine
Ford (MI)	Montgomery	Vento
Ford	Moody	Visclosky
Frank (MA)	Moran	Washington
Franks (CT)	*Morella*	Waters
Frost	*Morrison (WA)*	Waxman
Gallo	Mrazek	Weiss
Gejdenson	Murtha	Wheat

Gephardt	Nagle	Whitten
Geren	Natcher	Williams
Gibbons	Neal	Wilson
Gilchrest	Neal (NC)	Wise
Gillmor	Nowak	Wolpe
Gilman	Oberstar	Wyden
Glickman	Obey	Yates
Gonzalez	Olin	*Zimmer*
Gordon	Olver	

---- NAYS 148 ---

Allard	*Hancock*	*Ramstad*
Allen	*Hansen*	Ray
Archer	*Hastert*	*Regula*
Armey	Hayes	*Rhodes*
Baker (LA)	*Hefley*	*Rinaldo*
Ballenger	*Herger*	*Ritter*
Barrett (NE)	*Holloway*	*Roberts*
Barton	*Hopkins*	Roe
Bateman	*Hunter*	Roemer
Bennett	Hutto	*Rogers*
Bereuter	*Hyde*	*Rohrabacher*
Bilirakis	*Inhofe*	*Ros-Lehtinen*
Bliley	*Ireland*	*Roth*
Boehner	*James*	*Santorum*
Broomfield	*Johnson, Sam*	Sarpalius
Bunning	Kanjorski	*Saxton*
Burton	*Kasich*	*Schaefer*
Callahan	Kolter	*Schiff*
Camp	*Kyl*	*Schulze*
Clinger	LaFalce	*Sensenbrenner*
Coble	*Lightfoot*	Skelton
Combest	*Lowery (CA)*	*Smith (NJ)*
Costello	Luken	*Smith (OR)*
Coughlin	*Marlenee*	*Solomon*
Cox	*Martin (NY)*	*Spence*
Crane	Mazzoli	Stallings
Cunningham	*McCandless*	*Stearns*
Davis	*McCollum*	Stenholm
de la Garza	*McCrery*	*Stump*
DeLay	*McDade*	*Sundquist*
Dickinson	*McEwen*	Tauzin
Doolittle	*McGrath*	Taylor (MS)
Dornan	*McMillan*	*Taylor (NC)*
Dreier	*Miller (OH)*	*Thomas (WY)*
Duncan	Mollohan	Thornton
Edwards (OK)	*Moorhead*	*Vander Jagt*

Emerson	Murphy	Volkmer
Ewing	*Myers*	*Vucanovich*
Fields (TX)	*Nichols*	*Walker*
Fish	*Nussle*	*Walsh*
Gallegly	Ortiz	*Weber*
Gaydos	Orton	*Weldon (PA)*
Gekas	*Oxley*	*Wolf*
Gingrich	Parker	*Wylie*
Goodling	*Paxon*	Yatron
Goss	Penny	*Young (AK)*
Grandy	*Petri*	*Young (FL)*
Gunderson	Poshard	*Zeliff*
Hall (OH)	*Quillen*	
Hammerschmidt	Rahall	

---- NOT VOTING 26 ---

Alexander	Dixon	Manton
Anthony	Donnelly	*Michel*
Barnard	Dymally	Mink
Boxer	Fazio	Oakar
Bruce	Hatcher	*Packard*
Campbell (CA)	*Lagomarsino*	Pelosi
Campbell (CO)	*Lent*	Schroeder
Collins (MI)	Levine (CA)	Traxler
Dannemeyer	*Livingston*	

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alzheimer's association

Testimony of Harry Johns, President and CEO of the Alzheimer's Association
Fiscal Year 2014 Appropriations for Alzheimer's-related Activities
at the U.S. Department of Health and Human Services

Subcommittee on Labor, Health and Human Services, Education and Related Agencies
Committee on Appropriations
United States House of Representatives

March 13, 2013

The Alzheimer's Association appreciates the opportunity to comment on the Fiscal Year (FY) 2014 appropriations for Alzheimer's disease research, education, outreach and support at the U.S. Department of Health and Human Services.

Founded in 1980, the Alzheimer's Association is the world's leading voluntary health organization in Alzheimer's care, support and research. Our mission is to eliminate Alzheimer's disease and other dementias through the advancement of research; to provide and enhance care and support for all affected; and to reduce the risk of dementia through the promotion of brain health. As the world's largest nonprofit funder of Alzheimer's research, the Association is committed to accelerating progress of new treatments, preventions and, ultimately, a cure. Through our funded projects and partnerships, we have been part of every major research advancement over the past 30 years. Likewise, the Association works to enhance care and provide support for all those affected by Alzheimer's and reaches millions of people affected by Alzheimer's and their caregivers.

Alzheimer's Impact on the American People and the Economy

In addition to the human suffering caused by the disease, Alzheimer's is creating an enormous strain on the health care system, families and the federal budget. Alzheimer's is a progressive brain disorder that damages and eventually destroys brain cells, leading to a loss of memory, thinking and other brain functions. Ultimately, Alzheimer's is fatal. Currently, Alzheimer's is the sixth leading cause of death in the United States and the only one of the top ten without a means to prevent, cure or slow its progression. Over five million Americans are living with Alzheimer's, with 200,000 under the age of 65. While deaths from other major diseases, including heart disease, stroke and HIV continue to experience significant declines, those from Alzheimer's have increased 68 percent between 2000 and 2010.

With the first of the baby boomer generation now turning 65, the U.S. population aged 65 and over is expected to double by 2030. Although Alzheimer's is not normal aging, age is the biggest risk factor for the disease. Taken together, these factors will result in

more and more Americans living with Alzheimer's - as many as 16 million by 2050, when there will be nearly one million new cases each year. Due to these projected increases, the graying of America threatens the bankrupting of America. Caring for people with Alzheimer's will cost all payers - Medicare, Medicaid, individuals, private insurance and HMOs -- $20 trillion over the next 40 years, enough to pay off the national debt and still send a $10,000 check to every man, woman and child in America. In 2012, America will have spent an estimated $200 billion in direct costs for those with Alzheimer's, including $140 billion in costs to Medicare and Medicaid. Average per person Medicare costs for those with Alzheimer's and other dementias are three times higher than those without these conditions. Average per senior Medicaid spending is 19 times higher.

A primary reason for these costs is that Alzheimer's makes treating other diseases more expensive, as most individuals with Alzheimer's have one or more co-morbidity that complicate the management of the condition(s) and increase costs. For example, a senior with diabetes and Alzheimer's costs Medicare 81 percent more than a senior who only has diabetes. Nearly 30 percent of people with Alzheimer's or another dementia who have Medicare also have Medicaid coverage, compared with 11 percent of individuals without Alzheimer's or dementia. Alzheimer's disease is also extremely prevalent in nursing homes, where 64 percent of Medicare residents live with the disease. Unless something is done, the costs of Alzheimer's in 2050 are estimated to total $1.1 trillion (in today's dollars). Costs to Medicare and Medicaid will increase nearly 500 percent and there will be a 400 percent increase in out-of-pocket costs.

With Alzheimer's, it is not just those with the disease who suffer - it is also their caregivers and families. In 2011, 15.2 million family members and friends provided unpaid care valued at over $210 billion. Caring for a person with Alzheimer's takes longer, lasts longer, is more personal and intrusive, and takes a heavy toll on the health of the caregivers themselves. More than 60 percent of Alzheimer's and dementia caregivers rate the emotional stress of caregiving as high or very high, with one-third reporting symptoms of depression. Caregiving may also have a negative impact on health, employment, income and family finances. Due to the physical and emotional toll of caregiving on their own health, Alzheimer's and dementia caregivers had $8.7 billion in additional health costs in 2011.

Changing the Trajectory of Alzheimer's

Until recently, there was no federal government strategy to address this looming crisis. In 2010, thanks to bipartisan support in Congress, the National Alzheimer's Project Act (NAPA) (P.L. 111-375) passed unanimously, requiring the creation of an annually-updated strategic National Alzheimer's Plan (Plan) to help those with the disease and their families today and to change the trajectory of the disease for the future. The Plan is required to include an evaluation of all federally-funded efforts in Alzheimer's research, care

and services -- along with their outcomes. In addition, the Plan must outline priority actions to reduce the financial impact of Alzheimer's on federal programs and on families; improve health outcomes for all Americans living with Alzheimer's; and improve the prevention, diagnosis, treatment, care, institutional-, home-, and community-based Alzheimer's programs for individuals with Alzheimer's and their caregivers. NAPA will allow Congress to assess whether the nation is meeting the challenges of this disease for families, communities and the economy. Through its annual review process, NAPA will, for the first time, enable Congress and the American people to answer this simple question: *Did we make satisfactory progress this past year in the fight against Alzheimer's?*

As mandated by NAPA, the Secretary of Health and Human Services, in collaboration with the Advisory Council on Alzheimer's Research, Care and Services, has developed the first-ever *National Plan to Address Alzheimer's Disease* in May of 2012. The Advisory Council, composed of both federal members and expert non-federal members, is an integral part of the planning process as it advises the Secretary in developing and evaluating the annual Plan, makes recommendations to the Secretary and Congress, and assists in coordinating the work of federal agencies involved in Alzheimer's research, care, and services.

Having a plan with measurable outcomes is important. But unless there are resources to implement the plan and the will to abide by it, we cannot hope to make much progress. If we are going to succeed in the fight against Alzheimer's, Congress must provide the resources the scientists need. Understanding this, the President's FY 2013 budget request included $80 million for Alzheimer's research and $20 million for education, outreach and support. These funds are a critically needed down payment for needed research and services for Alzheimer's patients and their families.

A disease-modifying or preventive therapy would not only save millions of lives but would save billions of dollars in health care costs. Specifically, if a treatment became available in 2015 that delayed onset of Alzheimer's for five years (a treatment similar to anti-cholesterol drugs), savings would be seen almost immediately, with Medicare and Medicaid spending reduced by $42 billion in 2020.

Today, despite the federal investment in Alzheimer's research, we are only just beginning to understand what causes the disease. Americans are growing increasingly concerned that we still lack effective treatments that will slow, stop, or cure the disease, and that the pace of progress in developing breakthrough discoveries is much too slow to significantly impact on this growing crisis. For every $31,000 Medicare and Medicaid spends caring for individuals with Alzheimer's, the National Institutes of Health (NIH) spends only $100 on Alzheimer's research. Scientists fundamentally believe that we have the ideas, the technology and the will to develop new Alzheimer's interventions, but that progress depends on a prioritized scientific agenda and on the resources necessary to carry out the scientific strategy for both discovery and translation for therapeutic development.

For too many individuals with Alzheimer's and their families, the system has failed them, and today we are unnecessarily losing the battle against this devastating disease. Despite the fact that an early and documented formal diagnosis allows individuals to participate in their own care planning, manage other chronic conditions, participate in clinical trials, and ultimately alleviate the burden on themselves and their loved ones, as many as half of the more than five million Americans with Alzheimer's have never received a formal diagnosis. Unless we create an effective, dementia-capable system that finds new solutions to providing high quality care, provides community support services and programs, and addresses Alzheimer's health disparities, Alzheimer's will overwhelm the health care system in the coming years. For example, people with Alzheimer's and other dementias have more than three times as many hospital stays as other older people. Furthermore, one out of seven individuals with Alzheimer's or another dementia lives alone and up to half do not have an identifiable caregiver. These individuals are more likely to need emergency medical services because of self-neglect or injury, and are found to be placed into nursing homes earlier, on average, than others with dementia. Ultimately, supporting individuals with Alzheimer's disease and their families and caregivers requires giving them the tools they need to plan for the future and ensuring the best quality of life for individuals and families impacted by the disease. It is vital that we make the investments in Alzheimer's that were laid out in the President's FY 2013 budget. While the President's budget requested $100 million for research and support services, the needs of the Alzheimer's community has grown. **The Alzheimer's Association urges Congress to fully fund the research, education, outreach and support activities and the priorities included in the National Alzheimer's Plan required under P.L. 111-375.**

Additional Alzheimer's programs

National Alzheimer's Call Center: The National Alzheimer's Call Center, funded by the AoA, provides 24/7, year-round telephone support, crisis counseling, care consultation, and information and referral services in 140 languages for persons with Alzheimer's, their family members and informal caregivers. Trained professional staff and master's-level mental health professionals are available at all times. In the 12 month period ending July 31, 2011, the Call Center handled over 300,000 calls through its national and local partners, and its online message board received over 40,000 visits a month. Additionally, the Association provides a two-to-one match on the federal dollars received for the call center. **The Alzheimer's Association urges Congress to support $1.3 million for the National Alzheimer's Call Center.**

Healthy Brain Initiative (HBI): The Centers for Disease Control and Prevention's (CDC) HBI program works to educate the public, the public health community and health professionals about Alzheimer's as a public health issue. Although there are currently

no treatments to delay or stop the deterioration of brain cells caused by Alzheimer's, evidence suggests that preventing or controlling cardiovascular risk factors may benefit brain health. In light of the dramatic aging of the population, scientific advancements in risk behaviors, and the growing awareness of the significant health, social and economic burdens associated with cognitive decline, the federal commitment to a public health response to this challenge is imperative. The FY2013 Senate Labor-HHS bill included report language commending HBI for its leadership in bringing attention to the public health crisis of Alzheimer's disease and for its work on cognitive impairment data collection in 45 states, the District of Columbia and Puerto Rico. Additionally, the committee noted that developing a population-based surveillance system with longitudinal follow-up is a key recommendation in the National Public Road Map to Maintaining Cognitive Health, which was developed jointly by the CDC and the Alzheimer's Association. The bill increased funding for HBI by $10 million in order to further develop this system and to develop effective public health messages to promote cognitive health in older adults. **The Alzheimer's Association urges Congress to support $11.8 million for the Healthy Brain Initiative.**

Alzheimer's Disease Supportive Services Program (ADSSP): The ADSSP at the AoA supports family caregivers who provide countless hours of unpaid care, thereby enabling their family members with Alzheimer's and dementia to continue living in the community. The program develops coordinated, responsive and innovative community-based support service systems for individuals and families affected by Alzheimer's. **The Alzheimer's Association urges Congress to support $13.4 million for the Alzheimer's Disease Supportive Services Program.**

Conclusion

The Association appreciates the steadfast support of the Subcommittee and its priority setting activities. We look forward to continuing to work with Congress in order to address the Alzheimer's crisis. We ask Congress to address Alzheimer's with the same bipartisan collaboration demonstrated in the passage of the National Alzheimer's Project Act (P.L. 111-375) and with a commitment equal to the scale of the crisis.

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Developmental Biology: Frontiers for Clinical Genetics

Human embryo and early fetus research

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Studies of human embryos and fetuses have highlighted developmental differences between humans and model organisms. In addition to describing the normal biology of our own species, a justification in itself, studies of early human development have aided identification of candidate disease genes mapped by positional cloning strategies, understanding pathophysiology, where human disorders are not faithfully reproduced by models in other species, and, more recently, potential therapies based on human embryonic stem and embryonic germ cells. In this article, we review these applications. We also discuss when and how to study human embryo and early fetuses and some of the regulations of this research.

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Key words: human embryo, fetus, embryology, embryonic stem cell, embryonic germ cell, differentiation, human development

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Since the 19th century, developmental biologists have recognized that a general plan of development is shared among vertebrates. Writing about vertebrate embryos, the developmentalist, Karl Ernst von Baer (1792–1876) noted, 'I am quite unable to say to what class they belong. They may be small lizards, or small birds, or very young mammalia, so complete is the similarity in the mode of formation of the head and trunk of these animals. They extremities are still absent, but even if they existed, in the earliest stage of development we should learn nothing, because all arise from the same fundamental form' (1).

The recognition that many developmental processes share a repertoire of transcription factors, signaling molecules and receptors has fostered the study of 'model organisms' from yeast to mouse. Many model organisms offer advantages for studying vertebrate development. Chick and quail embryos are readily accessible for tissue transplantation. Mice have 3-month generations and high fecundity – the average female of many strains will produce four to eight litters with a litter size comprising 4–12 pups. The availability of a fully sequenced and annotated genome, a large repertoire of known mutants, and transgenic technology for modifying the genome have made mice the model organism of choice for many developmental genetic studies. Rats share many of the features of mice, including a fully sequenced and annotated genome, transgenic technology and repertoire of known mutants (albeit smaller) and are generally more amenable to physiological experimentation (2). So why study human embryos?

The answer, of course, is that model organisms are not human. They differ from humans in size, appearance, longevity, physiology, and performance (3). Mouse, the most popular model, diverged from a common ancestor 75–80 million years ago (4). This divergence has led to important differences in anatomy, even at the earliest developmental stages, and in some important biochemical pathways, such as purine salvage (5). The laboratory mouse does not produce monozygotic twins naturally (6). Some human mutations, such as trinucleotide repeat expansion, seem not to occur spontaneously in

mice (7). The high rate of chromosomal aneusomy in human zygotes is not found in mice (8). When human mutations are engineered in mice, the phenotypes may be different from the corresponding phenotypes in humans and not infrequently associated with a normal phenotype (9). Undoubtedly, these differences are genetically determined.

At the level of the genome, there are significant differences in gene repertoire, organization, imprinting, and expression. The mouse and human genomes each contain about 30,000 protein-coding genes. The proportion of mouse genes without any orthologue detectable in the human genome (and vice versa) seems to be less than 1%; however, local gene family expansions, involving genes related to reproduction, immunity and olfaction, have occurred in the mouse genome, creating lineage innovation specific to rodents. Some secreted proteins involved with reproduction, host defense, and immune response appear to have been under positive selection, which has driven rapid evolution (4).

Local gene order or synteny (literally 'same thread') has been observed for 342 conserved segments between human and mouse genomes that vary in length, from 303 Kb to 64.9 Mb. About 90.2% of the human genome and 93.3% of the mouse genome unambiguously reside within conserved syntenic segments. The nature and extent of conservation of synteny differs substantially among chromosomes with the X chromosomes represented as single, reciprocal syntenic blocks, albeit with many rearrangements, and human chromosome 20 corresponds entirely to a portion of mouse chromosome 2, with nearly perfect conservation of order along almost the entire length. Conservation of synteny is lower for other chromosomes and may have functional significance for development (4). In addition, regulatory control regions show less conservation than coding regions, implying that, while exonic sequence, and thus protein composition, may be very similar, species differences arise from differing regulation of gene expression.

So, in complementing the major advances of mouse transgenic investigation, the study of the repertoire, control and timing of gene expression in human embryos is important for directly understanding human development. As well as this fundamental interest in appreciating the normal biology of our own species, which many consider justification in itself, there are other applications for studying early human development (Fig. 1). These include determining expression domains as a means of prioritizing candidate disease genes identified by positional cloning strategies; investigating pathophysiology, where human disorders and diseases are not faithfully reproduced by models in other species; and, more recently, a reawakening of the potential for therapies based on human embryonic and fetal material. Examples are described in turn.

Understanding the normal human developmental process

Sex determination

The comparative study of sex determination and sexual differentiation has been important for highlighting those features that are specific to human development. Sex determination is the process by which the undifferentiated gonadal ridge becomes a testis or an ovary. In turn, this leads to sexual differentiation in which male and female genitalia and other somatic characteristics develop (10). Among mammalian species, the cellular content and gene repertoire are similar. Homeostatic mechanisms have been established that promote the formation of normal gonads and block abnormal gonadal development and ambiguous genitalia. These requirements are critical for sexual dimorphism. Subtle deviation from the established repertoire can have a major impact on fertility and, if disrupted across many members, species viability. Abnormal sexual development often occurs in breeding experiments between related species.

These differences can be highlighted by studying widely divergent species, such as humans and mice. Among the differences that have been observed are a lack of congruence in gene expression and a lack of genotype–phenotype correlation when humans are compared to mice. In both species, SRY appears to operate as a regulatory 'switch' that causes the undifferentiated gonad to develop as a testis. In mice, the expression of this gene in the developing gonad peaks on a single day of development, whereas in humans the gene continues to be expressed once first activated (11, 12). Delayed expression of SRY in mice is associated with formation of ovotestes, a phenomenon that has not been observed for humans (13). The *NROB1* gene, also known as *AHC*, which encodes the DAX1 transcription factor, plays complex roles in mammalian sex determination. When mutated, the predominant phenotype in human males is adrenal hypoplasia congenita and hypogonadotrophic hypogonadism (14). In mice, the knockout phenotype includes not only adrenal hypoplasia but also gonadal dysgenesis (15). When duplicated, 46, XY humans develop gonadal dysgenesis and male-to-female sex reversal,

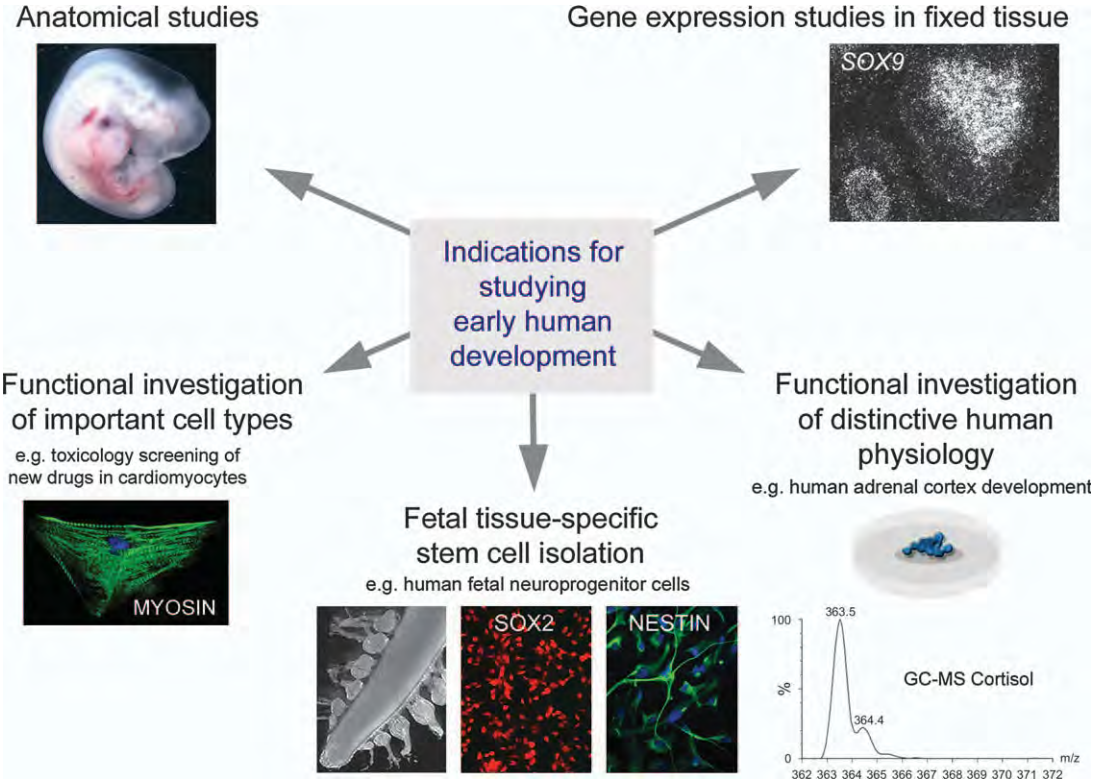

Fig. 1. Some of the indications for studying human embryos and fetuses. *SOX9* expression by radioactive mRNA *in situ* hybridization is shown in the gonadal ridge at 48 days post-conception. Gas chromatography/mass spectrometry identifies cortisol from the human fetal adrenal. SOX2/NESTIN+ tissue-specific stem cells/progenitors can be cultured from the developing spinal cord. Establishment of human fetal cardiomyocyte culture permits toxicology studies of new drugs.

a phenomenon that requires significantly greater overexpression in mice (14, 16, 17). In potential explanation, expression of the *NROB1* gene varies between humans and mice. In the mouse, Dax1 is expressed in male and female gonads coincident with *Sry* upregulation and then downregulated by embryonic day (E) 12, shortly after Sertoli cells have differentiated (18). In humans, *DAX1* expression commences in the indifferent gonadal ridge prior to detectable *SRY* expression and continues during testicular determination in developing Sertoli cells (12). Thus, when the *NROB1* gene is duplicated and overexpressed in dosage-sensitive sex reversal, the potential 'anti-testis' properties of DAX1 could act prior to and during SRY expression.

Germ cells

Interspecies developmental differences occur for germ cells as well as for support cell lineages. In the developing mouse testis, germ cells migrate into the genital ridge and become enclosed within testicular cords by E13. These early germ cells are referred to interchangeably as 'gonocytes' or 'pre-spermatogonia'. In the developing human testis, these events take place by 8 weeks of gestation. Detailed morphological studies by immunocytochemistry have revealed three distinct populations not observed in fetal mice (19). These have been characterized as gonocytes (OCT4pos/C-KITpos/MAGE-A4neg), 'intermediate germ cells' (OCT4low/neg/C-KITneg/MAGE-A4neg), and pre-spermatogonia (OCT4neg/C-KITneg/MAGE-A4pos). In the first trimester, most germ cells have a gonocyte phenotype; however, from 18 weeks of gestation, pre-spermatogonia are the most abundant cell type. Thus, functional differentiation of testicular germ cells takes place in humans during the second trimester of pregnancy and after birth in developing mouse gonads.

Endocrinology in the fetus

The transcriptional network that regulates mammalian pancreas development is remarkably well conserved (20). This is evidenced by major concordance between the knockout mice and the corresponding human mutation phenotypes of several genes, including those responsible for maturity onset diabetes of the young (20). However,

humans and rodents differ once the organ has formed; differences quite probably related to the role of insulin in promoting growth, a developmental feature which diverges progressively between mice and men with increasing gestational age. In mice, major beta cell development occurs at approximately E15, with islets only appearing near birth (20). In contrast, human beta cell development is apparent progressively from 8 weeks of development, with islets present by the end of the first trimester (Fig. 2) (21). In both species, beta cells are thought not to sense glucose under normal euglycemia; however, fetal hyperinsulinemia and the features of macrosomia accompany gestational diabetes in women, reinforcing the role of insulin as a significant growth factor during human development. Other aspects of endocrine development also highlight important differences between humans and other species. The fetal adrenal cortex, unique in higher primates, is discussed later in relation to congenital adrenal hyperplasia (CAH). However, like the pancreas, its biology in early human fetuses highlights that development is not simply an assembly line for post-natal life. Rather, important physiological function is apparent during intrauterine existence that is important in both health and disease.

Other examples

Differences in developmental expression have been observed for genes in other organ systems that account for interspecies variation in phenotype–genotype. The myosin VIIA gene is expressed in human and mouse cochleas. In the eye, the gene is expressed in human photoreceptor and retinal pigment epithelium (RPE), whereas in mouse, only in the RPE (22). When both copies are mutated, humans have sensorineural deafness, vestibular dysfunction and retinitis pigmentosa, whereas mutant mice have only the deafness and the vestibular dysfunction.

Prioritizing candidates: gene expression profiling to complement positional cloning of disease genes

DiGeorge syndrome

Because of interspecies differences in gene isoforms and differential use of genes within the repertoire for promoting development, analysis of gene expression in human embryos have proven useful for positional cloning of genes. For instance, a mutated gene that can cause the DiGeorge phenotype of thymic aplasia and other branchial arch abnormalities was mapped within

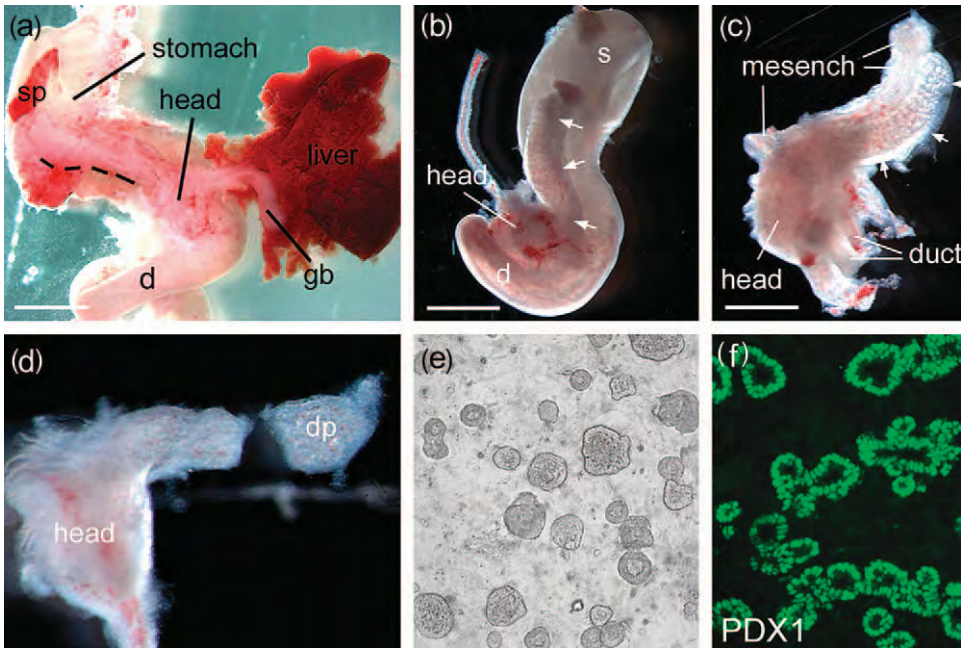

Fig. 2. The human early-fetal pancreas as a model for beta cell differentiation. (a) Dissection of stomach with attached pancreas. (b) Liver has been removed. (c) The head and the body/tail of the pancreas can be isolated from surrounding mesenchyme. (d) Explants can be taken for culture or tissue can be further processed to release the epithelial progenitor cells. (e) The epithelial progenitor cells can be cultured when they retain cell polarity by forming ring-like structures. (f) The cultured cells in (e) resemble the native PDX1+ pancreatic progenitor cells shown in a section of fixed tissue. Sp, spleen; gb, gall bladder; d, duodenum; s, stomach; arrows point to body and tail of pancreas; mesench, mesenchyme; dp, dorsal pancreas. Size bar represents 3 mm (a) and 1 mm (b–c).

the shortest region of deletion overlap of chromosome 10p. *BRUNOL3* (alternatively named *NAPOR*, *CUGBP2*, *ETR3*), the only gene that maps within this 300 Kb, is expressed in thymus during different developmental stages of embryonic and fetal development and thus a strong candidate for the phenotype (23).

Orofacial clefts

Expression data have been combined with genetic linkage analysis to identify candidate genes that can cause human orofacial clefts, a trait that is considered to have multifactorial inheritance, involving environmental influences and several genes. Using SAGE libraries and Affymetrix microarray analysis, genes were identified that are expressed in pharyngeal arch 1 and other craniofacial structures during the fourth and fifth week of human development. Some of these genes showed significant evidence of linkage in the presence of disequilibrium, making them candidates for orofacial clefts (24). Many of the genes had not been examined previously and warrant replication studies.

Studies of human development to understand human pathology

Chromosomal abnormalities

Chromosomal abnormalities are a frequent cause of human spontaneous abortions, observed in at least 50% of cases (25). Of these abnormalities, triploidy, the presence of an extra haploid set of chromosomes, occurs in 6% of spontaneous abortions. The triploidy arises from either digynic (two maternal haploid genomes) or diandric (two paternal haploid genomes) fertilizations. Studies using polymorphic molecular markers have shown that most digynic triploidy arise from errors in the second meiotic division, whereas virtually all cases of diandric triploidy arise from dispermy, rather than a meiotic error as has been postulated previously (26). Transcervical embryoscopy prior to dilatation and curettage in cases of missed abortion has been used to visualize embryos *in utero*, undisrupted by instrumental evacuation or spontaneous passage (27). When applied to triploid embryos, 17 out of 18 triploid embryos showed structural defects, including facial anomalies, limb abnormalities, microcephaly, and neural tube defects. Three embryos had disorganized growth. Embryonic abnormalities were observed in triploid embryos whose placentas showed partial hydatidiform moles, indicating that in aborted triploid embryos, the presence of two paternal genomes might have both embryonic and placental effects.

Embryoscopy has also been used to identify fetal abnormalities in other cases of missed abortions (28). Among 272 patients with missed abortion, the embryo or early fetus (12 cases) was visualized by transcervical embryoscopy in 233 cases, of which 221 were karyotyped. Among these 233 cases, 33 had normal external features, 71 were growth disorganized, and 129 had either isolated or multiple defects, including holoprosencephaly, anencephaly, encephalocele, spina bifida, microcephaly, facial dysplasia, limb reduction defect, cleft hand, syndactyly, pseudosyndactyly, polydactyly, various forms of cleft lip and an amniotic adhesion. Abnormal karyotype was observed in 75% of the cases. Morphological defect with a normal karyotype was observed in 18% of cases, and no embryonic or chromosomal abnormality could be diagnosed in 7% of the cases. Correlation of morphological and cytogenetic findings in spontaneous abortion specimens can provide useful information for genetic counseling in couples with a history of repeated pregnancy loss.

Congenital adrenal hyperplasia

A particularly pertinent example of studying human development to gain insight into disease relates to the fetal adrenal cortex, the structure and function of which is unique in higher primates (29). The virilization observed in CAH due to mutations in the enzyme cytochrome P450 21-hydroxylase intricately ties the function of the fetal adrenal cortex to sexual differentiation of the external genitalia in humans – associations that have not been observed in mice (30). The formation of the human lower vagina from evagination of the urogenital sinus has been demonstrated by the expression of uroplakins, which are specific molecular markers of urothelial differentiation. The androgen receptor (AR) is expressed in the epithelium and stroma of the urogenital sinus at 9 weeks of gestation, making these structures sensitive to the inhibitory effects of dihydrotestosterone on formation of the lower vagina. This promotes male development, yet renders the female with high levels of androgen susceptible to virilization. In contrast, the AR is not expressed in urogenital sinus urothelium, vaginal epithelium and Müllerian ducts at 14 weeks of development, making these tissues insensitive to androgen (31). These temporal changes are important.

Female androgen exposure in the first trimester, as in CAH, can cause major virilization of the vagina and external genitalia. After 12 weeks, vaginal development is unaffected and only clitoromegaly occurs. Under normal circumstances, adrenocortical physiology and a functional anterior pituitary-adrenal axis as early as 8 weeks of development protect the human female fetus. The production of adrenal androgens and their precursors in response to pituitary adrenocortical trophic hormone (ACTH) is tempered by negative feedback onto the anterior pituitary corticotrophs by cortisol (32). This generation of cortisol appears transient, diminishing by 14 weeks of development until its more familiar role nearer term, stimulating surfactant production by the fetal lung. Collectively, these fixed tissue and functional analyses of adrenal activity and target organ sensitivity provide experimental proof for the clinical need to treat the mothers of female CAH fetuses with dexamethasone prior to 8 weeks of development. However, perhaps this potent synthetic glucocorticoid, the use of which has raised concern of long-term programming effects (33, 34), could be withdrawn at some point after midgestation.

When to study human embryos?

Pre-implantation human embryos

Much emphasis has been placed on studying pre-implantation human embryos for pre-implantation genetic diagnosis (PGD). This involves analysis of single cells (blastomeres) removed from embryos 3 days after fertilization or polar bodies extruded from oocytes during meiosis (Fig. 3) (35). These tests are designed to determine which embryos are unaffected by a specific chromosomal or single-gene disorder. Those embryos identified as genetically normal are then transferred to the mother in preference to embryos found to be abnormal. PGD for single-gene disorders is intended to maximize the chances of obtaining a healthy conceptus, while eliminating the issue of pregnancy termination. Aneuploidy screening is performed for infertile patients who wish to improve the probability of successful *in vitro* fertilization by transferring viable embryos with normal chromosomes.

PGD methods have become increasingly complex. For single-gene disorders, several DNA fragments can be amplified simultaneously using multiplex-PCR, providing redundancy that can minimize misdiagnosis from allele dropout. Analysis of hypervariable loci can reveal the presence of DNA contaminants, if present. Chromosomal screening using fluorescence *in situ* hybridization (FISH) commonly analyzes up to nine chromosomes per cell and are offered to women of advanced reproductive age and those with a history of repeated spontaneous abortion (35). FISH using 24 centromere-specific probes now enables analysis of the whole chromosome complement (36). To enhance detection of submicroscopic chromosomal abnormalities, comparative genomic hybridization has been developed, most recently involving the use of DNA microarrays, comprising either bacterial artificial chromosomes or oligonucleotide probes that span the genome (37).

Where legislation allows, an additional research and potentially therapeutic use for human pre-implantation embryos is the generation of human embryonic stem (ES) cells. These cells represent an ill-defined *in vitro* conversion of the inner cell mass of the blastocyst to produce highly proliferative, pluripotent cells, in which senescence is suspended (38). Although no longer 'embryonic', it is worth noting in passing that fundamental differences are apparent between the ES cells of humans and mice, both in terms of gene expression and dependence on extrinsic factors, such as leukemia inhibitory factor (39). Similarly, as ES cells are pluripotent and thus capable of broad differentiation, preferences in lineage allocation may differ. For instance,

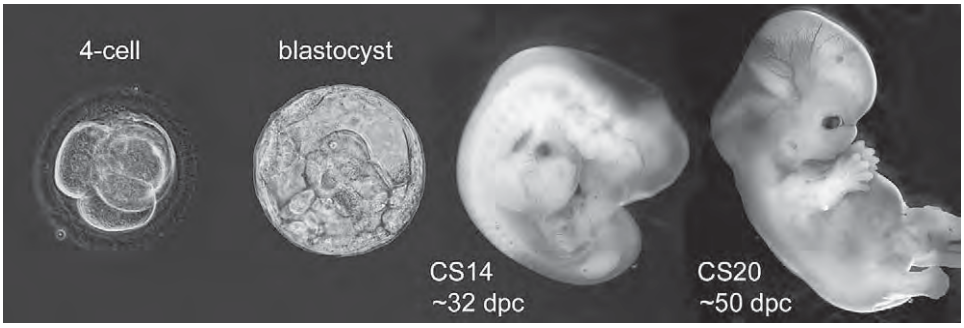

Fig. 3. Development from the four-cell stage through blastocyst formation and organogenesis. CS, Carnegie stage; dpc, days post-conception.

unlike the mouse, human ES cells can give rise to trophectoderm-like cells spontaneously either in the presence of the growth factor, BMP4, or in embryoid bodies (40, 41).

Human late embryos and early fetuses

Legislation, such as under the UK Human Fertilisation and Embryology Act of 1990, may permit studies of pre-implantation embryos under license up to 14 days post-fertilization. Later human development is inaccessible until ethical approval and informed consent permits the collection, in some countries, of the products of first trimester social/voluntary termination of pregnancy. Human embryos have been retrieved from cases undergoing termination of pregnancy from 3 weeks onward. Thus, there is a period of early embryonic development covering critical processes such as gastrulation that is not accessible for analysis. There are two methods of collection: surgical aspiration and medical termination of pregnancy using abortifacent, RU486 and mifepristone, both of which have the potential to yield undisrupted material (42). Although the embryos can be staged from timing the conception and from sonographic measurements, the preferred method involves the interpretation of morphologic landmarks into 23 phases of development (Carnegie stages) that was formalized in 1987 by O'Rahilly and Muller, and practically revised by Bullen and Wilson (Fig. 3) (43, 44). Carnegie stage 23 covers development up to 56 days post-conception. Staging later first trimester fetal development, particularly in surgical specimens, relies more on measurements, such as fetal hand and foot length, which are equated to weeks of gestation.

Some of the earlier examples give insights into what type of experiments can be contemplated using human embryonic and early-fetal material. The older first trimester material is ideally suited to studying events such as sexual differentiation or endocrine pancreas development from progenitor to the first islets of Langerhans (21). In contrast, younger embryonic stages are useful for studying aspects of organogenesis. The types of experiment are also varied.

Gene expression databases

A number of gene expression databases have been constructed. Some of these, such as the EST databases, include human embryonic and fetal material rather than focus on it. More specialized embryonic temporospatial mapping of gene expression has been conducted on human brain development (45). In this latter example, anatomy can fail to identify distinct regions of the developing central nervous system; however, these areas become apparent once accurately identified by discrete gene expression domains (e.g. by immunohistochemistry or mRNA *in situ* hybridization).

Functional analyses

Gene expression studies in fixed tissues are simply descriptive, in stark contrast to experiments in other model species that manipulate the genome (e.g. transgenic mice) or trace cell lineages (e.g. the classical experiments of developmental biology conducted in chick or frog). The inability to perform such experiments on intact human embryos for ethical reasons has limited the information that can be gained. However, improving molecular biology technologies redress this deficiency. In particular, primary culture models, in which genes are overexpressed or knocked down, are becoming more commonplace (46), opening up far greater opportunities for interrogation rather than simple observation. Primary culture models greatly increase the information that can be obtained compared to fixed archived tissue. For instance, cardiomyocytes differentiated from human ES cells may not resemble the adult cell type. However, reassurance would be gained by phenotypic resemblance to fetal cardiomyocytes, in effect part differentiation, as opposed to creating an entirely aberrant cell type, for which cell therapy would not be contemplated. Similarly, primary culture of a range of organs and cell types offers privileged access to untransformed human cells for drug toxicity screening, potentially reducing the risk associated with first human exposure to new drugs (47).

Isolating human stem or progenitor cell populations

Human embryonic and fetal tissues also offer additional stem cell populations for potential therapeutic applications. Fetal neurons, differentiated to dopamine-secreting cells, have already been entered into clinical trials, and this paradigm raises hope that similar strategies may be possible for other therapeutically desirable cell types, e.g. insulin-secreting beta cells for treating type 1 diabetes, or cardiomyocytes for treating cardiomyopathies or cardiac failure (48).

In addition to human ES cells, human embryonic germ (EG) cells represent a potential source of material for the production of cells for transplantation medicine (49). EG cells are derived from primordial germ cells in the developing gonadal ridge. Both ES and EG cells are pluripotent and capable of differentiation into many types of cells. Abnormalities in imprinted genes are associated with human diseases, including cancer; thus, there is concern that epigenetic defects in the progeny of ES cell lines may prove counterproductive as cell sources for transplantation. At least theoretically, the selection of human EG cells prior to their imprinting specific genes could eliminate the possibility of these disorders (50).

How to study embryos?

Human embryos have been used for chromosomal, genetic and expression analyses that have ranged in scope from single genes to whole genomes. Practical guides are available that provide methods for retrieving and handling human embryos for research purposes (2). Data about cell- and tissue-specific expression can be obtained from the Gene Expression Omnibus (http://www.ncbi.nlm.nih.gov/projects/geo). Because three-dimensional patterns of gene expression may have biological significance in developing human organs, efforts have been mounted to create such models along the lines of the resources that have been created for gene expression patterns in developing mice (46).

Limits exist within the scientific community for studying human embryos. Because of concerns involved with tampering with human life, experiments that involve creation of transgenic human embryos or embryonic chimeras have not been condoned, even when specific regulations do not exist.

What regulations exist for studying human embryos?

In the USA, both Federal and state laws and regulations govern the use of human embryos for research. Federal regulations permit funding for the study of human embryos provided that they were not obtained solely for research purposes (45 CFR 46.201-46.211). Federal funding of human ES cell research is confined to ES cell lines that were created prior to August 2001. Federal funding of cloning for reproductive or research purposes is prohibited. The Food and Drug Administration has claimed that human cloning technology represents an investigational new drug and, at this time, will not approve any human cloning projects for safety reasons (http://www.ncsl.org/programs/health/genetics/embfet.htm).

State statutes on embryonic and fetal research have evolved with the development of new technologies. State laws involving research on aborted fetuses or embryos vary with many states having restrictions. Some states permit research with consent of the patient. The sale of fetuses or embryos is restricted by almost half of the states. Louisiana specifically prohibits research on *in vitro* fertilized embryos. Illinois and Michigan prohibit research on live embryos.

Currently, a great deal of attention has centered on stem cell research derived from existing stem cell lines, aborted or miscarried embryos, unused *in vitro* fertilized embryos, and cloned embryos. State laws involving the use of ES cells from some or all sources vary widely. South Dakota's law forbids research on embryos regardless of the source. Laws in California, Connecticut, Massachusetts and New Jersey encourage ES cell research, including on cloned embryos. These states have guidelines for scientists that may include consent requirements and review and approval processes for new projects. New Jersey and California have allocated funds for stem cell research.

In the UK, the Human Fertilisation and Embryology Authority carries jurisdiction on human pre-implantation embryo research and issues licenses, subject to regular review and renewal, permitting research on such material gained with informed consent. This includes two licenses issued to UK groups attempting the derivation of new human ES cell lines for therapeutic purposes via somatic nuclear transfer.

The acquisition of material from first trimester termination of pregnancy in the UK follows similar guidelines to those in the USA, based around the recommendations of the Polkinghorne Committee, a UK Government committee that reported in 1989. This includes the need to separate clinical and research consent, the lack of financial or commercial incentive for the donor, and the need for the research consent to be acquired by individuals remote from the planned laboratory experiments.

Conclusions

Studies of human embryos have clearly highlighted developmental differences between humans and model organisms. The work on human developmental disorders has led to diagnostics that have improved pregnancy outcomes for

couples with recurrent pregnancy loss and at risk for having fetuses with genetic disorders. The identification of genes associated with normal and abnormal developmental phenotypes has made humans a 'model organism' whose findings can then be tested in other model organisms. The study of human embryonic development, thus, can lead to a better understanding of developmental biology in many organisms.

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Fetal Tissue Research: A Weapon and a Casualty in the War Against Abortion

By Heather D. Boonstra

HIGHLIGHTS

- *Medical research using human fetal tissue obtained from abortions has benefited millions of people worldwide and holds great promise for the continued advancement of basic science, as well as for the development of lifesaving vaccines and therapies.*
- *Since 1973, when abortion became legal nationwide, fetal tissue research has, time and again, become entangled in the abortion controversy.*
- *The current controversy—set off by a series of heavily edited and misleading videos—grew out of abortion opponents' long-standing campaign to vilify abortion and abortion providers, and it now threatens fetal tissue research itself.*

The debate over using human fetal tissue in medical research came roaring back on the national policy agenda last summer when a group of antiabortion activists began releasing deceptively edited videos about Planned Parenthood's handling of fetal tissue donations for this purpose. Fetal tissue research dates back to the 1930s, and has led to major advances in human health, including the virtual elimination of such childhood scourges as polio, measles and rubella in the United States.[1,2] Today, fetal tissue is being used in the development of vaccines against Ebola and HIV, the study of human development, and efforts to treat and cure conditions and diseases that afflict millions of Americans.

To ensure it meets the highest ethical standards, fetal tissue research has been subject to stringent laws and regulations for decades. Abortion foes are now accusing health care providers and researchers of violating these laws and ethical standards, in hopes of undermining the right to abortion and ending fetal tissue research. These attacks not only threaten sexual and reproductive health and rights, but also pose a threat to the large numbers of people who could benefit from fetal tissue research, given the wide range of conditions that such research might ameliorate. Any impediment to ongoing scientific inquiry in the field caused by the current controversy would have substantial consequences.

Importance of Fetal Tissue Research

Unlike embryonic stem cell research, which uses cells from days-old embryos created through in vitro fertilization, fetal tissue research uses tissue derived from induced abortion of pregnancies at or after the ninth week.[1,3] (Fetal tissue obtained from a miscarriage is often not suitable for research purposes because of concerns about potential chromosomal abnormalities that led to the miscarriage.[3]) Researchers most often acquire fetal tissue from a tissue bank or, sometimes, directly from a hospital or abortion clinic.[4]

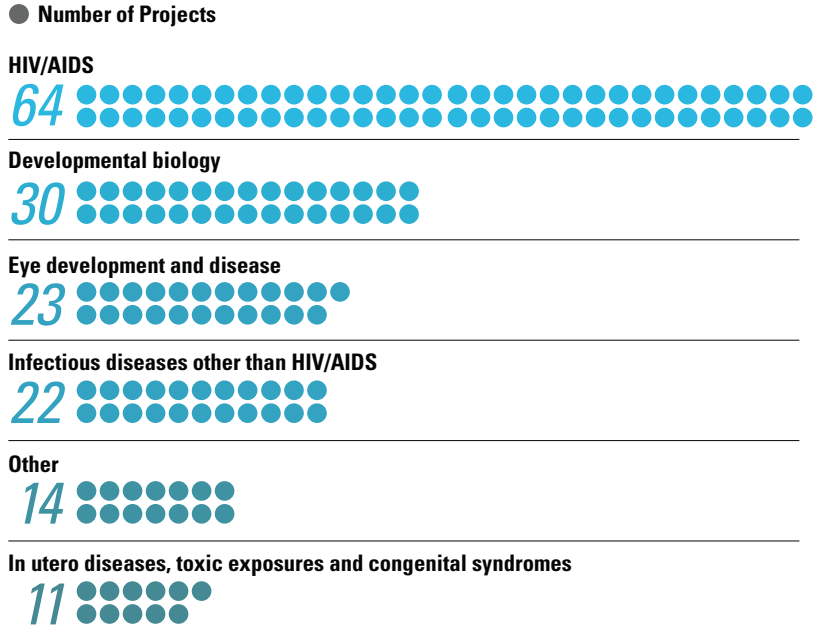
Because it is not as developed as adult tissue and is able to adapt to new environments, fetal tissue is critical to the study of a wide variety of diseases and medical conditions, according to the American Society for Cell Biology.[1] Researchers use fetal tissue—and cell cultures derived from such tissue, which can be maintained in a laboratory environment for decades—to study fundamental biological processes and fetal development. According to the U.S. Department of Health and Human Services, fetal tissue continues to be an important resource for researchers studying degenerative

eye disease, human development disorders such as Down syndrome, and early brain development (relevant to understanding the causes of autism and schizophrenia).[2]

Fetal tissue has also been used to develop vaccines that have saved and improved the lives of billions of people worldwide.[1,2,5] The 1954 Nobel Prize in Medicine was awarded for work using cell cultures originating from fetal tissue that led to the development of the polio vaccine. Vaccines for diseases such as measles, mumps, rubella, chickenpox, whooping cough, tetanus, hepatitis A and rabies were also created using fetal cell cultures, and researchers are now using fetal cells to develop vaccines against other diseases, including Ebola, HIV and dengue fever.

WIDESPREAD APPLICATIONS

The National Institutes of Health provides grants for a wide array of fetal tissue research projects.



Note: Data are for fiscal year 2014. *Source: Nature.*

In addition, researchers use fetal tissue in transplantation research. Fetal tissue has several unique properties that make it particularly suitable for transplantation. Not only do fetal cells grow at a much faster rate than adult cells, they also elicit less of an immune response, which lowers the risk of tissue rejection.[6] Clinical trials transplanting fetal cells are currently underway for people with spinal cord injury, stroke and ALS (Lou Gehrig's disease), and may soon begin for those with Alzheimer's disease, Parkinson's disease and multiple sclerosis.[1]

The National Institutes of Health (NIH) has been supporting research using fetal tissue since the 1950s, and in FY 2014, NIH provided roughly $76 million for this work.[3] According to an analysis of NIH research grants published in *Nature*, NIH funded 164 projects using fetal tissue in 2014, most often for research on infectious diseases, eye function and disease, and developmental biology (see chart).[7,8]

Many of the nation's leading academic medical centers are involved in fetal tissue research.[7,9,10] Researchers at the University of North Carolina at Chapel Hill are using cell cultures derived from fetal tissue for their work on hepatitis B and C—specifically, on how the viruses evade the human immune system and cause chronic liver diseases. At the University of Wisconsin-Madison, fetal cell cultures are used to study heart disease, including sudden cardiac arrest. At Stanford University, fetal tissue has been used to study Huntington's disease, juvenile diabetes, autism and schizophrenia. And scientists at Colorado State University are conducting HIV research using fetal tissue.

Federal Law and Regulation

Soon after the U.S. Supreme Court's *Roe v. Wade* decision in 1973 legalizing abortion nationwide, antiabortion leaders in Congress seized on fetal tissue research as a weapon in the war against abortion. Fetal tissue research was perhaps an inevitable target: It provided an aura of legitimacy to abortion itself and, at the same time, could be easily exploited to show how abortion "dehumanizes"

the fetus.[11] Accordingly, antiabortion activists employed graphic visuals to shock members of Congress, try to personify the fetus, and demonize abortion providers and the procedure itself.

This first incarnation of the controversy coincided with public revelations about the infamous Tuskegee syphilis study—a study that enrolled black men living in Alabama to investigate the long-term effects of syphilis. In 1973, an ad hoc advisory panel convened by the Department of Health, Education and Welfare (now the Department of Health and Human Services) concluded that, in retrospect, the study was "scientifically unsound" and "ethically unjustified."[12] In response to the Tuskegee revelations, Congress felt pressure to create protections for human research subjects, and by 1974, Congress passed the National Research Act. The law created the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research to develop guidelines on the ethical principles that apply to research on all human subjects, as well as on particular principles that apply to research involving fetuses and using fetal tissue.

The commission's report on research on the fetus, issued in 1975, led to the creation of regulations during the Ford administration that set out the rules of the road for federally funded fetal tissue research. The regulations—which are still in effect—specify that "no inducements, monetary or otherwise, will be offered to terminate a pregnancy." They also provide that "individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy."

Fetal tissue research receded as a political issue until the late 1980s, when a group of NIH scientists sought approval from the Reagan administration for a proposed project involving the transplantation of fetal tissue. After deliberating on the request, the administration appointed an advisory panel—which included a chair and several members who were well-known opponents of abortion rights—to examine the ethical, legal and scientific questions raised by this type of research. In 1988, the panel issued its report and, despite its mixed composition, it concluded that "in light of the fact that abortion is legal and that the research in question is intended to achieve significant medical goals…the use of such tissue [for research] is acceptable public policy."[13]

Key recommendations of the panel were later codified into law with the passage of the NIH Revitalization Act of 1993. The legislation won broad bipartisan support in Congress, including from several prominent senators with solid antiabortion records. Among them were Sens. Robert Dole (R-KS), a longtime advocate for people with disabilities, and Strom Thurmond (R-SC), who had a daughter with juvenile diabetes.[14,15]

The NIH Revitalization Act of 1993 added several provisions to the existing regulations governing fetal tissue research. One such provision prohibits anyone from accepting payment for human fetal tissue other than "reasonable payments associated with the transportation, implantation, processing, preservation, quality control, or storage of human fetal tissue." Thus, although individuals may be compensated for any costs they incur in the acquisition, receipt or transfer of fetal tissue, they are prohibited from making a profit from these activities, regardless of whether the project is federally funded or not.

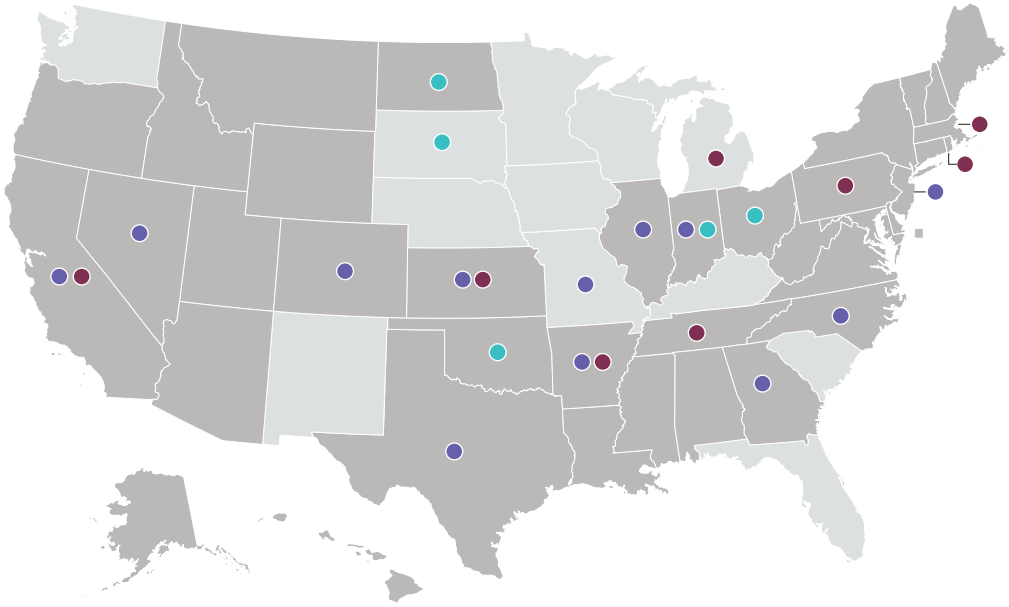
The law also imposes additional requirements when the donated tissue is used in federally funded research involving the transplantation of fetal tissue for therapeutic purposes. Among these are provisions for informed consent and prohibiting physicians and researchers from altering the timing or method used to terminate the pregnancy solely for the purposes of obtaining the tissue. Although all of these requirements technically apply only to federally funded transplantation research, as a practical matter, they set the standard for all research using fetal tissue. For example, the policies and procedures for fetal tissue donation issued by Planned Parenthood Federation of America and by the National Abortion Federation incorporate the substance of these federal requirements.[16,17]

State Policies

At the state level, fetal tissue donation is regulated by the Uniform Anatomical Gift Act (UAGA),

FETAL TISSUE POLICIES

In the states, fetal tissue donation is generally governed by the Uniform Anatomical Gift Act (UAGA). In addition, many states have specific statutes on fetal tissue donation and research.



- Donation explicitly permitted under UAGA **(TOTAL = 38+DC)**
- Donation not addressed under UAGA **(TOTAL = 12)**
- Prohibits profiting from fetal tissue donation or procurement **(TOTAL = 12)**
- Requires consent before fetal tissue is donated **(TOTAL = 8)**
- Bans all fetal tissue research **(TOTAL = 5)**

Note: Three additional states have laws that apply only to abortion after viability. Kentucky prohibits experiments using tissue from a postviability abortion. Nebraska and Wyoming prohibit "giving away, sale, transfer or distribution" of tissue from a postviability abortion.

versions of which are in effect in every state.[13,18] According to an analysis by the Guttmacher Institute, 38 states and the District of Columbia have UAGA laws that explicitly treat fetal tissue the same way as other human tissue, permitting it to be donated by the woman for research, therapy or education. The remaining 12 states have laws that are silent, neither allowing nor disallowing the donation of fetal tissue (see map). UAGA also prohibits profiting from the sale or purchase of anatomical gifts for transplantation or therapy.

Fetal tissue donation and research are also regulated in some states by specific statutes. Often, these statutes incorporate many of the same standards set by federal law and regulations. For example, 12 states prohibit making a profit from the donation or transfer of fetal tissue for research purposes, and eight states require the woman's consent for research.

Five states have laws that ban research using fetal tissue obtained from abortions throughout pregnancy. (Four other states also ban research using postabortion fetal tissue, but these laws have been struck down by the courts.) One of these states with a ban in effect, Indiana, also has a law that requires the disposal of postabortion fetal tissue in an established cemetery or by cremation, presumably precluding any possibility of donation for research.

Political Firestorm

The current furor over the use of fetal tissue in research ignited last summer, after the release of heavily edited videos purporting to capture undercover sting operations targeted at Planned

Parenthood. The series of videos—released in close cooperation with members of Congress who want to ban abortion[19]—show an antiabortion activist posing as a representative of what turned out to be a sham biomedical research company, in frank discussions with various Planned Parenthood officials about tissue donation policies and reimbursement.

The fallout from the videos has been swift, severe and wide-ranging. The stated targets are Planned Parenthood, abortion providers and the legitimacy of abortion. The videos also threaten to undermine fetal tissue research itself, however, by sowing confusion, and by using graphic descriptions and images to turn the public against this research.

The primary goal of this current campaign has been to portray Planned Parenthood as callous and its providers as possibly criminal. Antiabortion policymakers have accused Planned Parenthood of violating several provisions of the NIH Revitalization Act of 1993, such as profiting from the sale of fetal tissue and altering the abortion procedure solely for the purpose of obtaining tissue. Opponents of abortion have also accused providers of using a procedure that violates the so-called "partial birth" abortion ban. As an instigator of the videos, David Daleiden explained in an interview with *Politico*, "For me, the goal was to document and illustrate for the public really, really clearly how Planned Parenthood harvests and sells the body parts of the babies that they abort."[20]

Antiabortion elected officials ran with this narrative and immediately called for investigations of the organization. In October 2015, congressional leaders formed a special committee to carry out an official inquiry into Planned Parenthood—bringing the total number of investigations into Planned Parenthood in the House and Senate to five since the first video was released. In January 2016, the House's first substantive piece of business was yet another attempt to cut off funding for Planned Parenthood, one of several such efforts recently to scale back abortion rights and women's health care. Also, officials in 11 states have concluded investigations into claims that Planned Parenthood profited from fetal tissue donation, and each one of these investigations has cleared the organization of wrongdoing.[21]

Nonetheless, the grandstanding has continued unabated. Antiabortion leaders, lawmakers and all the Republican presidential candidates have used the opportunity to demonize abortion and paint a ghoulish picture of organ harvesting, all in an effort to gin up public disgust and attract public support for themselves and against abortion and Planned Parenthood. Indeed, the videos and the hype around them appear to have provoked at least four arson attacks on Planned Parenthood clinics since July 2015 and set the stage for yet another extreme act of violence in Colorado Springs over Thanksgiving weekend.[10] It was there that Robert Lewis Dear Jr. allegedly killed three people and injured nine others at a Planned Parenthood health center. During his arrest, Dear shouted "no more baby parts," suggesting that the constant barrage of inflammatory rhetoric around the fetal tissue issue over the prior months played a role in triggering his actions.[22]

High Stakes

Beyond the attacks on Planned Parenthood, however, the use of fetal tissue in research also is under direct attack. Since July, bills have been introduced in Congress and in several states that would make it more difficult to donate tissue or use fetal tissue in research. Other bills would ban fetal tissue research outright. This trend is almost certain to continue through 2016 as the issue is sure to be exploited in state and federal elections.

Meanwhile, the videos appear to have had a chilling effect on science. According to Theresa Naluai-Cecchini, a scientist at the Birth Defects Research Laboratory at the University of Washington (a federally funded entity that has served as a source of donated fetal tissue to researchers nationwide for more than 50 years), tissue donations have dropped dramatically since July 2015.[10] Naluai-Cecchini told *Mother Jones* that if this trend continues, research that may save lives would take considerably longer.

Some scientists involved in fetal tissue research have been afraid to speak out.[7] They have seen how abortion providers have been targeted,

and now they too fear for their personal safety. Others have spoken out strongly to defend the importance of their work, pointing out that tissue that would otherwise be discarded has played a vital role in lifesaving medical advances and holds great promise for new breakthroughs. In an October 2015 open letter to Congress, 41 scientists called for the end to political interference with science and research: "Fetal tissue research has already saved and improved the lives of countless people. [We] cannot allow political agendas to undermine our nation's legacy of leadership in medical and scientific innovation."[23] In another action, the Association of American Medical Colleges released a statement on January 6, 2016 signed by 59 academic medical centers, scientific societies and allied groups—from the University of Alabama School of Medicine to Duke University School of Medicine, from the University of Wisconsin-Madison to Tulane University School of Medicine.[24] The statement expresses "grave concerns" about the numerous legislative proposals now in play in Congress and in many states, and it calls on lawmakers to reject any proposals that restrict access to fetal tissue for research.

Ironically, in the wake of all the heightened focus on fetal tissue donation, Planned Parenthood officials report they have seen an uptick in the number of women obtaining abortion who request that the fetal tissue be donated to research. The role that Planned Parenthood plays in providing postabortion tissue to researchers, however, is small: Just 1% of the approximately 700 health centers that are part of the Planned Parenthood network are equipped for fetal tissue donation. And in another response to the disinformation campaign and to try to quell some of the controversy, Planned Parenthood announced in October 2015 that its clinics will no longer seek reimbursement for their costs related to fetal tissue donation, even though the practice is perfectly legal and commonplace.

Bioethicist R. Alta Charo has argued that enabling the use of fetal tissue to advance scientific research for the benefit of humankind must be seen as something of a moral imperative. "Virtually every person in this country has benefited from research using fetal tissue," she wrote in the *New England Journal of Medicine*. "Every child who's been spared the risks and misery of chickenpox, rubella, or polio can thank the Nobel Prize recipients and other scientists who used such tissue in research yielding the vaccines that protect us….Any discussion of the ethics of fetal tissue research must begin with its unimpeachable claim to have saved the lives and health of millions of people."[25]

As the full impact of the current firestorm surrounding fetal tissue research is still unfolding, it remains to be seen how much this research will continue be used as a weapon against abortion or become a serious target itself—or both. To be sure, the current controversy threatens not just access to safe and legal abortion and the providers who care for the women who seek this essential health service. It also threatens the millions of people globally who could benefit from fetal tissue research—and that includes nearly all of us, whatever our views on abortion rights may be. ■

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WHAT DO YOU THINK?
Which three researchers

Early Tissue and Cell Culture in Vaccine Development

En español

In order to develop vaccines that could be mass-produced, researchers first had to grow the viruses or bacteria with which to develop those vaccines – in large quantities and with great consistency. Compared with bacteria, which can be grown in a laboratory environment when placed in a suitable growth medium, viruses cannot reproduce on their own and require living cells to infect. After a virus infects a cell, it uses the cell's own components to produce more copies of itself.

Wellcome Library, London
One stage in the preparation of the rabies vaccine: a rabbit brain on a square of muslin. Pasteur Institute, India, circa 1910.

So while material for early bacterial vaccines could be grown in a lab without laboratory animals, researchers trying to develop material for viral vaccines faced an additional challenge. With techniques for growing viruses outside of live hosts not yet available, they were limited to obtaining materials from infected animal hosts.

During the early efforts to develop a vaccine against polio, researchers discovered that the virus could cause disease not only in humans but also in monkeys. This led to early field trials in the 1930s of vaccine candidates developed using material taken from polio-infected monkeys, such as monkey spinal cords. These candidates proved to be dangerous, sometimes causing paralysis in the limb where the vaccine was administered; vaccines derived using nervous system tissue have a higher side effect profile than those developed using other methods (the myelin in the vaccine material can stimulate an adverse neurological reaction). The trials ceased, and researchers moved on with the goal of finding another way to grow the virus for vaccine development.

The Promise of Cell Culture in Vaccine Development

Hopes of growing poliovirus in the lab without the use of live animals drove many of the researchers in the 1930s and 1940s. Cell cultures involve growing cells in a culture dish, often with a supportive growth medium like collagen. They offer a level of control that was unavailable using live animals, and can also support large-scale virus production. (For more about cell cultures and cell lines, as well as cell lines made using human cells, see our article "Human Cell Strains in Vaccine Development.") Early efforts to grow poliovirus in culture, however, repeatedly ended in failure.

In 1936, Albert Sabin and Peter Olitsky at the Rockefeller Institute successfully grew poliovirus in a culture of brain tissue from a human embryo. The virus grew quickly, which was promising, but Sabin and Olitsky were concerned about using this as starting material for a vaccine, fearing nervous system damage for vaccine recipients. They tried to grow poliovirus in cultures using tissue that had been taken from other sources, but were unsuccessful.

Breakthrough in Boston

Thirteen years after Sabin and Olitsky's success with growing poliovirus in brain tissue, researchers at the lab of John Enders at the Children's Hospital in Boston successfully grew the virus in a culture of skin and muscle tissue from a human embryo—in a very fortunate happenstance. At the time, the researchers were focused on trying to isolate and grow varicella, the chickenpox virus. They had already succeeded in growing mumps and influenza viruses and had moved on to varicella, which they knew grew in human cells. After preparing flasks with human embryonic tissue, they inoculated four flasks with throat washings from chickenpox patients. Another four flasks were inoculated with a strain of poliovirus as a control group. The chickenpox virus did not grow in this case, but to the researchers' great surprise, poliovirus did.

They went on to grow two other strains of poliovirus, and in many different types of human embryonic tissue, without using nervous system tissue. They were able to grow the virus rapidly and to very high concentrations using the "roller tube" apparatus created by researcher George Otto Gey in the 1930s. (Gey also established perhaps the most famous human cell line, the HeLa, or Henrietta Lacks line.) While many tissue cultures at the time were done in flasks, Gey realized that the environment in the flask did not adequately simulate the environment inside a living body, where tissues are exposed to periods of nutrients being supplied as well as waste

were in a race to develop a polio vaccine?

Albert Sabin, David Bodian, and Jonas Salk

Maurice Hilleman, Hilary Koprowski and Jonas Salk

David Bodian, Albert Sabin, and Maurice Hilleman

Jonas Salk, Albert Sabin, and Hilary Koprowski

removal. Instead of a flask, he placed tissue on the sides of test tubes, and then placed the tubes horizontally into holes in a wooden cylinder. The cylinder slowly turned like a wheel, rotating the tubes so that the tissue would alternate coming into contact with air and a nutrient fluid added to the tube.

The researchers in Enders's lab used the same technique, growing poliovirus much more rapidly than could be achieved in static flasks. For demonstrating that poliovirus could be reliably grown without using nervous tissue, Enders and his colleagues Thomas Weller and Frederick Robbins were awarded the Nobel Prize in Physiology or Medicine in 1954.

Their discovery proved to be the breakthrough needed to develop a polio vaccine. In 1951, Jonas Salk and his colleagues at the University of Pittsburgh found that poliovirus could also be propagated on a large scale in monkey kidney cells.

Over time, most vaccine development efforts shifted to the use of cell strains—cultures made up of only a single type of cell. These strains can be derived from tissue cultures, which contain multiple types of cells; while viruses can be grown in tissue cultures, cell strains allow for continuous observation and control that may not be possible in cultures containing multiple types of cells. This same transition was made in the development of polio vaccines; a monkey kidney cell strain is used to grow poliovirus for the inactivated polio vaccine made today.

Current Vaccines Developed Using Animal Cell Strains

Today, many different animal cell strains are available for use in scientific research and development. Several vaccines currently available in the United States were developed using the Vero cell line, started from African green monkey kidney cells:

- Rotavirus vaccines [Rotarix/GlaxoSmithKline, RotaTeq/Merck]
- Polio [IPOL/Sanofi Pasteur]
- Smallpox [ACAM2000/Sanofi Pasteur – **Used only for selected military personnel**]
- Japanese encephalitis [Ixiaro/Intercell – **Used only for those traveling to areas with known outbreaks of disease**]

Future U.S. vaccines may use other animal cell strains, including the Madin Darby Canine Kidney (MDCK) line, which was started in 1958 with kidney cells from a cocker spaniel. (Some European vaccines are already made using MDCK.)

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Assessment Questions

Before the 1950s, why was it difficult to grow viruses in labs?

A) Viruses would get contaminated with bacteria.
B) A method for growing them outside a live animal host had not been developed.
C) Viruses were not recognized yet.
D) All of the above

Which virus drove a great deal of the interest in developing tissue and cell culture

techniques?

A) Smallpox virus
B) The common cold virus
C) Cholera
D) Poliovirus

What is a cell strain?

A) A culture made of a single type of cell
B) A tissue culture
C) A culture of many types of cells
D) A virus

View Progress

History of Vaccines
A VACCINE HISTORY PROJECT OF THE COLLEGE OF PHYSICIANS OF PHILADELPHIA

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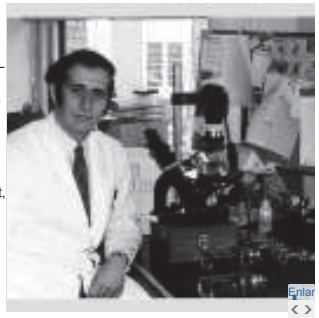
Different Types of Vaccines

Vaccines are made using several different processes. They may contain live viruses that have been attenuated (weakened or altered so as not to cause illness); inactivated or killed organisms or viruses; inactivated toxins (for bacterial diseases where toxins generated by the bacteria, and not the bacteria themselves, cause illness); or merely segments of the pathogen (this includes

En español

Human Cell Strains in Vaccine Development

Note: The terms "cell strain" and "cell line" are sometimes used interchangeably. In this article, "cell strain" is used to describe a culture of a single type of cell; "cell line" is used to describe an immortalized *culture of a single type of cell – that is, one that replicates infinitely, like the well-known HeLa cell line that was started with cancer cells taken from Henrietta Lacks.*



Courtesy Stanley Plotkin, MD
Stanley Plotkin

Animals have been used in the production of human vaccines since vaccine farms were established to harvest cowpox virus from calves in the late 1800s. From that point, and through the first half of the 20th century, most vaccines would continue to be developed with the use of animals, either by growing pathogens in live animals or by using animal cells.

Although many vaccines and anti-toxin products were successfully developed this way, using animals in vaccine development – particularly live animals – is not ideal. Research animals are costly and require extensive monitoring, both to maintain their health and to ensure the continued viability of the research. They may be carrying other bacteria or viruses that could contaminate the eventual vaccine, as with polio vaccines from the mid 20th century that were made with monkey cells and eventually found to contain a monkey virus called SV40, or Simian Virus 40. (Fortunately, the virus was not found to be harmful to humans.) Moreover, some pathogens, such as the chickenpox virus, simply do not grow well in animal cells.

Even when vaccine development is done using animal products and not live animals – such as growing influenza vaccine viruses in chicken eggs – development can be hindered or even halted if the availability of the animal products drops. If an illness were to strike the egg-producing chickens, for example, they might produce too few eggs to be used in the development of seasonal flu vaccine, leading to a serious vaccine shortage. (It's a common misconception that influenza vaccines could be produced more quickly if grown in cell cultures compared to using embryonated chicken eggs. In fact, growing the vaccine viruses in cell cultures would take about the same amount of time. However, cell cultures do not have the same potential availability issues as chicken eggs.)

For these and other reasons, using cell culture techniques to produce vaccine viruses in human cell strains is a significant advance in vaccine development.

How Cell Cultures Work

Cell cultures involve growing cells in a culture dish, often with a supportive growth medium like collagen. A *primary* cell culture consists of cells taken directly from living tissue, and may contain multiple types of cells such as fibroblasts, epithelial, and endothelial cells.

Cell *strains*, however, are designed to be a culture that contains only one type of cell. This is done by taking subcultures from the original culture until only one type remains. Primary cultures can be manipulated in many different ways in order to isolate a single type of cells; spinning the culture in a centrifuge can separate large cells from small ones, for example. Eventually, when only a single type of cell remains, researchers can try to establish a cell line. Cell lines allow for continuous observation and control that may not be possible in larger tissue cultures containing multiple types of cells.

Cell lines may be subject to the Hayflick Limit, a rule named for researcher Leonard Hayflick. Hayflick determined that a population of normal cells will reproduce only a finite number of times before they cease to reproduce. However, in contrast to those subject to Hayflick's discovery, some cell lines can be immortalized: that is, the cells have undergone some mutation that allows them to reproduce indefinitely. One example is the so-called HeLa cell line, started from cervical cancer cells taken in the 1950s from a woman named Henrietta Lacks.

Using cell strains and cell lines, researchers can grow human pathogens like viruses in a particular type of cell to attenuate them – that is, to weaken them. One way viruses are adapted for use in vaccines is to alter them so that they are no longer able to grow well in the human body. This may be done, for example, by repeatedly growing the virus in human cells kept in culture at a much lower temperature than normal body temperature. In order to keep replicating, the virus adapts to become better at growing at the lower temperature, thus losing its original ability to grow well at normal body temperatures. Later, when it's used in a vaccine and injected into a living human body at normal temperature, it still provokes an immune response but can't replicate enough to cause illness.

Vaccines Developed Using Human Cell Strains

The first vaccine created with the use of human cell strains was the rubella vaccine developed by Stanley Plotkin at the Wistar Institute in Philadelphia.

In 1941, Australian ophthalmologist Norman Gregg first realized that congenital cataracts in babies were the result of their mothers being infected with rubella during pregnancy. Along with cataracts, it was eventually determined that congenital rubella syndrome (CRS) could also cause deafness, heart disease, encephalitis, mental retardation, and pneumonia, among many other conditions. At the height of a rubella epidemic that

both subunit and conjugate vaccines).
MORE ▶

began in Europe and spread to the United States in the mid-1960s, Plotkin calculated that 1% of all births at Philadelphia General Hospital were affected by congenital rubella syndrome. In some cases, women who were infected with rubella while pregnant terminated their pregnancies due to the serious risks from CRS.

Following one such abortion, the fetus was sent to Plotkin at the laboratory he had devoted to rubella research. Testing the kidney of the fetus, Plotkin found and isolated the rubella virus. Separately, Leonard Hayflick (also working at the Wistar Institute at that time) developed a cell strain using lung cells from an aborted fetus. Many viruses, including rubella, grew well in the resulting cell strain, and it proved to be free of contaminants. The strain was eventually called WI-38.

Plotkin grew the rubella virus he had isolated in WI-38 cells kept at 86°F (30°C), so that it eventually grew very poorly at normal body temperature. (He chose the low temperature approach following previous experiences with attenuating poliovirus.) After the virus had been grown through the cells 25 times at the lower temperature, it was no longer able to replicate enough to cause illness in a living person, but *was* still able to provoke a protective immune response. This rubella vaccine is still used in the United States today as part of the combined MMR (measles, mumps, and rubella) vaccine.

Ethical Issues with Human Cell Cultures

Although it has now been used in the United States for more than 30 years, Plotkin's rubella vaccine was initially ignored in the U.S. in favor of vaccines developed using duck embryo cells and dog kidney cells. In the late 1960s, there was concern in the country that a vaccine developed using a human cell line could be contaminated with other pathogens, though this concern did not seem to have any documented evidence behind it. This is somewhat interesting in light of the discovery earlier in the decade that polio vaccines developed using animal cells were contaminated with a simian virus, which was one of the reasons researchers began using human cell lines in the first place.

Plotkin's vaccine was first licensed in Europe in 1970 and was widely used there with a strong safety profile and high efficacy. In light of that data, and of larger side effect profiles with the other two rubella vaccines, it was licensed in the United States in 1979 and replaced the rubella vaccine component that had been previously been used for Merck's MMR (measles, mumps, rubella) combination vaccine. Plotkin's vaccine has been used in the country ever since. In 2005 the CDC declared rubella eliminated from the United States, though the threat from imported cases remains. The World Health Organization declared the America free from rubella in 2015.

Groups that object to abortion have raised ethical questions about Plotkin's rubella vaccine (and other vaccines developed with similar human cell strains) over the years.

Because of its position on abortion, members of the Catholic Church have asked for its moral guidance on the use of vaccines developed using cell lines started with fetal cells. This includes the vaccine against rubella as well as those against chickenpox and hepatitis A, and some of the rabies and mumps vaccines. The official position according to the National Catholic Bioethics Center is that individuals should, when possible, use vaccines not developed with the use of these cell strains. However, in the case where the only vaccine available against a particular disease was developed using this approach, the NCBC notes:

> One is morally free to use the vaccine regardless of its historical association with abortion. The reason is that the risk to public health, if one chooses not to vaccinate, outweighs the legitimate concern about the origins of the vaccine. This is especially important for parents, who have a moral obligation to protect the life and health of their children and those around them.

The NCBC does note that Catholics should encourage pharmaceutical companies to develop future vaccines without the use of these cell strains. To address concerns about fetal cells remaining as actual *ingredients* of the vaccines, however, they specifically note that fetal cells were used only to begin the cell strains that were used in the preparation of the vaccine virus:

> Descendant cells are the medium in which these vaccines are prepared. The cell lines under consideration were begun using cells taken from one or more fetuses aborted almost 40 years ago. Since that time the cell lines have grown independently. It is important to note that descendant cells are not the cells of the aborted child. They never, themselves, formed a part of the victim's body.

In total only two fetuses, both obtained from abortions done by maternal choice, have given rise to cell strains used in vaccine development. Neither abortion was performed for the purpose of vaccine development.

Current Vaccines Developed Using Human Cell Strains

Two main human cell strains have been used to develop currently available vaccines, in each case with the original fetal cells in question obtained in the 1960s. The WI-38 cell strain was developed in 1961 in the United States, and the MRC-5 cell strain (also started with fetal lung cells) was developed in 1965 in the United Kingdom. No new or additional fetal cells are required in order to sustain the two cell strains.

The vaccines below were developed using either the WI-38 or the MRC-5 cell strains.

- Hepatitis A vaccines [VAQTA/Merck, Havrix/GlaxoSmithKline, and part of Twinrix/GlaxoSmithKline]
- Rubella vaccine [MERUVAX II/Merck, part of MMR II/Merck, and ProQuad/Merck]
- Varicella (chickenpox) vaccine [Varivax/Merck, and part of ProQuad/Merck]
- Zoster (shingles) vaccine [Zostavax/Merck]
- Adenovirus Type 4 and Type 7 oral vaccine [Barr Labs] *
- Rabies vaccine [IMOVAX/Sanofi Pasteur] *

** Vaccine not routinely given*

Several vaccines currently available in the United States were developed using animal cell lines, primarily using cells from African green monkeys. These include vaccines against Japanese encephalitis, rotavirus, polio, and smallpox. Of these, only rotavirus and polio vaccines are routinely given.

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Assessment Questions

What is a reason that growing influenza viruses in chicken eggs is not ideal?

A) Chickens don't get influenza.
B) Animal illness or bad weather can interrupt the supply of chicken eggs.
C) Viruses won't grow in chicken eggs.
D) None of the above.

True or false? An advantage of using human cell strains to grow vaccine viruses is avoiding the non-human viruses that may be found in non-human animal cells.

A) True
B) False

The first vaccine to be developed with the use of human cell strains was the _____ vaccine.

A) smallpox
B) yellow fever
C) measles
D) rubella

View Progress

Fetal Research
Hansen, John T;Sladek, John R, Jr
Science; Nov 10, 1989; 246, 4931; ProQuest Central
pg. 775

20. For simplicity, we adopt here a quasi-atomic picture for the resonant satellites of Cu. An alternate model is based is the "ligand-to-metal charge transfer" described, for example, in A. Fujimori, E. Takayama-Muromachi, Y. Uchida, *Solid State Commun.* **63**, 857 (1987), and in the reference therein.
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Fetal Research

JOHN T. HANSEN AND JOHN R. SLADEK, JR.

This article reviews some of the significant contributions of fetal research and fetal tissue research over the past 20 years. The benefits of fetal research include the development of vaccines, advances in prenatal diagnosis, detection of malformations, assessment of safe and effective medications, and the development of in utero surgical therapies. Fetal tissue research benefits vaccine development, assessment of risk factors and toxicity levels in drug production, development of cell lines, and provides a source of fetal cells for ongoing transplantation trials. Together, fetal research and fetal tissue research offer tremendous potential for the treatment of the fetus, neonate, and adult.

HUMAN DEVELOPMENT OCCURS IN TWO ENTIRELY DIFFERENT environments, one prenatal and the other postnatal. Prenatal development encompasses the embryonic and fetal periods, whereas postnatal development involves the passage through infancy, childhood, and adolescence to adulthood. These two environments could not be more different. The safe and nutritive environment of the womb predictably yields to the more hostile existence of life after birth. Nevertheless, the relatively short prenatal existence has always held a fascination for us as we marvel at the apparent recapitulation of our developmental history. Advances in scientific understanding now are at the point where the homunculus of our ancestors' imaginations has given way to an appreciation of the intricate patterning faithfully reproduced by our genetic blueprint. Our ability to intervene prenatally when nature's course deviates has long been limited to the physician's crude palpations and auscultations, methods woefully inadequate to diagnose, let alone treat, fetal problems. Only through persistent scientific inquiry, driven by our inherent curiosity about our development, have we now reached the threshold of prenatal diagnosis and treatment necessary to ensure the mother's safety or save an endangered life. The fetus, once a captive of its own environment, an enigma to be protected but left untreated, finally has gained the status of patient. Accordingly, fetal research itself enters an important new era.

In this article, we review some of the significant contributions of fetal research and fetal tissue research over the past 20 years. It is important to draw a distinction between fetal research, that is, research performed on the living fetus in utero, versus fetal tissue research that focuses on tissues or cells derived from the dead fetus, obtained as a result of spontaneous or induced abortion (*1*). By its very nature, scientific inquiry that involves fetal research or the use of fetal tissues often is obscured in the larger ethical, moral, and legal questions surrounding the use of fetuses, especially human fetuses, in research of any kind. These concerns are not trivial, for they strike at the heart of our moral dilemma regarding abortion, or the use of invasive procedures on a patient (the fetus) who can neither be informed nor grant consent. The resolution of these concerns and the answers to the ethical and legal questions will require honest, open dialogue from all aspects of society before, and if, a consensus is ever forthcoming. Our intent is not to debate whether fetal research should continue; rather, our focus will be on why fetal research and fetal tissue research are done at all, what procedures are feasible, and how this research benefits mankind.

Prenatal Diagnosis

Fetal research plays a vital role in the continued ability to diagnose a variety of fetal disorders, from genetic inborn errors in metabolism to congenital malformations (Table 1). Approximately 150,000 children in the United States alone, representing 3 to 5% of all live births each year, are born with congenital abnormalities (*2*). Ultrasonography, a noninvasive procedure that permits visualization of the fetus without apparent risk to fetus or mother, is one of the most important diagnostic advances available to the physician (*3*) and is used as an aid for the accurate guidance of instruments. Ultrasonography is also used to assess fetal movements and gross fetal malformations. For example, neurological defects such as anencephaly, spina bifida, and hydrocephalus can be diagnosed with ultrasonography. Heart defects, which occur on the order of 1% of all live births (*4*), and various obstructive disorders of the gastrointestinal

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or urinary tracts also may be visualized with this noninvasive approach.

In contrast, early diagnosis of inherited chromosomal abnormalities, fetal disease, and metabolic deficiencies require invasive intervention. Amniocentesis, the withdrawal of amniotic fluid, has dramatically changed the physician's ability to diagnose, counsel, and implement treatment (*5*). The assessment of chromosomal abnormalities, amniotic infections, fetal lung maturation, and the severity of hemolytic disease related to Rhesus (Rh) factors is now possible; however, most amniocentesis is used for cytogenetic studies (*6*). In addition to direct chromosomal analysis, recombinant DNA technology now makes it possible to diagnose a large number of genetic disorders. Presently, more than 4000 disorders in man are known or suspected of being due to a single gene mutation, and as many as 300 gene mutations in humans may be X-linked (*7, 8*). By means of recombinant technology, many gene mutations may be identified either directly or with the use of restriction fragment length polymorphisms (RFLP). Disorders such as Huntington's disease, Duchenne muscular dystrophy, sickle cell anemia, hemophilia, and cystic fibrosis have been diagnosed by the use of RFLP. Inborn errors in metabolism also may be assessed by culturing fetal cells suspended in the amniotic fluid sample and subjecting their resulting gene products to enzyme analysis assays. Although prenatal diagnosis of most inborn errors of metabolism are made by analyzing the gene product, several direct determinations of unique metabolites in the amniotic fluid sample are also possible (*9*). For example, hexosaminidase A, the deficient enzyme of the autosomal recessive disorder Tay-Sachs disease, can be diagnosed directly (*10*). Endocrine disorders such as adrenogenital syndrome are diagnosed during the prenatal period by direct assay for the elevated levels of 17α-hydroxyprogesterone in amniotic fluid (*5*). Amniocentesis also is a vital diagnostic procedure for the detection of neural tube defects, such as spina bifida, encephalocele, and anencephaly. These neural tube defects, for example, affect about 1 to 2 in 1000 live-born infants in the United States and Canada (*6*). These defects result from the failure of the embryonic neural tube to close, and their diagnosis relies on the determination of elevated levels of α-fetoprotein, a glycoprotein normally found in fetal serum (*9*). The α-fetoprotein leaks through the membrane covering such neural tube defects and accumulates in the amniotic fluid and maternal serum (*6*).

One significant drawback of amniocentesis is that it usually is not performed before 15 or 16 weeks gestation, and any final diagnosis dependent on cell culture must be delayed an additional 2 to 3 weeks (*3, 6, 9*). Moreover, the rate of pregnancy loss relating to amniocentesis is approximately 0.5% in the United States (*11*). Earlier diagnosis of chromosomal abnormalities is possible by using ultrasound-guided chorionic villus sampling, which may be performed as early as 8 weeks gestation. Chorionic villus sampling, although valuable for gathering karyotyping data at earlier gestational ages, does pose a slightly higher risk of fetal loss than amniocentesis (*12*).

Fetoscopy, that is, percutaneous transabdominal uterine endoscopy, provides additional advantages for prenatal diagnosis. Anatomical malformations may be directly visualized, and fetoscopy may be used to obtain blood or tissue biopsy samples (*6, 9*). Since 1983, a newer sampling procedure for obtaining fetal blood samples, called percutaneous umbilical blood sampling (PUBS), has proved valuable for diagnosing fetal hemolytic disease and a number of genetic disorders (*13*). During PUBS, an ultrasonographically guided needle is inserted directly into an umbilical vessel to withdraw a fetal blood sample. The procedure may be performed on an outpatient basis, does not require maternal sedation, and is safer for the fetus than fetoscopy (*13*). Nevertheless, PUBS is still considered an experimental procedure and should only be performed at selected medical centers (*13*). Procedures that involve collecting amniotic fluid, blood, urine, or other body fluids are used to diagnose almost 100 genetic diseases that result from single gene mutations (*8*). Tissue biopsies are especially valuable in prenatal diagnoses when chorionic villus sampling or amniocentesis results are equivocal, and for gathering information about multifactorial inherited congenital anomalies not easily or readily diagnosed by chromosomal or biochemical abnormalities present in the amniotic or other fetal fluid samples (Table 2).

Table 1. Examples of noninvasive and invasive procedures used to diagnose or treat fetal disorders. Details are provided in (*3, 6, 9, 47*).

Noninvasive	Invasive
Patient history	Amniocentesis
Uterine size	Chorionic villus sampling
Fetal activity	Percutaneous umbilical blood sampling
Fetal heart rate	Fetoscopy
Ultrasonography	Blood or tissue biopsies
Estimate age	Structural abnormalities
Evaluate growth	Fetal therapy
Detect gross malformations	Blood transfusions
Determine multiple gestation	Drug administration
Determine sex	Surgical intervention
	Fetal cell transplants

Diagnostic procedures such as those described above are possible because of technical advances developed from fetal research. Refinements of these procedures are first developed in suitable lamb or nonhuman primate animal models and then judiciously introduced into the clinical setting (*9*). Additionally, a number of biopsy procedures are being developed and perfected. For example, blood, skin, or liver may be biopsied by the use of fetoscopy. About 100 enzyme deficiency disorders can be diagnosed from cultured fibroblasts, and another 100 deficiencies are diagnosed from specific cell types obtained from fetal tissue biopsies (*8*). However, before these invasive procedures become standard clinical practice, they must be carefully tested for their safety and effectiveness in clinical volunteers. To illustrate this point, some enzyme deficiencies can only be diagnosed from fetal liver cells. Needle biopsies of the fetal liver are possible, but questions concerning liver damage, intraperitoneal bleeding, or fetal injury surround this procedure. The answers to these questions were obtained by experimenting with fetal liver biopsy procedures on fetuses of patients undergoing second-trimester abortions (*9*). The biopsy procedures were successful. Consequently, enzyme deficiencies such as glucose-6-phosphate deficiency, which occurs in von Gierke's disease and is related to the liver's ability to store glycogen, may now be diagnosed (*9*). Similarly, several rare enzyme deficiencies of the urea cycle, for example, carbamyl-phosphate synthetase and ornithine transcarbamylase, may be diagnosed from fetal liver biopsies (*14*).

Research on the fetus is essential before diagnosed disorders can be treated. The efficacy of vaccines, such as the rubella vaccine for the prevention of German measles, or the titration of drugs can only be tested in pregnant women. The fetus is not an innocent bystander if maternal treatment necessitates medical intervention. Virtually all commonly used drugs with the possible exception of insulin, heparin, dextrose, and thyroxine pass through the placenta to varying degrees (*15*). Therefore, the safety of medications such as hormones, diuretics, anticonvulsants, anesthetics, and analgesics must be tested first in utero to determine their effect on the fetus. Moreover, fetal disorders such as cardiac arrhythmias are responsive to antiarrhythmic drugs such as digitalis and may be treated directly while in utero (*9, 16*). In instances where substances do not cross the placenta, or do so poorly and at low levels, medications or nutritional supplements may be administered directly into the amniotic fluid

Table 2. Diagnostic and therapeutic benefits and application of fetal research and fetal tissue research. A more complete listing of specific benefits and applications may be found in (*1, 3, 47, 48*).

Fetal research	Fetal tissue research
Amniocentesis	Cell growth—normal and abnormal
Blood transfusions	Cell line development
Chorionic villus sampling	Cell plasticity
Drug therapy	Drug testing
Fetoscopy	Fetal cell transplantation
Percutaneous umbilical artery sampling	Immunology
Pregnancy management	Karyotyping studies
Ultrasonography	Vaccine development
Ventriculoamniotic shunts	
Vesicoamniotic shunts	

where oral ingestion and gastrointestinal absorption by the fetus can occur.

Surgical Intervention

For those disorders affecting a single organ system or resulting from an isolated congenital malformation, unencumbered by multifactorially inherited abnormalities, surgical intervention may provide the most promising prognosis. Obstructive hydrocephalus and urethral obstruction are among several anatomical malformations amenable to surgical intervention in utero.

Obstructive hydrocephalus, a condition that occurs with an incidence of about 5 to 25 per 10,000 births and is characterized by dilation of the brain's ventricular system due to the obstruction of the normal cerebrospinal fluid (CSF) pathways, leads to significant brain compression and neurologic dysfunction. The surgical insertion of a ventriculoamniotic shunt with a one-way valve that permits the release of CSF into the amniotic fluid offers one possibility for decompressing the brain (*17*). Obstructive uropathy and the resulting damage to the developing kidney also may be corrected by the surgical placement of a suprapubic drainage catheter. The catheter is guided into the distended fetal urinary bladder by the aid of sonography, and the accumulated urine is drained into the amniotic fluid (*18*). These surgical procedures, and others still under development, were made possible because suitable animal models were available (*19*). This experimentation is difficult because only larger animal species such as rabbits, lambs, or nonhuman primates can be used. The animal models for obstructive disorders such as those discussed above mimic the clinical condition and replicate closely the human pathophysiology. The monkey is particularly useful for these studies because, like humans, the pregnant monkey uterus is susceptible to premature labor and late gestational miscarriage (*9*). However, suitable animal models for most human genetic and metabolic disorders do not exist.

The Future of Fetal Research

The benefits of fetal research include (i) the development of vaccines, (ii) advances in prenatal diagnosis, (iii) detection of anatomical malformations, (iv) assessment of safe and effective medications, and (v) the development and refinement of in utero surgical therapies. Animal models have been essential in the advancement of most of these applications and are vital for determining potential risks before clinical applications. Frequently, appropriate animal models are not available or are inadequate for risk assessment. In these instances clinical fetal research becomes important; many diseases and malformations occur during fetal development and if the problems can be addressed early, often before birth, the neonate stands a much better chance of living a normal life. Current federal regulations limit fetal research to only those procedures that pose "minimal risk" to the fetus or that can be of direct therapeutic benefit to an endangered fetus (*1*). Perhaps, until we fully explore the ethical issues surrounding fetal research, this is an appropriate standard. Nevertheless, advances continue to be made in laboratory animal experiments and in countries where the potential benefits of clinical fetal research are regarded as outweighing the potential erosion of ethical standards (*20*). Clearly, there has been a decline in the number of investigators willing to face criticism consequent to conducting clinical fetal resarch in spite of the potential benefits generated by such studies (*1*). Thus, fetal research at present appears to have plateaued and may advance only slowly until the larger questions affecting social responsibility are addressed.

Fetal Tissue Research

Fetal tissue research differs from fetal research in that it involves studies on fetal cells rather than on living fetuses. Fetal tissue research has benefited a number of biomedical areas by providing cell lines to study gene regulation, pattern formation during embryogenesis, and model systems for cell interaction and function. Vaccines, such as the polio vaccine, have been developed in fetal tissues, and a variety of studies on cell growth and regulation have led to an understanding of chromosomal abnormalities, cancer and tumorigenesis, and cellular immunology (Table 2). These advances are possible because of some of the unique characteristics of fetal cells. They have the ability to rapidly divide and grow in culture, are pluripotent with respect to their developmental lineage, may be cryopreserved and subsequently reanimated, have lower antigenicity, and will survive and grow if transplanted into a supportive host environment.

Fetal cells are used to establish cell lines that provide model systems with which to study events in cell differentiation and growth. In vitro and in vivo analyses of stem cell lineages are instrumental in helping researchers better understand complex cell interactions during normal and abnormal fetal development (*21*). The process of culturing and growing fetal cells has been used by molecular biologists to understand gene regulation, protein synthesis, and other cellular mechanisms. Genetic engineering experiments have advanced to the point where investigators can now immortalize cells and develop gene constructs that can be used to design cells that express specific functional or secretory activities (*22*). Additionally, fetal cells are used to replicate human viruses that may be used to develop and test vaccines (*23*). The rapidly dividing fetal cells of the central nervous system are used to test their susceptibility to the acquired immunodeficiency syndrome (AIDS) virus, studies crucial for determining the rate of infection of fetal cells to maternally transmitted AIDS (*24*). Finally, fetal cells are used to screen new pharmaceutical agents to determine their risk as teratogens or carcinogens. These experiments are essential before clinical trials may be undertaken. One need only recall the thalidomide episode of the 1960s as a grim reminder of the value of careful fetal screening before patient use. Maternal intake of the sedative thalidomide early in pregnancy, as reported in Germany and England, led to an unusually high incidence of limb-reduction deformities (*25*). Once thalidomide was recognized as the causative agent, it was withdrawn from the market, but not before an estimated 3000 malformed infants were born (*26*).

One of the more exciting and promising applications of fetal

tissue research has been the use of fetal cells as therapeutic tools to treat clinical disorders. In one such instance, fetal cells were used to treat another fetus in utero. In June 1988, French physicians Jean-Louis Touraine, an immunologist, and obstetrician Daniel Raudrant treated a 30-week-old fetus diagnosed with a rare, and nearly always fatal, immune deficiency disease (bare lymphocyte syndrome) by injecting immune cells from the thymus and liver of two aborted fetuses into the umbilical cord of the deficient fetus (*27*). This daring clinical experiment was based on the results of animal studies that demonstrated that second trimester fetal liver contains a rich source of hematopoietic stem cells (*28*). At this stage, the donor fetus immune system is not yet developed, so normally histoincompatible stem cells may be transplanted into the immunodeficient host fetus to establish a viable population of reconstituted T cells (*29*). After the birth of this infant, a second injection of cells was given; subsequent blood tests suggest that some of the cells have seeded and multiplied in the infant's spleen, liver, and bone marrow. Although there is hope that this infant will develop a normal immune system, the prognosis is still guarded.

Fetal cells are also being examined in animal studies and clinical trials for their potential to reverse insulin-deficient diabetes mellitus, a disease that affects millions of people worldwide, including an estimated 11 million in the United States (*30*). Animal experiments demonstrate that if fetal pancreas is transplanted before the differentiation of the problematic exocrine cells (which produce the lytic digestive enzymes), subsequent development of the islet cells necessary for insulin production will occur (*31*). However, one limitation for the success of fetal pancreatic transplants has been the presence of significant quantities of immunogenetic lymphoid tissue in the pancreas. Selective cell culturing before transplantation of the pancreas has been successful in removing most of the immunogenetic cells (*32*). If this approach ultimately proves successful, it will be an important advance in this field of transplantation because immunosuppression to avoid graft rejection is undesirable in diabetics who already are at increased risk for infection. Cell transplant efforts such as this highlight the benefits of using fetal cells: their ability to survive and multiply necessitates the grafting of only small numbers of cells; their lower or absent antigenicity eliminates the requirement of tissue matching and immunosuppression; and they are adaptable to the host environment. Although fetal islet cell transplantation is still experimental, initial clinical trials suggest that some patients who have received grafts can produce their own insulin, thus decreasing their requirement of daily exogenous insulin (*33*). However, these results are not universal and a number of questions remain (*34*).

Nowhere else is the revolutionary idea of fetal cell transplantation as a therapeutic tool more evident than as a treatment for neurodegenerative disorders such as parkinsonism or Alzheimer's disease. Because these diseases are progressive and affect millions of people in the United States alone, medical researchers have explored the feasibility of grafted fetal nerve cells to restore damaged neural circuits. The economic impact of these neurodegenerative diseases is significant when one considers the lost productivity, forced early retirement, and costs of therapy and nursing care.

The field of neural transplantation has a long and varied history, but its full potential perhaps was revealed as a result of pioneering studies by Olson and colleagues (*35*). These investigators demonstrated that the anterior eye chamber provided a nutritive and immunologically "privileged site" for the transplantation of cells. Moreover, subsequent experiments showed that grafted neurons could reinnervate a previously denervated target (*36*). However, adult neurons do not divide and, once damaged or lost, cannot be replenished from endogenous sources. Because of this, grafts of fetal neurons were investigated and found to be capable of partially reestablishing damaged neural circuits (*37*). Not only could fetal cells survive and establish neural contacts, but they also had the ability to synthesize and release appropriate transmitter substances (*38*). Additionally, implanted fetal nerve cells could ameliorate specific cognitive (*39*), neuroendocrine (*40*), and motor deficits (*41*). Virtually every region of the central nervous system, from the olfactory neuroepithelium to the spinal cord, can be grafted, with minimal immunological consequence (*35*).

Although a variety of animal models of neurodegenerative disorders are used by transplant neurobiologists, the nonhuman primate model of Parkinson's disease has provided the greatest incentive for fetal grafting experiments. The selective neurotoxin *N*-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) administered to monkeys produces a parkinsonian-like syndrome characterized by rigidity, resting tremor, progressive akinesia, flexed posture, and episodes of freezing during movement (*42*). Moreover, MPTP rather selectively affects the dopaminergic cells of a brainstem region known as the substantia nigra, causing their degeneration in a manner that anatomically and physiologically mimics human parkinsonism (*43*). The loss of the neurotransmitter dopamine from these neurons, which project to target neurons in a large subcortical region termed the striatum, appears responsible for the movement disorders of parkinsonism. Many Parkinson's disease patients, therefore, benefit from the administration of the drug L-dopa, a dopamine precursor, which is converted to dopamine in the brain to replenish the dopamine deficient striatum.

However, L-dopa therapy is ineffective in a large percentage of patients, and other patients progressively become refractory to the drug over a period of 5 to 10 years. Because few pharmacologic options remain for these patients, neural grafting of dopamine-producing cells has been considered as one alternative. Initial studies in rodents with grafted fetal tissue from the mesencephalon brain region giving rise to dopaminergic neurons of the substantia nigra were promising (*41*). The use of fetal dopaminergic neurons appeared obvious because one could replace degenerating cells in the host with cells of like origin that presumably carry the correct genetic programs for dopamine synthesis, cell growth, connectivity, transmitter release, and receptivity.

Subsequent experiments by Redmond and colleagues (*43*) in African Green monkeys that were rendered parkinsonian by MPTP administration confirmed earlier rodent studies and demonstrated the efficacy of fetal nerve cell transplantation in nonhuman primates. Seven and one-half months after transplantation of fetal nigral neurons, these investigators observed significant behavioral improvement, as well as dopamine neuron survival and increased levels of dopamine in the host striatum. The implanted neurons appeared integrated with the host, extending numerous small fibers into the adjacent neural parenchyma. Long-term studies and experiments to determine the specificity of fiber sprouting from the implanted neurons are not yet completed, so caution is warranted (*44*). Nevertheless, current scientific wisdom suggests that fetal dopaminergic neurons presently may be the best tissue source to graft in parkinsonian patients, usurping the use of the adrenal medullary autografts, which exhibit very poor survival in monkeys (*45*) and have minimal effects as used presently in humans (*46*). Several centers around the world, including two in the United States, have already performed human fetal nigral grafts in patients with Parkinson's disease. It is still too early to objectively assess the results.

The Future of Fetal Tissue Research

The benefits of studying fetal cells are many, and the clinical potential for their use as therapeutic tools is just now being realized

(Table 2). Vaccine development, study of human viruses and the development of specific therapies for the treatment of infections such as AIDS, the assessment of risk factors and toxicity levels in drug production, and the initiation of transplantation trials are important and necessary contributions of fetal cell research to biomedical science (*1*). Ongoing animal experiments and a source of human fetal cells are critical for studying fatal blood diseases (sickle-cell anemia, aplastic anemia, and leukemia), or for addressing nervous system disorders including optic nerve damage, degenerative disorders of the brain, and spinal cord damage. On the horizon lies the potential to reverse insulin-deficient diabetes and immunodeficiency disorders and to address cognitive dysfunctions. Current federal and state regulations permit the use of fetal tissues and cells obtained from dead fetuses, and all 50 states have adopted the Uniform Anatomical Gift Act, which sustains this essential need for continued research to advance our scientific knowledge and biomedical applications (*1*). Such advances have brought us to the point where we no longer stand by helplessly in the face of fetal malformations, nor are we left impotent to respond to treatable disorders. With a growing ability to diagnose and treat, with a new-found knowledge to shape and direct developmental events, and with an awareness of how to replace and restore that which is old, we must remain cognizant of the delicate interplay between responsible moral behavior and the desire to maintain and improve the quality of human life.

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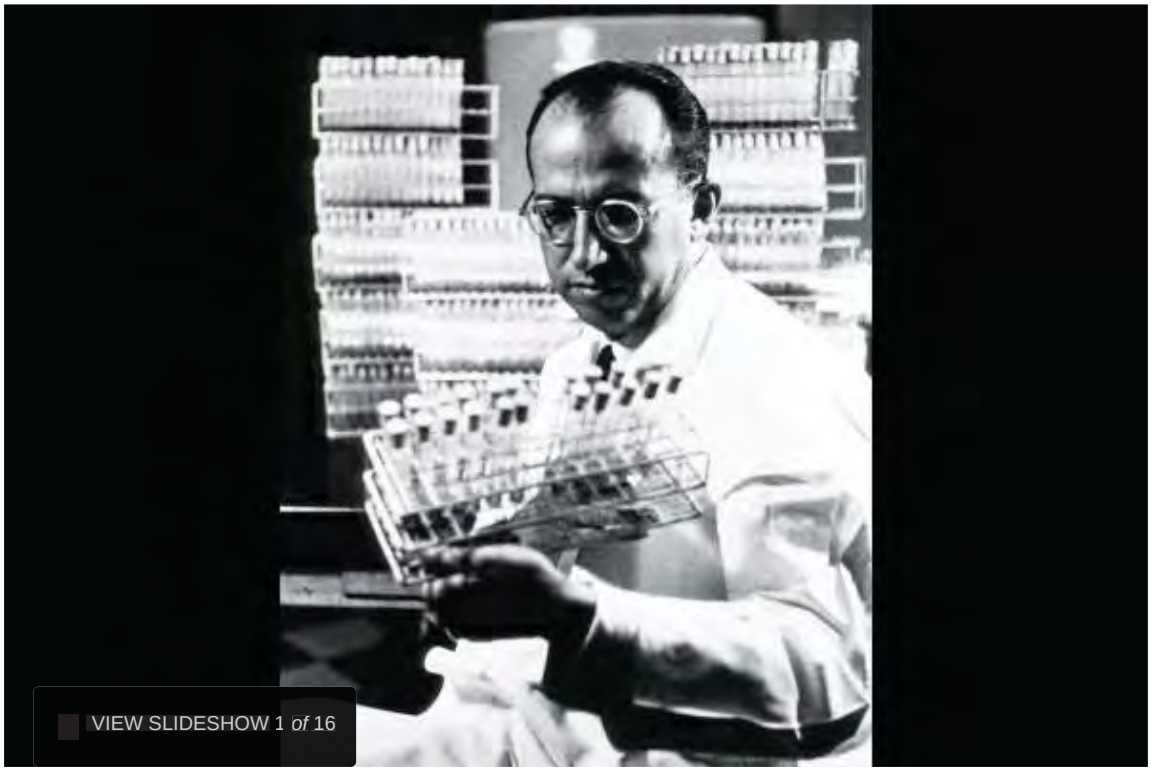
Wiping Out Polio: How The U.S. Snuffed Out A Killer

By JASON BEAUBIEN • OCT 15, 2012



On April 12, 1955, Dr. Jonas Salk and his research team at the University of Pittsburgh released the first successful vaccine for polio. In 1979, the U.S. reported its last case of the paralyzing virus.

COURTESY OF IMAGES FROM THE HISTORY OF MEDICINE (NLM).

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Sixty years ago, polio was one of the most feared diseases in the U.S.

As the weather warmed up each year, panic over polio intensified. Late summer was dubbed "polio season." Public swimming pools were shut down. Movie theaters urged patrons not to sit too close together to avoid spreading the disease. Insurance companies started selling polio insurance for newborns.

The fear was well grounded. By the 1950s, polio had become one of the most serious communicable diseases among children in the United States.

In 1952 alone, nearly 60,000 children were infected with the virus; thousands were paralyzed, and more than 3,000 died. Hospitals set up special units with iron lung machines to keep polio victims alive. Rich kids as well as poor were left paralyzed.

Then in 1955, the U.S. began widespread vaccinations. By 1979, the virus had been completely eliminated across the country.

Now polio is on the verge of being eliminated from the world. The virus remains endemic in only two parts of the globe: northern Nigeria and the border between Afghanistan and Pakistan.

Throughout this week, we'll be reporting on the fight to eradicate the last few pockets of polio. We kick off with a look back at how the U.S. and the rest of the world wiped out the virus for good.

The first major polio epidemic in the United States hit Vermont in 1894 with 132 cases. A larger outbreak struck New York City in 1916, with more than 27,000 cases and 6,000 deaths. As the number of polio cases grew, the paralytic disease changed the way Americans looked at public health and disability.

Franklin D. Roosevelt contracted polio 12 years before he became president. Roosevelt concealed the extent to which he suffered from polio, but he acknowledged having it. His presidency put polio front and center on the national stage. In 1938, Roosevelt founded the National Foundation for Infantile Paralysis and spearheaded the March of Dimes for polio research. In 1946, President Harry Truman declared polio a threat to the United States and called on Americans to do everything possible to combat it.

"The fight against infantile paralysis cannot be a local war," Truman declared in a speech broadcast from the White House. "It must be nationwide. It must be total war in every city, town and village throughout the land. For only with a united front can we ever hope to win any war."

"Polio was a fear of parents throughout this country," says Dr. John L. Sever, recalling his childhood in Chicago. He later helped launch the Rotary International's global drive against polio.

Early attempts to develop a vaccine ran into numerous hurdles. A vaccine tested on 10,000 children by two researchers at New York University provided no immunity and left nine children dead. Other vaccine trials used "volunteers" at mental institutions.

At the University of Pittsburgh, Jonas Salk launched what was then the largest human trial in history, injecting nearly 2 million American kids with a potential vaccine. When it was announced that his vaccine worked, Salk was hailed as a humanitarian hero.

Famed CBS newsman Edward R. Murrow asked Salk who owned the patent to his vaccine. The scientist replied: "There is no patent. Could you patent the sun?"

The battle of science against disease, however, wasn't as smooth and simple as movie house newsreels from the time depicted it. At one point, a botched batch of vaccine paralyzed and even killed some of the recipients.

Salk's main rival in the vaccine race, Albert Sabin at Cincinnati Children's Hospital, couldn't gain political support in the U.S. for what he viewed as his superior vaccine. So at the height of the Cold War, he tested it in the Soviet Union instead.

Both Salk's and Sabin's vaccines are still used today. But Sabin's version, which requires just two drops in a child's mouth, proved much easier to use in mass immunization campaigns.

Sever says this oral vaccine was key to wiping out polio in the developing world: "After all, if you could count to two, you could be an immunizer."

The U.S. recorded its last case of polio in 1979, among isolated Amish communities in

several states. Then the effort to eradicate polio globally began in earnest. The Western Hemisphere reported its last case, in Peru, in 1991.

In 1988, the World Health Organization set a new goal: eliminate polio. Since then, international institutions have poured billions of dollars into the eradication effort. They're getting very close to their target: So far this year, there have been fewer than 200 polio cases globally.

But the intensive immunization efforts against polio right now can't let up at all, warns Joel Breman at the National Institutes of Health.

"We've seen what can happen when there's any break in the chain," Breman says. "In 2003 and 2004, northern Nigeria stopped vaccinating, even though they had endemic transmission. And boom! Twenty-one other countries that claimed and had proven to have eliminated polio became reinfected all over."

Transcript

ROBERT SIEGEL, HOST:

From NPR News, this is ALL THINGS CONSIDERED. I'm Robert Siegel.

MELISSA BLOCK, HOST:

And I'm Melissa Block.

Polio was once one of the most feared diseases in America. Now it's on the verge of eradication. Cases of the paralytic disease, which is spread mainly through infected feces, have dropped from hundreds of thousands a year in the 1950s to just a few hundred today. And the virus remains endemic in only two parts of the world - northern Nigeria and the Afghanistan/Pakistan border. Now the decades-long fight against polio has reached what public health officials hope is a final showdown.

For our series Chasing Down Polio, NPR's Jason Beaubien looks back at that fight and the vaccines that helps turn the tide.

JASON BEAUBIEN, BYLINE: Polio been around for centuries. But it gained momentum in the early part of the 20th century. The first major polio epidemic in the United States hit Vermont in 1894. A larger outbreak struck New York City in 1916. As the number of polio cases grew, the paralytic disease changed the way Americans looked at public health and disability.

In 1921 Franklin Delano Roosevelt contracted polio. Twelve years later, he was inaugurated as president.

PRESIDENT FRANKLIN DELANO ROOSEVELT: I, Franklin Delano Roosevelt, do solemnly swear that I will faithfully execute the office of president of the United States...

BEAUBIEN: FDR concealed the extent to which he suffered from polio but he acknowledged having it. His presidency put polio front and center on the national stage. In 1938, Roosevelt founded the National Foundation for Infantile Paralysis and he spearheaded the March of Dimes for polio research. Tens of thousands of people all across the country were being paralyzed each year by the disease. Special hospital wards were set up with iron lungs to keep polio victims alive.

In the wake of World War II, President Harry Truman declared polio a threat to the United States and called on Americans to do everything possible to combat it.

(SOUNDBITE OF ARCHIVED SPEECH)

PRESIDENT HARRY TRUMAN: The fight against infantile paralysis cannot be a local war, it must be nationwide. It must be total for every city, town, and village throughout the land. For only with a united front can we ever hope to win any war.

BEAUBIEN: By the early 1950's polio was a leading killer of American kids. Dr. John L. Sever spent decades working as part of Rotary International's global campaign against polio. Sever remembers when he was growing up in Chicago how terrified people were of the disease.

DR. JOHN L. SEVER: It was really feared.

BEAUBIEN: Rich kids as well as poor were being left paralyzed. Late summer was dubbed polio season. Public swimming pools were shutdown, insurance companies even sold polio insurance for newborns.

SEVER: The fear of having your child get this and being paralyzed for life, possibly dying of polio, was a fear of parents throughout this country.

BEAUBIEN: Early attempts to develop a vaccine against ran into numerous hurdles. A vaccine tested on 10,000 kids by two researchers at New York University provided no immunity and left nine children dead. Other vaccine trials injected volunteers at mental institutions with potential polio vaccines. Scientists were struggling to cultivate the virus in laboratory settings.

Jonas Salk, from the University of Pittsburg, launched what was then the largest human vaccine trial in history, involving nearly two million American kids.

(SOUNDBITE OF A NEWSREEL)

UNIDENTIFIED MAN: Nineteen fifty-five, a year of anxiety and triumphs. A major medical hurdle was crossed with the discovery by Dr. Jonas Salk of the Anti-Polio Vaccine, which was to spread a mantel of protection over millions of American children.

BEAUBIEN: Salk was hailed as a humanitarian hero. Famed CBS newsman Edward R. Murrow asked Salk who owned the patent to his miraculous vaccine. Salk replied, there is no patent. Could you patent the sun?

The battle of science versus disease, however, wasn't as smooth and as simple as newsreels from the time depicted it. A production mistake at a lab producing Salk's vaccine exposed thousands of children to the live polio virus, paralyzing dozens of them and killing five. Salk's main rival in the vaccine race, Albert Sabin, at Cincinnati Children's Hospital, had to go to the Soviet Union at the height of the Cold War to test his polio vaccine.

Both Salk and Sabin's vaccines are still used today but Sabin's version, which requires just two drops in a child's mouth, proved much easier to use in mass immunization campaigns. And Sever, with Rotary International, says the simplicity of Sabin's oral vaccine was key to wiping out the disease in much of the developing world.

SEVER: After all, if you could count to two, you could be an immunizer.

(LAUGHTER)

BEAUBIEN: The last U.S. cases of polio occurred in 1979 among isolated Amish communities in several states. And then efforts to eradicate polio globally began in earnest.

CIRO DE QUADROS: Yeah, my name is Ciro de Quadros and I'm the executive vice president of the Sabin Vaccine Institute here in Washington, D.C.

BEAUBIEN: De Quadros led the World Health Organization's drive in the 1980s to eliminate polio from the Americas. And the last case in the Western Hemisphere was reported in Peru in 1991. De Quadros also led the campaign to wipe out smallpox. He says smallpox was easier to tackle.

QUADROS: You know, smallpox was a disease that you could see in the face of the people. You don't need to have a sophisticated laboratory, you know, and transport of specimens here and there. Then you had a vaccine which was heat stable. You could put your vaccine in the pocket and go around and vaccinate.

BEAUBIEN: Polio, on the other hand, can be a complicated diagnosis. The polio vaccine isn't nearly as effective as the one for smallpox. And it needs to be kept refrigerated or it's useless.

QUADROS: Polio vaccine, you know, is a vaccine that has interference with other enteroviruses in the environment, so that you need to give several doses, you know, until you reach a good level of immunity. You need to repeat that again, again and again, both in the routine (unintelligible) and through mass campaigns. And you can imagine that it's totally different than the smallpox.

BEAUBIEN: Smallpox was declared eradicated in 1980. In 1988, the World Health Organization set a new goal of doing the same to polio by the year 2000. That target obviously was missed. Groups such as UNICEF, the World Health Organization, the Bill and Melinda Gates Foundation, and Rotary International have poured billions of dollars into the effort to rid the world of polio and the are very close to their goal. So far this year, there have been fewer than 200 polio cases globally.

Joel Breman, at the National Institutes of Health, however warns that the intensive immunization efforts against polio right now can't let up at all.

JOEL BREMAN: We've seen what can happen when there's any break in the chain. About 2003 and '04, northern Nigeria stopped vaccinating even though they had endemic transmission - and boom, 21 other countries that had proven to have eliminated polio became re-infected all over.

BEAUBIEN: Nigeria, Afghanistan, and Pakistan are the only countries where polio still has a foothold. And the final history of this terrifying disease could hinge on whether the virus can be eradicated in one of Africa's most chaotic nations.

Jason Beaubien, NPR News. Transcript provided by NPR, Copyright NPR.

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Commentary

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The United States Revised Uniform Anatomical Gift Act (2006): New challenges to balancing patient rights and physician responsibilities

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Abstract

Advance health care directives and informed consent remain the cornerstones of patients' right to self-determination regarding medical care and preferences at the end-of-life. However, the effectiveness and clinical applicability of advance health care directives to decision-making on the use of life support systems at the end-of-life is questionable. The Uniform Anatomical Gift Act (UAGA) has been revised in 2006 to permit the use of life support systems at or near death for the purpose of maximizing procurement opportunities of organs medically suitable for transplantation. Some states have enacted the Revised UAGA (2006) and a few of those have included amendments while attempting to preserve the uniformity of the revised Act. Other states have introduced the Revised UAGA (2006) for legislation and remaining states are likely to follow soon.

The Revised UAGA (2006) poses challenges to the Patient Self Determination Act (PSDA) embodied in advance health care directives and individual expression about the use of life support systems at the end-of-life. The challenges are predicated on the UAGA revising the default choice to *presumption of donation intent* and the use of life support systems to ensure medical suitability of organs for transplantation. The default choice trumps the expressed intent in an individual's advance health care directive to withhold and/or withdraw life support systems at the end-of-life. The Revised UAGA (2006) overrides advance directives on utilitarian grounds, which is a serious ethical challenge to society. The subtle progression of the Revised UAGA (2006) towards the presumption about how to dispose of one's organs at death can pave the way for an affirmative "duty to donate". There are at least two steps required to resolve these challenges. First, physicians and hospitals must fulfill their responsibilities to educate patients on the new legislations and document their preferences about the use of life support systems for organ donation at the end-of-life. Second, a broad based societal discussion must be initiated to decide if the Revised UAGA (2006) infringes on the PSDA and the individual's right of autonomy. The discussion should also address other ethical concerns raised by the Revised UAGA (2006), including the moral stance on 1) the interpretation of the refusal of life support systems as not applicable to organ donation and 2) the disregarding of the diversity of cultural beliefs about end-of-life in a pluralistic society.

Background

In 1990, the U.S. Congress passed the Patient Self-Determination Act (PSDA) reinforcing individuals' rights to determine their final health care. The PSDA became effective in 1991 so that patients can make decisions about their medical care and specify whether they want to accept or refuse specific medical care [1]. Patients' wishes can be clearly documented at an earlier point of time in advance health care directives and/or patients can identify legally authorized representatives to make health care decisions (power-of-attorney for health care) on their behalf in the event of an incapacitating illness.

The PSDA requires Medicare and Medicaid providers, including hospitals, to give adult individuals, at the time of inpatient admission, certain information about their rights under state laws governing advance health care directives, including: (1) the right to participate in and direct their own health care decisions; (2) the right to accept or refuse medical or surgical treatment; (3) the right to prepare advance health care directives and (4) information on the provider's policies governing the utilization of these rights [2].

Scope of advance health care directives

Almost 16 years later, advance health care directives and power-of-attorney for health care still play a limited, yet important, role in assisting with health care decisions about the use of life support systems and medical technologies at the end-of-life [3]. About 21% of critically ill patients admitted to intensive care units for life support systems at the end-of-life have formal advance health care directives [4].

Criticisms have been rightfully expressed concerning the current deficiencies of construction, documentation, accessibility and applicability of advance health care directives [5]. The main reasons limiting the applicability of advance health care directives include: 1) physicians' uncertainties about diagnosis, treatment efficacy, and prognosis and 2) lack of knowledge, insight, and courage of persons authorized as power-of-attorney for health care to fulfill their assigned roles. These shortfalls raise concerns about the effectiveness of advance health care directives to prepare patients and families for uncertain and difficult decisions at the end-of-life [6]. To accommodate these concerns, advance care planning should be built on effective communication to individualize medical care and decision making despite future uncertainties. Advance care planning requires physicians to take time to discuss advance health care directives with patients and identify the specific circumstances in which care preferences should be followed [5].

Considering the above shortfalls, this commentary highlights additional and unique challenges posed by the Revised Uniform Anatomical Gift Act (UAGA) 2006 on advance health care planning and directives about the use of life support systems at the end-of-life [7]. Some states have already enacted the Revised UAGA (2006) and a few of those have included amendments while attempting to preserve the uniformity of the revised Act [8]. Other states have introduced the Revised UAGA (2006) for legislation and remaining states are likely to follow soon.

Scope of deceased organ donation

In 2006, the publication of two influential reports from the Institute of Medicine and National Conference on Donation After Cardiac Death opened a new era for deceased organ donation [9,10]. Traditionally, organs for transplantation have been donated by individuals who fulfilled strict criteria of neurologic or brain death and had already been on life support systems [11]. Organ donation after cardiac death applies to individuals who sustain death because of circulatory or cardiorespiratory arrest and without the requirement for antecedent neurologic or brain death criteria. The two reports conclude that donation after cardiac death is an ethically acceptable form of organ donation. As of January 2007, federal regulations require Medicare-approved hospitals to design policies and procedures for donation after cardiac death from patients at or near death [12].

Scope of the Revised UAGA (2006)

The National Conference of Commissioners on Uniform State Laws (NCCUSL) promulgated the Revised UAGA (2006) with the substantial and active participation of the major stakeholders representing donors, recipients, physicians, procurement organizations, regulatory agencies and the US Department of Health & Human Services. The stakeholders represented a broad spectrum of organizations with special interest or advocacy for the practice of organ transplantation. The primary intent of revising the UAGA in 2006 was to solve the critical organ shortage by maximizing the likelihood of organ donation. To accomplish this objective, the Revised UAGA (2006) increases opportunities of organ procurement after cardiac death for transplantation [7]. The anatomical gifting of organs (heart, lungs, kidneys, liver, pancreases, small bowel, etc.) after cardiac death requires the initiation and/or continuation of life support systems at the end-of-life to ensure their medical suitability for transplantation.

The Revised UAGA (2006) reaffirms that if a donor has a document of gift, there is no reason to seek consent from the donor's family as they have no right to give it legally [7]. If an individual has not made a document of gift during life, the Revised UAGA (2006) presumes the intent to donate organs and, therefore, has expanded the list of per-

sons (in section 9a) who can consent to organ donation on behalf of that individual. The Revised UAGA (2006) considers that every individual has the right to donate his (her) organs at or near death. Finally, if an individual prefers not to donate, this must be documented in a signed, explicit refusal.

The Revised UAGA (2006) section 14 was drafted in accordance with the controlling federal law requiring hospitals to notify an organ procurement organization (OPO) of any individual whose death is imminent or who has died in-hospital to increase opportunities of organ procurement for transplantation [13]. In cases of potential organ donation, measures necessary to ensure the medical suitability of an organ for transplantation are administered to a patient who is dead or near death to allow time for determination if the patient could be a prospective donor. That provision applies to situations of sudden in-hospital or out-of-hospital cardiac death when resuscitation is unsuccessful [9]. Organ preservation requires the administration of life support systems until the OPO has determined if a patient can be a prospective donor. The Revised UAGA (2006), section 14(c), requires life support systems already administered to a patient who has been referred to the OPO for evaluation to be continued until it is determined that the patient has organs that are medically suitable for transplantation. This section applies to a patient who is already on life support systems either in the emergency department or intensive care unit at the end-of-life.

The Revised UAGA (2006), section 14, emphasizes the general direction in an advance health care directive or power-of-attorney for health care that the patient's wish *not to have life prolonged* by the administration of life support systems should *not* be construed as an expression of a contrary intent for the use of life support systems for donation purpose [7]. In effect, a patient on life support systems at the end-of-life (and without signed refusal) is defaulted to the presumption of intent to donate organs, and therefore life support systems cannot be withdrawn until the OPO's evaluation for organ donation is complete. The OPO can then determine that the patient *is* a prospective donor.

If determined to be a prospective donor, the Revised UAGA (2006), section 21, creates a default rule requiring that measures necessary to ensure the medical suitability of an organ for transplantation may not be withheld or withdrawn. The initiation and/or continuation of life support systems is the default rule and overrides a prospective donor's expression in an advance health care directive not to have life prolonged by life support systems. To resolve the tension between the presumed intent to donate organs and the expressed intent not to have life support systems administered merely to prolong life, section 21 presumes that for a prospective donor the desire to save lives by making an anatomical gift trumps the desire to have life support systems withheld or withdrawn. The Revised UAGA (2006) requires a prospective donor to expressly provide *contrary intent* to prevent the use of life support systems for organ donation purposes in either a declaration or advance health care directives.

In 2007, an amendment was introduced to the Revised UAGA (2006), section 21, to recognize the conflict between initiation and/or continuation of life support systems based on becoming a prospective donor and the expressed wishes of appropriate end-of-life care in advance health care directives. Section 21(b) (2007) requires the attending physician to resolve the conflict with the prospective donor or surrogate decision maker for clarification of intent and any contraindications for appropriate end-of-life care.

The Revised UAGA (2006) and advance health care directives

With the new UAGA legislation, advance health care planning should include education on the new requirement of the Revised UAGA (2006) about the use of life support systems for organ donation at the end-of-life. These changes are predicated on the UAGA revising the default choice to presumption of donation intent and, therefore, the requirement for life support systems to ensure medical suitability of organs for transplantation. Figure 1 summarizes how document of gift, advance health care directives, contrary intent declaration and refusal determine the pathway for withholding and/or withdrawal of life support systems at the end-of-life. Only a refusal and contrary intent declaration can permit the withholding and/or withdrawal of life support systems and the administration of appropriate end-of-life care as expressed in advance health care directives (figure 1).

Patients with documents of gift are considered donors irrespective of advance health care directives and they are required to comply with organ procurement protocols (figure 1). In the default pathway, (i.e. the absence of refusal and contrary intent declaration) life support systems are required, irrespective of advance health care directives, until the evaluation of medical suitability of organs for transplantation has been completed. Regardless of whether it is morally right to construe refusal of life support in an advance directive as not applicable for organ donation, the final authority of the OPO to determine donor's medical suitability raises additional normative ethical issues. Three factors can inflate the pool of prospective donors unpredictably: 1) the OPO can apply liberal criteria about medical suitability for donation because the definition of eligible donors is very broad

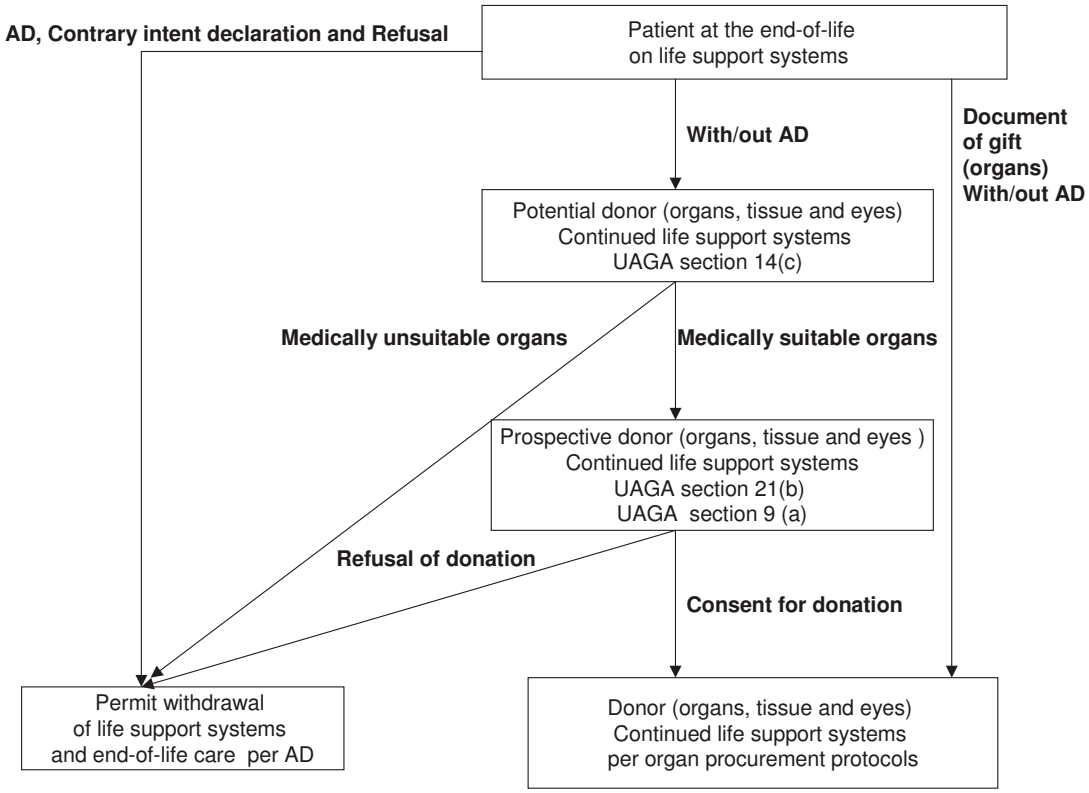

Figure 1
The revised Uniform Anatomical Gift Act (UAGA) 2006, advance health care directives (AD) and use of life support systems at the end-of-life. The UAGA (2006) Section 14(c) defaults a patient already on life support systems to the presumption of intent for organ donation (i.e. potential donor) and mandatory notification of organ procurement organization for evaluation. Life support systems cannot be withdrawn in a potential donor until organ procurement organization has completed the evaluation of medical suitability of organs for transplantation. If the organ procurement organization has determined that a potential donor has organs medically suitable for transplantation, the potential donor becomes a prospective donor. For a prospective donor, life support systems cannot be withheld or withdrawn. For a prospective donor, section 21(b) requires the attending physician to resolve the conflict between intent in advance health care directives to withhold and/or withdraw life support systems at the end-of-life verus their use for organ donation purpose. Section 9(a) expands the list of persons who can consult, on behalf of a prospective donor, with the attending physician to resolve the aforementioned conflict and provide donation consent (or refusal). Document of gift or donation consent permits the use of life support systems and organ procurement protocols on donors. If a potential donor has medically unsuitable organs, refusal of gift or contrary intent declaration to instruct the withholding and/or withdrawing of life support systems for organ donation purpose, life support systems can be withdrawn and end-of-life care is provided as expressed in advance health care directives.

[12], 2) the OPO has the discretion to offer for transplantation organs of marginal (inferior) quality that would be otherwise rejected [14], 3) the OPO's decisions and actions are defaulted to be "in good faith" and are the subject of immunity from criminal, civil and administrative liabilities [7]. Specific conditions such as overwhelming infections, disseminated malignancy and communicable infectious diseases are absolute exclusion criteria for organ donation. However, the majority of potential organ donors are unlikely to meet any of these specific exclusion criteria [15].

The laxity of criteria of medical suitability for donation is most disturbing to patients who become prospective donors without documents of gift and who have unequivocal advance health care directives expressing intent for

withholding and/or withdrawal of life support systems at the end-of-life (figure 1). Under such circumstances, the Revised UAGA (2006) requires the attending physician to address and resolve the conflict between the use of life support systems for donation purposes and appropriate end-of-life care with families and/or surrogate-decision makers while keeping the patient on life support systems.

The Revised UAGA (2006) and end-of-life care

In the endeavor to solve the critical organ shortage, the Revised UAGA (2006) has transformed the traditional 'altruistic' to a disturbing 'utilitarian' approach towards organ procurement for transplantation. National palliative and hospice care organizations [16,17] promoting excellence in end-of-life care should have been better represented as stakeholders when drafting the revised UAGA. As a consequence, the UAGA drafting committee was able to set aside the advancements in end-of-life care accomplished over the past decade [18,19]. While the drafting committee has refuted that the Revised UAGA (2006) was drafted to accomplish the goals of special interest groups [20], the Act undoubtedly has created unintended consequences jeopardizing the general public's interest and disregarding longstanding respect of individual autonomy and diversity of cultural beliefs about end-of-life in a pluralistic society. The premises underlying the subtle progression of the Revised UAGA (2006) towards the presumption about how to dispose of one's organs at or near death can pave the way for an affirmative "duty to donate" to the detriment of human liberty in a free society [21].

The Revised UAGA (2006) has not adopted presumed consent for organ procurement. Nevertheless, the most disturbing consequence of the Act is that patients will be forced to have life support systems initiated or continued

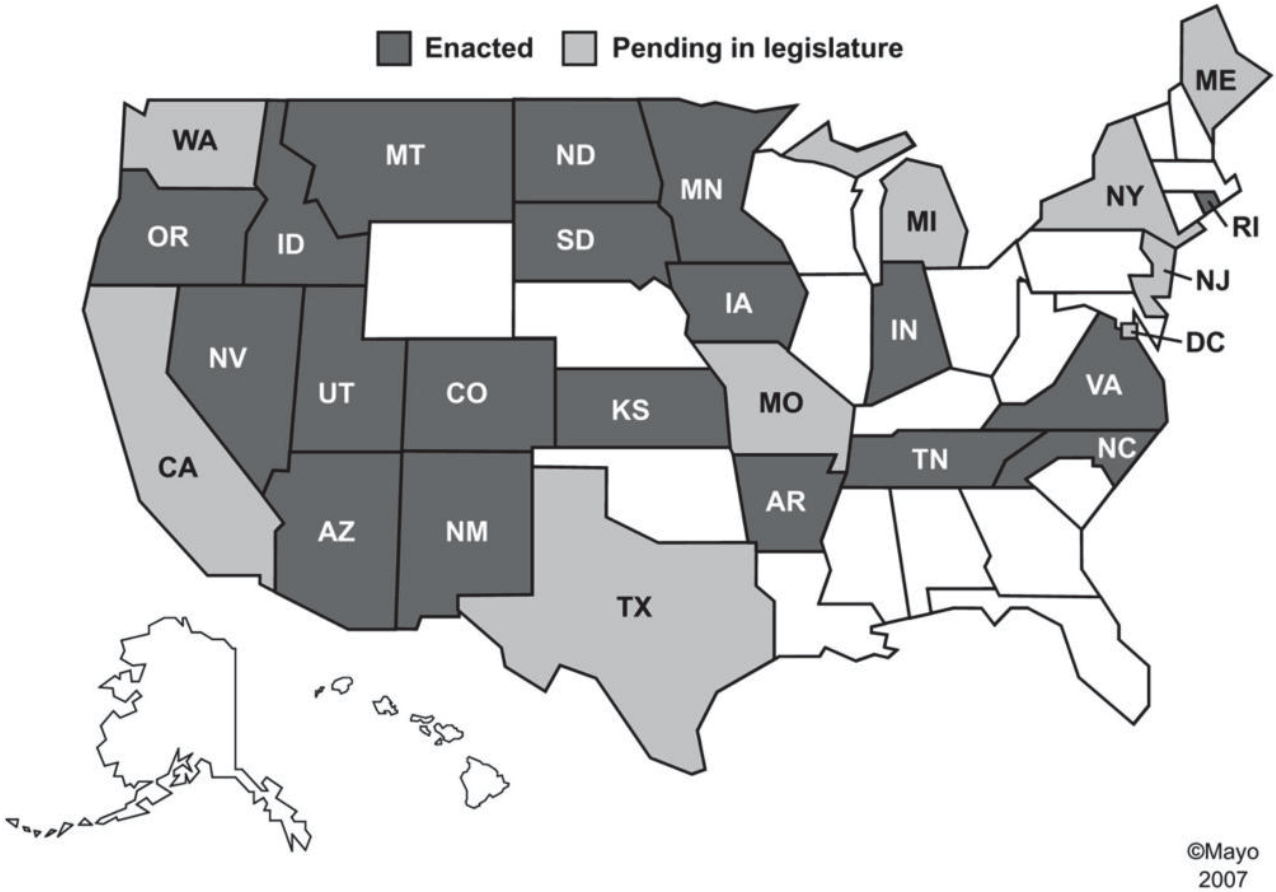

Figure 2
The enactment status of the United States Revised Uniform Anatomical Gift Act (UAGA) 2006 as of September 2007. The Revised Uniform Anatomical Gift Act (UAGA) 2006 is enacted in many states and a few of those have included amendments (dark shade areas). Other states have introduced the Revised UAGA (2006) for legislation (light shade areas). The data source is the National Conference of Commissioners on Uniform State Laws.

Table 1: Glossary of terms

"**Advance health care directive**" means a power-of-attorney for health care or a record signed or authorized by a prospective donor containing the prospective donor's direction concerning a health care decision for the prospective donor.
"**Anatomical gift**" means a donation of all or part (an organ, an eye, or tissue) of a human body to take effect after the donor's death for the purpose of transplantation, therapy, research, or education. "
"**Contrary intent**" means a document expressing that no measures to be taken to ensure the medical suitability of an organ for transplantation and authorize and instruct the withholding and/or withdrawing of such medical measures and treatment including life support systems for that purpose.
"**Declaration**" means a record signed by a prospective donor specifying the circumstances under which life support systems may be withheld or withdrawn from the prospective donor.
"**Document of gift**" means a donor card or other record used to make an anatomical gift. The term includes a statement or symbol on a driver's license, identification card, or donor registry.
"**Donor**" means an individual whose body or part is the subject of an anatomical gift.
"**Health care decision**" means any decision regarding the health care of the prospective donor.
"**Life support systems**" means the use of machines and/or administration of medications for artificial support of vitals organs. Mechanical ventilators support the respiratory system. Medications and/or mechanical means (e.g. external cardiac compression devices, internal cardiac assist devices or artificial heart-lung machines) support the circulatory system.
"**Medically suitable organs**" means the determination of medical suitability of organs by the organ procurement organization who performs the examination and evaluation of potential donors.
"**Organ procurement organization**" means a private organization operating under government contract to provide services covering all aspects of deceased organ donation to include 1) donor evaluation, selection and consenting and 2) preparation, recovery and transportation of procured organs. Each organization is assigned to a specific geographic area or donation service area within the US. There are 58 organizations covering all states including the District of Columbia, Puerto Rico, the United States Virgin Islands, or any territory or insular possession subject to the jurisdiction of the US.
"**Organ procurement protocols**" means medical treatment and surgical procedures performed on donors to ensure successful procurement of viable organs for transplantation.
"Power-of-attorney for health care" means a legally authorized representative to make health care decisions on behalf of an individual in the event of an incapacitating illness and inability to make own health care decisions.
"**Prospective donor**" means an individual who is dead or near death and has been determined to have one or more parts that could be medically suitable for transplantation, therapy, research, or education. The term includes an individual who made an anatomical gift during life and, therefore, is a donor. The term also includes a non-donor individual at or near the time of death with parts that are medically suitable for donation who could become a donor if the individual's family made an anatomical gift (section 9). The term does not include an individual who made a refusal as the refusal bars other persons from making an anatomical gift on that individual's behalf.
"**Refusal**" means a record created that expressly states intent to bar other persons from making an anatomical gift of an individual's body or part.
"**Section 9 (a)**" sets a prioritized list of classes of persons (power-of-attorney for health care, spouse, adult children, parents, adult siblings, adult grandchildren, grandparents, an adult who exhibited special care and concern for the decedent, persons who were acting as the guardians of the person of the decedent at the time of death, any other person having the authority to dispose of the decedent's body) who can make an anatomical gift of a decedent's body or part if the decedent was neither a donor nor had signed a refusal. The same list of classes of persons can be consulted for section 21(b) whether they would be willing to make a gift when the prospective donor is near death.
"**Section 14(c)**" When a hospital refers an individual at or near death to a procurement organization, the organization may conduct any reasonable examination necessary to ensure the medical suitability of a part that is or could be the subject of an anatomical gift for transplantation, therapy, research, or education from a donor or a prospective donor. During the examination period, measures necessary to ensure the medical suitability of the part may not be withdrawn unless the hospital or procurement organization knows that the individual expressed a contrary intent."
"**Section 21(b)**" If a prospective donor has a declaration or advance health-care directive and the terms of the declaration or directive and the express or implied terms of a potential anatomical gift are in conflict with regard to the administration of measures necessary to ensure the medical suitability of a part for transplantation or therapy, the prospective donor's attending physician and prospective donor shall confer to resolve the conflict. If the prospective donor is incapable of resolving the conflict, an agent acting under the prospective donor's declaration or directive, or, if none or the agent is not reasonably available, another person authorized by law other than this [Act] to make health-care decisions on behalf of the prospective donor, shall act for the donor to resolve the conflict. The conflict must be resolved as expeditiously as possible. Information relevant to the resolution of the conflict may be obtained from the appropriate procurement organization and any other person authorized to make an anatomical gift for the prospective donor under Section 9. Before resolution of the conflict, measures necessary to ensure the medical suitability of the part may not be withheld or withdrawn from the prospective donor if withholding or withdrawing the measures is not contraindicated by appropriate end-of-life care."

while awaiting the assessment of their organs for donation. In an epidemiologic study of the use of intensive care at the end-of-life in the US, one in five Americans die using intensive care services [15]. It is likely that the Revised UAGA (2006) will further increase the ratio of Americans dying in intensive care units by legitimizing presumed consent for the use of life support systems for organ donation.

The application of life support systems for the purpose of organ donation without explicit consent is contraindicated at end-of-life and inconsistent with recommended practice guidelines for quality palliative care [19,22]. Life support systems have no palliative benefit and inflict unwarranted traumatic and distressing experiences to dying patients and their families [23,24]. While section 21(b) (2007) concedes to the obvious conflict between

life support systems for organ donation and appropriate end-of-end life care for the dying patients, the amendment is insufficient to protect patients and families from potential violations of their rights to quality palliative care. Section 21(b) (2007) requires the attending physician to balance contraindications for end-of-life care against the need to preserve organs, which can only be done after the OPO has completed medical evaluation to determine if a patient can be considered a prospective donor. Section 21(b) (2007) also includes the OPO as an agent to assist with conflict resolution with regard to end-of-life care, yet, the same agent has other undisclosed incentives, i.e. maximizing organ procurement opportunities [12]. There are no real safeguards to prevent the OPO from either prolonging or manipulating end-of-life decision making for prospective donors in order to obtain donation consent.

The Revised UAGA (2006) requirement of life support systems for patients with clearly contrary end-of-life wishes represents a radical departure from the PSDA (1991) and original intent of advance health care directives. In fact, it can be argued that the Revised UAGA (2006) intrudes into patients' autonomy and infringes on their rights to self-determination of medical care at the end-of-life.

Conclusion

Some states have already enacted the Revised UAGA (2006) and a few of those have included amendments while attempting to preserve the uniformity of the revised Act (Figure 2). Other states have introduced the Revised UAGA (2006) for legislation and remaining states are likely to follow soon. The Revised UAGA (2006) increases physicians' and hospitals' responsibilities to fulfill their legal and moral obligations towards patients' rights for self-determination of their medical care and quality of palliation at the end-of-life. Therefore, it is imperative for patients, families and physicians to become familiar with the new US legislations about organ donation, so that the document of gift and advance health care directives are not in conflict and symbolize the commitment to patient's autonomous decision-making at the end-of-life. The premises underlying the subtle progression of the Revised UAGA (2006) towards the presumption about how to dispose of one's organs at or near death can pave the way for an affirmative "duty to donate" to the detriment of human liberty in a free society. Therefore, a broad based societal discussion must be initiated to decide if the Revised UAGA (2006) infringes on PSDA and the individual's right of autonomy. The discussion should also address other ethical concerns raised by the Revised UAGA (2006), including the moral stance on 1) the interpretation of the refusal of life support systems as not applicable to organ donation and 2) the disregarding of the diversity of cultural beliefs about end-of-life in a pluralistic society.

Abbreviations

PSDA = Patient Self Determination Act

OPO = Organ procurement organization

UAGA = Uniform Anatomical Gift Act

US = United States

See table 1 for a glossary of terms.

Competing interests

There are no affiliations or financial involvement with any organization or entity with a direct financial interest in the subject matter or materials discussed in the manuscript. The authors declare that they have no competing interests.

Authors' contributions

The JLV, MYR and JLM attest they have made substantial contributions in drafting the manuscript and revising it critically for important intellectual content; that they have given final approval of the version to be published; and that they have participated sufficiently in the work to take public responsibility for appropriate portions of the content. JLV, MYR and JLM read and approved the final manuscript

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This report has been reviewed by a group other than the authors according to procedures approved by a Report Review Committee consisting of members of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine.

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The serpent has been a symbol of long life, healing, and knowledge among almost all cultures and religions since the beginning of recorded history. The image adopted as a logotype by the Institute of Medicine is based on a relief carving from ancient Greece, now held by the Staatlichemuseen in Berlin.

Deliberations of the Human Fetal Tissue Transplantation Research Panel

James F. Childress

This case study focuses on the deliberations of the Human Fetal Tissue Transplantation Research Panel during the period September–December 1988. It analyzes the major debates that occurred about conflicting principles and values as a majority of the panel reached the conclusion that the use of human fetal tissue in transplantation research, following deliberate abortions, is "acceptable public policy" if certain "guidelines" are in place. The panel's deliberations occurred in an evolving context that comprised medical-scientific, social-political, legal, and cultural factors. To interpret the panel's deliberations and recommendations, it is necessary to discuss aspects of this context and the background to the panel's efforts.

In addition to drawing on the references and other bibliographic materials listed below, the author held telephone conversations in June 1990 with several people who had been involved at the National Institutes of Health (NIH) and the Department of Health and Human Services (DHHS) in decision making, question formation, panelist selection, and other activities involved with human fetal tissue trans

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BACKGROUND AND CONTEXT

By the mid-1980s, promising animal research on fetal tissue transplantation that had been under way for some time both in the United States and abroad had led several researchers in other countries to experimentally transplant human fetal tissue, following elective or spontaneous abortions, into human patients with Parkinson's disease. In addition, in the United States, NIH had awarded an extramural grant to Hans Sollinger of the University of Wisconsin to study transplantation of human fetal pancreatic cells into patients with diabetes. In late 1987 NIH received a request from intramural investigators at the National Institute of Neurological and Communicative Disorders and Stroke for permission to undertake research transplanting human fetal neural tissue, following elective abortions, into patients with Parkinson's disease. Even though he had the legal authority to approve this research—and some members of his staff urged him to do so—James B. Wyngaarden, the director of NIH, sought approval from the Office of the secretary of DHHS to "permit maximum review of this sensitive area of research" (Office of Science Policy and Legislation, 1988). Wyngaarden's memorandum of October 23, 1987, to Robert Windom, then assistant secretary for health, noted that the proposed research had "the potential for publicity and controversy" and "may be characterized in the press as an indication that the Department is encouraging abortions," even though the "research will in no way be a factor in a woman's decision to have an abortion and no Federal funds will directly or indirectly support abortion." The memorandum also stressed NIH's conviction that "on balance . . . the importance of this research outweighs any potential for adverse publicity."

In a March 22, 1988, memorandum to the director of NIH, the assistant secretary for health declared a moratorium on the use of federal funds to support human fetal tissue transplantation research (hereafter, HFTTR) that used tissue from induced abortions until NIH could convene "special outside advisory committees" to hear testimony, deliberate, and offer their recommendations. His memorandum identified 10 questions that such committees should address (see Appendix A), which focused mainly on the connection or linkage between abortion and the use of human fetal tissue in research. The assistant secretary's staff

developed the questions on the basis of an analysis of the existing literature and after consultation with three academic bioethicists. Whereas the NIH director's memorandum focused on the public controversy that might result from the federal government's sponsorship of such research, the assistant secretary's staff perceived the problem as largely ethical.

There are several relevant features of the context of the deliberations of NIH, DHHS, and the HFTTR panel. First, there had been earlier research that used human fetal tissue, and many of these projects had support from NIH. In fiscal year 1987, NIH awarded 116 grants and contracts (estimated at $11.2 million) for research that involved the use of human fetal tissue (Office of Science Policy and Legislation, 1988). Most of this research, however, had no direct therapeutic intent and did not involve transplantation. One widely reported earlier example of the use of human fetal tissue in research was in the development of the polio vaccine. Some commentators (e.g., Nolan, 1988) distinguish using cadaveric fetal tissue to *develop* a treatment from using it *as* a treatment.

Second, animal research had shown that transplantation of human fetal neural tissue might provide therapeutic benefits for patients with Parkinson's disease. Fetal tissue has special features that make it potentially useful in this case—for example, it is immunologically more naive than developed tissue, and it grows and differentiates rapidly. Furthermore, fetal tissue is widely available from the 1.5 million abortions performed in the United States each year.

Third, the U.S. Supreme Court decision in *Roe* v. *Wade* in 1973 overturned restrictive abortion laws but failed to resolve the serious moral and political debate and conflict about abortion in the United States. Opponents of abortion have been quite active since then and have regularly challenged practices, policies, or laws that appear to encourage abortions.

Fourth, beyond the legal framework for abortion, the transfer of human cadaveric tissue is governed by the Uniform Anatomical Gift Act (UAGA), which was adopted by all 50 states and the District of Columbia in the late 1960s and early 1970s. In general, the UAGA permits either parent, subject to the known objection of the other, to donate fetal tissue, following spontaneous or deliberate abortions, for research, education, or transplantation. However, some states restrict the use of fetal materials following induced abortions in some research (DHHS/NIH, 1988; see vol. 1, p. 11, and vol. 2, app. F). Federal regulations permit research "involving the dead fetus, macerated fetal material, or cells, tissue, or organs excised from a dead fetus . . . in accordance with any applicable State or local laws regarding such activities" (45 CFR 46.210). Many of the existing federal regulations focus on research involving the living

fetus rather than on the use of tissue derived from fetal remains. Also of relevance is the National Organ Transplant Act of 1984 with subsequent amendments, which will be discussed later.

PROCESS

During early summer 1988, NIH appointed the panel to meet in the fall to respond to Assistant Secretary Windom's questions and then to submit its finished report to the NIH Director's Advisory Committee, a diverse outside group that advises NIH on policy matters. NIH had reason to expect that a favorable recommendation from the panel and the advisory committee would lead to DHHS authorization to NIH to approve the research. On the recommendation of an internal, informal ad hoc committee, NIH appointed Arlin Adams, a retired federal judge from Philadelphia, to chair the fetal tissue panel; as a Republican opposed to abortion, he was considered an ideal choice. In addition, NIH appointed special panel chairpersons for scientific issues (Kenneth J. Ryan, a physician and scientist) and ethical and legal issues (LeRoy Walters, an ethicist).

Members of Congress, members of the executive branch, and organizations with an interest in the research, among others, submitted nominations for the 21-person panel; the various categories of nominations were ethicists, lawyers, biomedical researchers, clinical physicians, public policy experts, and religious leaders. The ad hoc committee (which included the panel's chair and co-chairs and a member of the NIH Director's Advisory Committee) considered the nominations in early July, emphasizing in their selections the qualifications of proposed panelists and the need for more women and minority panel members. There was vigorous outside support for particular nominees, much of which centered on opponents of abortion; three—James Bopp, James Burtchaell, and Daniel Robinson—were selected. In a departure from the nominations model being used, one senator asked to review the proposed list and personally discussed the proposed panelists with NIH officials prior to their invitation to serve. One of the conditions for serving on the panel was that the prospective panelist had to agree to be available for the first meeting, which was already planned for September 16–18, 1988. After the members of the panel were announced, defenders of HFTTR worried about the presence of strong opponents of abortion on the panel; critics of HFTTR, on the other hand, thought they discerned an overall bias among the panel in favor of such research. (For a list of panelists, see Appendix B.)

Just prior to the panel's first meeting, the White House leaked a draft executive order that proposed a ban on transplantation research

using human fetal tissue following elective abortions. Otis Bowen, then secretary of health and human services, responded that he would not impose new curbs on HFTTR until the advisory committees could make their final recommendations or until he received a direct order from the President. Over the next several weeks, 50 members of Congress wrote to the President urging him to promulgate the executive order that would signify his commitment to protecting unborn lives; several hundred physicians and others also wrote, offering their strong support for the proposed order. However, no action was taken.

In September 1988, the HFTTR panel convened to hear scientific, legal, and ethical views from more than 50 invited speakers as well as testimony from representatives of public interest groups. All meetings of the panel were opened to the public after an initial announcement of several closed, executive sessions drew a vigorous negative reaction. When it became clear that the three-day meeting would not be sufficient for the panel to complete its deliberations and offer its response, a second meeting was set for October 20–21. In a draft report considered at the second meeting, the panel offered relatively brief responses to the assistant secretary's questions but little justification for them. During the meeting there was discussion about whether such justifications could be developed without a third meeting; the panel decided to submit only what had been developed and accepted by the time of adjournment. But at the end of the second meeting, James Bopp and James Burtchaell brought in a long dissent to the report. Several other panelists were concerned that this long dissent would overwhelm the brief responses in the report, especially considering that the recommendations were left without sufficient justification. A third meeting was scheduled for December 5, with members of the panel preparing and circulating in advance drafts of "considerations" for each response to the assistant secretary's 10 questions. At that meeting the report was put into final form: it contains the responses and considerations, along with the panel vote, for each question; a brief summary of the current scientific literature relevant to HFTTR; three concurring statements (Judge Arlin Adams; Aron Moscona, joined by two other panelists; and John Robertson, joined in whole or in part by ten other panelists); two dissenting statements (by David Bleich and by James Bopp and James Burtchaell); and a final dissenting letter (Daniel Robinson). Volume 2 of the report contains the written testimony submitted to the panel.

After observing the meetings, science writer Jeffrey Fox described the panel's process: "Despite the diversity of views held by members of the *ad hoc* panel, the group steadfastly tried to follow a consensual approach during its deliberations. Although consensus was difficult to achieve, the panel members consistently tried to accommodate one

another's respective positions. Thus, in most cases, very disparate philosophical positions were melded into a coherent stance that was deemed acceptable by a substantial majority of the panel. However, neither of these observations should be taken to suggest that the debate within the panel was somehow constrained by the majority viewpoint, as indeed it was not" (Fox, 1988). The panelists spent a great deal of time debating and modifying the wording of particular responses to gain as much consensus as possible. The majority frequently compromised on the exact wording, but the minority often voted against the response that had been carefully worked out through compromise.

The panel experienced other constraints, including the pressure to complete a report as quickly as possible and the lack of staff and resources; originally the panel had been expected to offer a report on the basis of one meeting. The tight schedule, the pressure for a prompt report, and the limited resources all contrasted sharply with the arrangements for other bodies dealing with ethical issues in science and health care, such as the National Commission for the Study of Ethical Problems in Biomedical and Behavioral Research, the President's Commission for the Study of Ethical Problems in Medicine, and the Task Force on Organ Transplantation. Another major constraint was the 10 questions raised by the assistant secretary. As noted earlier, these questions focused on issues related to abortion rather than on issues parallel to transplantation of other cadaveric tissue. Thus, it is not surprising that the panel's deliberations concentrated to a great extent on ethical and societal concerns about abortion without directly addressing the morality of abortion.

THE MORAL STATUS OF THE FETUS AND THE MORALITY OF ABORTION

With this sketch of the background, context, and process of the panel's deliberations and recommendations, we can now turn to an examination of the major explicit and implicit issues it faced. One of the major issues involved the status of fetal life—for example, whether the fetus should be viewed as tissue, as a potential human life, or as a living human being. Certainly the members of the panel differed greatly in their individual views on this question, which required some of them to oppose the use of fetal tissue following abortions. Others contended that it was possible to separate, morally and practically, abortions and the use of fetal tissue, despite the fact that elective abortions provide the bulk of tissue for HFTTR.

Some panel members contended that their acceptance of various guidelines or safeguards to separate abortion decisions from decisions about the use of fetal tissue did not imply that they viewed abortion as immoral. The recommended guidelines were intended to reduce the

likelihood that the possibility of donation would influence the pregnant woman's decision to abort. Even if abortion were not viewed as immoral, these guidelines could be accepted for various reasons, including (1) the desire to allay the moral controversy in our society about abortion, or (2) the desire to reduce the vulnerability of some pregnant women to exploitation and coercion because of the need for fetal tissue. These reasons are sufficient to justify the guidelines, without the presupposition that abortion is immoral.

Thus, while accepting the proposition that "it is of moral relevance that human fetal tissue for research has been obtained from induced abortions," the majority of the panel nevertheless held that, in view of the significant medical goals of HFTTR and the legality of abortion, "the use of such tissue is acceptable public policy." In the consideration it noted for this response, the panel observed that "a decisive majority of the panel found that it was acceptable public policy to support transplant research with fetal tissue either because the source of the tissue posed no moral problem or because the immorality of its source could be ethically isolated from the morality of its use in research" (DHHS/NIH, 1988:2). Thus, the panelists who voted for using fetal tissue for research subscribed to one of two views: (1) that abortion is morally acceptable and the use of aborted fetal tissue for HFTTR is morally acceptable; or (2) that abortion is "immoral or undesirable," although legal, and HFTTR can be morally separated from abortion and can proceed with appropriate safeguards. The majority rejected the position that HFTTR should be prohibited from receiving federal funds because it is, morally speaking, inextricably linked to or would lead to immoral abortions.

COMPLICITY, COLLABORATION, AND COOPERATION IN MORAL EVIL

During the panel's deliberations, James Burtchaell, a theologian at Notre Dame University, invoked the language of complicity, collaboration, and cooperation in the moral wrongdoing of others to stress what he considered the impossibility of separating, at least in practice, the use of fetal tissue from the (immoral) abortions that produced it (Bopp and Burtchaell, 1988:63–70). Particularly important for Burtchaell was a form of indirect association that implied moral approval. Cooperation that involves casual actions—for example, driving the get away car after a robbery—must be distinguished from actions that only symbolize, convey, or express approval but do not materially contribute to the actions themselves. Burtchaell invoked various analogies. One involved the banker in a town in Florida who decided to accept deposits from participants in the drug trade on the grounds that this action would

benefit the community and that the drug trade would continue regardless of what the banker did. Another was of the researcher who visits an abortionist each week to obtain fetal tissue but who each time expresses his disapproval while planning to return the next week. Burtchaell contends that these actions involve complicity in the moral wrongdoing of others, whether drug trafficking or abortion.

According to written testimony from the Bishops' Committee for Pro-Life Activities of the National Conference of Catholic Bishops, "it may not be wrong in principle for someone unconnected with an abortion to make use of a fetal organ from an unborn child who died as the result of an abortion; but it is difficult to see how this practice can be institutionalized [including arrangements to ensure informed consent] without threatening a morally unacceptable collaboration with the abortion industry" (DHHS/NIH, 1988:E42; for a slightly different version, see G1). What may be possible in the abstract, in principle, or in theory is not possible in practice because of the institutionalization of abortion and the way fetal tissue is currently procured. James Bopp and James Burtchaell write in their dissent: "Our argument, then, is that whatever the researcher's intentions may be, by entering into an institutionalized partnership with the abortion industry as a supplier of preference, he or she becomes complicit, though after the fact, with the abortions that have expropriated the tissue for his or her purposes. It is obvious that if research is sponsored by the National Institutes of Health, the Federal Government also enters into this same complicity" (Bopp and Burtchaell, 1988:70).

There are at least two responses to the charge of moral cooperation in the wrongdoing of others. One is to deny that the primary action, in this case, abortion, is morally wrong; another is to deny that the use of aborted fetal tissue implies approval of abortion. The panel did not try to resolve the debate about the morality of abortion, but the majority insisted that it is at least possible to draw a moral line between the use of fetal tissue and the abortions that make the tissue available in such a way as to ensure that unacceptable moral cooperation does not occur (DHHS/NIH, 1988:2). The majority of the panel noted that it is possible to use organs and tissues from homicide and accident victims without implying approval of homicides and accidents and without diminishing efforts to reduce their occurrence (Robertson, 1988:31–32). Even if one were to accept that abortion is immoral, "it does not follow that use of fetal remains makes one morally responsible for or an accomplice in abortions that occur prior to or independent of later uses of fetal remains" (Robertson, 1988:31). In addition, the majority statement underlined the fact that abortions are already being performed with the result that fetal tissue that could benefit others is being discarded rather than used.

Several members of the panel strongly objected to the analogies to Nazi research on living subjects invoked by James Bopp and James Burtchaell to illustrate moral complicity in the wrongdoing of others (Bopp and Burtchaell, 1988:63–70). Critics contended that there are several morally relevant differences between the use of tissue from dead fetuses following debatably immoral abortions and the clearly immoral actions of Nazi investigators who experimented on living subjects against their will (Robertson, 1988:32–33; Moscona, 1988:27–28). In a concurring statement, a majority of the panelists noted that the complicity claim "is considerably weakened when the act making the benefit possible is legal and its immorality is vigorously debated, as is the case with abortion. Given the range of views on this subject, perceptions of complicity with abortions that will occur regardless of tissue research should not determine public policy on fetal tissue transplants" (Robertson, 1988:33).

Panelists also noted that the loose concept of complicity in the moral wrongdoing of others could be turned in other directions, perhaps even against the positions held by those who invoked it in the context of HFTTR. For example, critics of the application of the concept of complicity in HFTTR argued that a failure to provide sex education, contraceptives, and social support for pregnant women could be construed as modes of complicity and cooperation in the actions of abortion. In this instance, the alleged complicity or cooperation is the material contribution of causal factors through omission.

Recognizing that some potential participants in research, whether as patients or as professionals, might want to avoid any connection and thus any felt complicity with abortion, the panel recommended that "potential recipients of such tissues, as well as research and health care participants, should be properly informed as to the source of the tissues in question" (DHHS/NIH, 1988:1–2).

INCREASE IN THE NUMBER OF ABORTIONS

One fundamental question in the fetal tissue controversy is whether its use in transplantation research would result in an increase in the number of abortions and if so, whether it would still be justified. Answers to this question hinge in part on matters that should be resolvable by empirical data—the reasons why women have abortions. The panel's report noted that "the reasons for terminating a pregnancy are complex, varied, and deeply personal" and "regarded it highly unlikely that a woman would be encouraged to make this decision [to abort] because of the knowledge that the fetal remains might be used in research" (DHHS/NIH, 1988:3). In addition, the panel noted the lack of any evidence

that, over the past 30 years, the possibility of donating fetal tissue for research purposes had resulted in an increase in the number of abortions (DHHS/NIH, 1988:3). Furthermore, according to the panel majority, it is possible to set up guidelines or safeguards to reduce the likelihood of an impact on the incidence of abortion. Defenders of the minority position argue, however, that knowledge of this possibility of benefit from the provision of fetal tissue would make a difference in some, perhaps even many, cases. There are several possible scenarios addressed by the critics and defenders of HFTTR; they are organized below more systematically than in the HFTTR panel's report.

General Altruism

First, would the possibility of donating fetal tissue to benefit unrelated and unknown patients through transplantation play a role in a woman's decision to abort? Neither the defenders nor the critics of HFTTR can find strong evidence for their claims about the potential impact of this possibility on individual abortion decisions (DHHS/NIH, 1988:3). The debate thus hinges on speculations about women's abortion decisions and on answers to the moral question about which way society should err in such a situation of doubt.

Critics charge that HFTTR would reduce some pregnant women's ambivalence about abortion so that the possibility of an altruistic act—what could be called "general altruism"—would probably lead to some abortions that would not otherwise have occurred. Defenders of HFTTR respond that such a claim is speculative: there is only sketchy evidence about women's decision making about abortion and no evidence that the long-time possibility of donating fetal tissue to benefit others through research (although only rarely through transplantation research) has led to any abortions that would not otherwise have occurred (DHHS/NIH, 1988:3). Even if it was known that the possibility of donating fetal tissue provided a "motivation, reason, or incentive for a pregnant woman to have an abortion," this would not constitute a prohibited "inducement" (under federal law) because it is not a promise of financial reward or personal gain and is not coercive (DHHS/NIH, 1988:4).

In such complex personal decisions as abortion, it is difficult to determine the role of various motives, such as general altruism, and particularly whether these motives are necessary or sufficient for an action. In the case of panel members, however—whether their motives were to protect the fetus, to prevent exploitation and coercion of pregnant women, or to allay moral controversy—the majority of them proposed guidelines to reduce the likelihood that HFTTR would lead some women to abort when they would not otherwise have done so. These guidelines

include efforts to prevent the stimulation or encouragement of general altruistic motives on the part of pregnant women.

According to the panel, "the decision and consent to abort must precede discussion of the possible use of the fetal tissue and any request for such consent as might be required for that use," and "informed consent for an abortion should precede informed consent or even the preliminary information for tissue donation," except when the pregnant woman requests such information (DHHS/NIH, 1988:3–4). Ideally, the request and the decision to donate should follow the abortion decision itself, but because postmortem tissue deteriorates quickly and cryogenic storage is not possible for many transplants, "the pregnant woman must be consulted before the abortion is actually performed" (DHHS/NIH, 1988:10).

In a concurring statement prepared largely by John Robertson and joined, at least in part, by 10 other panel members, a majority of the panelists allow that even an increase in the number of abortions would not be a decisive reason for rejecting federal support of HFTTR: "Yet even if *some* increase in the number of family planning abortions due to tissue donation occurred, it would not follow that fetal tissue transplants should not be supported. Surely it does not follow that *any* increase in the number of abortions makes fetal tissue transplants unacceptable" (Robertson, 1988:34). Drawing a distinction between means, ends, and consequences, this argument denies that an increase in the number of elective abortions is a means to the end of HFTTR. Instead, an increase in the number of elective abortions is a possible consequence, a risk, of the use of HFTTR. Risk is a probabilistic notion and includes the probability of a negative outcome. It is thus necessary to judge the likelihood of a negative outcome along with its magnitude. The risk of an increase in fetal deaths is comparable to other losses of life in the pursuit of important societal goals, such as automobile design, highway engineering, and bridge building. According to Robertson's concurring statement, "[t]he risk that *some* lives will be lost, however, is not sufficient to stop those projects when the number of deaths is not substantial, when the activity serves worthy goals and when reasonable steps to minimize the loss have been taken" (Robertson, 1988:34). Furthermore, a "more stringent policy is not justified for fetal tissue transplants just because the risk is to prenatal life from *some* increase in the number of legal abortions" (Robertson, 1988:34–35).

Noting that the risk of an increase in the number of abortions is speculative at best, the report's concurring statement stresses that similar speculative and tenuous risks that the society might encourage, as well as legitimate deaths resulting from homicide, suicide, and accidents, to gain organs for transplantation are not viewed as a sufficient reason to stop using organs from these sources (Robertson, 1988:35 [fn. 23]). In a

later response (Mason, 1990), Assistant Secretary for Health James Mason contended that in the argument above, the concurring statement simply disregarded moral and ethical considerations. Nevertheless, its signers view it as offering a different balance of moral and ethical considerations instead of a denial of those considerations. In addition, the panel maintained that its recommended guidelines would reduce the probability of an increase in the number of abortions.

A different risk-benefit calculation appears in the dissent by J. David Bleich, who holds that "these mitigating safeguards [the ones proposed by the panel] notwithstanding, intellectual integrity compels recognition that the goal of preventing an increment in the total number of abortions performed is not totally attainable" (Bleich, 1988:39). He interprets the majority's proposals as an effort to balance interests "through a policy of damage containment" (Bleich, 1988:40). By contrast, he notes that the duty to rescue human life through fetal tissue transplants is diminished because the studies at issue are *research* protocols with uncertain, distant benefits rather than certain immediate good for identified lives, and because the "moral harm" of the increase in the number of abortions is certain and immediate. Hence, "on balance, the duty to refrain from a course of action that will have the effect of increasing instances of feticide must be regarded as the more compelling moral imperative" (Bleich, 1988:43). This formulation appears to leave open the possibility of a different balance if the procedure reached the point, without federally funded research, of providing an immediate, certain benefit. By contrast, the majority of the panel held that the increase in the number of abortions was not certain and immediate and could be avoided at least in part through the proposed guidelines.

Specific Altruism

The second scenario raises the possibility that a pregnant woman (or a woman contemplating pregnancy) might donate fetal tissue to help a family member or acquaintance, which could result in abortions that would not otherwise have occurred. In contrast to the motivation of general altruism considered above, this motivation might be called specific altruism, that is, beneficence toward specific known individuals. Because of dramatic proposals by a few women to become pregnant in order to abort and donate fetal tissue to help a beloved family member, and its recognition of the strength of specific altruistic motives, the panel recommended this guideline: "There should be no Federal funding of experimental transplants performed with fetal tissue from induced abortions provided by a family member, friend, or acquaintance. Absent such prohibition, the potential benefits to friends and family members

might encourage abortion or encourage pregnancy for the purpose of abortion—encouragements that the panel strongly opposed" (DHHS/NIH, 1988:8). Another formulation reads: "The pregnant woman should be prohibited from designating the transplant-recipient of the fetal tissue" (DHHS/NIH, 1988:3). In yet another recommendation with the same import, the panel held that "anonymity between donor and recipient shall be maintained, so that the donor does not know who will receive the tissue, and the identity of the donor is concealed from the recipient and transplant team" (DHHS/NIH, 1988:4).

These recommendations clearly reflect the panel's concerns about maternal welfare as well as concerns about the morality of abortion. Moreover, they are based on the lack of evidence that "a prohibition against the intrafamilial use of fetal tissue would affect the attainment of valid clinical objectives" (DHHS/NIH, 1988:8). For example, in fetal tissue transplants for diabetes, it would be medically contraindicated to use intrafamilial transplants, but no definitive conclusions can be drawn at this time about other conditions for which fetal tissue transplantation may be a possibility. Nevertheless, in the considerations it noted for its response, the panel referred to expert testimony that "if circumstances change . . . there may be reasons to modify the prohibition . . . it was strongly urged that the Secretary for Health and Human Services review these recommendations at regular intervals" (DHHS/NIH, 1988:8). In the last section of the concurring statement, which was prepared by John Robertson and signed by ten other panelists (with the exception of this section, in which one of the ten did not concur), this position is elaborated: "If the situation changes so that the supply of fetal tissue from family planning abortions proves inadequate, the ban on donor designation of recipients and aborting for transplant purposes should be re-examined. The ethical and legal arguments in favor of and against such a policy would then need careful scrutiny to determine whether such a policy remains justified" (Robertson, 1988:38).

Incentives of Financial Gain

In a third way—beyond general and specific altruism—the possibility of HFTTR could provide another motive for abortion in the shape of financial incentives for the provision of fetal tissue. Congress had already addressed this issue by passing an amendment (which Ronald Reagan signed into law) to the National Organ Transplant Act that prohibited the transfer of human organs (including fetal organs and their subparts) for "valuable consideration, or payment." The panel's report supported this position, stressing that "it is essential . . . that no fees be paid to the woman to donate, or to the clinic for its efforts in procuring fetal

tissue (other than expenses incurred in retrieving fetal tissue)" (DHHS/NIH, 1988:9). As is true of several of the panel's other recommendations, this one could be justified as a way to protect fetuses from abortion, to protect women from exploitation and coercion, to reduce moral controversy, and even to help avoid societal commodification of "human" body parts.

SOCIETAL LEGITIMATION OF ABORTION DECISIONS AND PRACTICES

Although the topic of societal legitimation tends to collapse into issues of complicity in and encouragement of abortions, it may be useful to consider it separately. According to Dorothy Vawter (1990), "to legitimate an act or practice is to justify or promote it in such a manner that others will become more inclined to regard it as acceptable and to engage in it." On the one hand, critics contend that federally funded HFTTR following elective abortions would tend to legitimate abortion because of the difficulty—or even the impossibility—of distinguishing within the expenditure of federal funds (1) approval of the use of fetal tissue from elective abortions and (2) approval of the elective abortions that produced the fetal tissue. Rabbi David Bleich argued in the panel's report that "[f]ederal funding conveys an unintended message of moral approval for every aspect of the research program" (Bleich, 1988:40[fn. 2]). By contrast, defenders of the research could argue that the approval of the use of federal funds in treatment of end-stage renal disease through organ transplantation does not constitute approval of the homicides, suicides, and accidents that provide the occasions for organ donation (Robertson, 1988:35[fn. 23]). Furthermore, they might note that there is no evidence that efforts to reduce such events have abated in order to maintain the supply of needed organs.

A second version of the societal legitimation argument focuses on society's acceptance of the benefits of human fetal tissue donations following elective abortions rather than on government funding. It would be difficult, perhaps even impossible, critics argue, for society to accept the benefits of HFTTR without becoming increasingly inclined to accept as legitimate the abortions that make the benefits possible. (Such a legitimation would be likely to occur even if no federal funds were used to support HFTTR protocols.) Thus, if HFTTR were to confer substantial benefits in the form of new life-saving or life-enhancing procedures, society would become less likely to delegitimate abortion by declaring many acts of abortion illegal (provided future Supreme Court decisions make such declarations more possible). It is not likely that society will renounce either the benefits of HFTTR or the decisions and practices that make the benefits possible.

Because of the panel's focus on federal funding, it only addressed the first version of the societal legitimation argument. The panel maintained that this symbolic societal legitimation could be avoided by the separation measures it proposed (see the earlier discussion of complicity). The second version of the societal legitimation argument focuses more on society's acceptance of abortion decisions and practices rather than on individual decisions, and it may not be directly countered by the panel's arguments that its proposed separation measures would reduce the likelihood that HFTTR would encourage abortion decisions by particular women.

A final criticism of societal legitimation appears in the panel's report in the dissenting letter by Daniel Robinson, who argued "that induced abortion is a moral wrong and that it cannot be redeemed by any actual or potential 'good' secured by it. Thus, the possible medical benefits held out by research tissues obtained by such measures cannot be exculpatory" (Robinson, 1988:73). This argument was offered after the report was completed, but the panel could have responded that it attempted to *separate* abortion decisions and practices from decisions and practices regarding the use of fetal tissue. HFTTR using fetal tissue from elective abortions in no way redeems or exculpates the abortions themselves. It only involves the use of tissue that would otherwise be discarded or incinerated, without implying approval (or, for that matter, disapproval) of the abortions themselves, just as the use of tissue from adult cadavers does not imply approval of—or redeem or exculpate—the homicides or negligent accidents that resulted in death.

DISPOSITIONAL AUTHORITY OVER FETAL REMAINS

The fourth question posed by Assistant Secretary Windom was as follows: "Is maternal consent a sufficient condition for the use of the tissue, or should additional consent be obtained? If so, what should be the substance and who should be the source(s) of the consent, and what procedures should be implemented to obtain it?" This question engendered one of the most divisive debates of the HFTTR panel as members wrestled with the problem of dispositional authority over fetal tissue following abortions, including the authority to transfer fetal tissue for use in transplantation research. The vote in favor of the sufficiency of maternal consent (within limits) was 17 yes, 3 no, and 1 abstention, the smallest majority of any answer to any question.

The argument surrounding this question also focused on ways to separate the abortion decision of the pregnant woman from the decision about the use of fetal tissue. The majority held that "fetal tissue from induced abortions should not be used in medical research without

the prior consent of the pregnant woman. Her decision to donate fetal remains is sufficient for the use of tissue, unless the father objects (except in cases of incest or rape)" (DHHS/NIH, 1988:60). Critics of this view contended that when the pregnant woman "resolves to destroy her offspring, she has abdicated her office and duty as the guardian of her offspring, and thereby forfeits her tutelary powers" (Bopp and Burtchaell, 1988:47). From this perspective the abortion decision deprives the pregnant woman of any subsequent authority over the disposition of the fetus. Thus, this viewpoint requires a total separation between the decision to abort and the decision to use or transfer tissue for use; this separation is put into practice by disqualifying the woman who decides to abort from making a decision about fetal tissue use.

Of the several possible modes of transfer of fetal tissue—donation, abandonment, expropriation, or sales—the panel recommended donation, which is the dominant method of transfer of cadaveric organs and tissues in the United States. Donation is carried out mainly in the form of *express donation* by the decedent or by the decedent's next of kin but also by *presumed donation* for corneas in several states. "Express donation by the pregnant woman after the abortion decision is the most appropriate mode of transfer of fetal tissue because it is the most congruent with our society's traditions, laws, policies, and practices, including the Uniform Anatomical Gift Act and current Federal research regulations" (DHHS/NIH, 1988:6). (The panel heard some evidence that fetal tissue probably has been viewed at times as abandoned and has been used without maternal consent [DHHS/NIH, 1988:11].) The panel further argued that a woman's choice of a legal abortion does not disqualify her legally and should not disqualify her morally from serving as "the primary decisionmaker about the disposition of fetal remains, including the donation of fetal tissue for research." Against arguments that the decision to abort leaves only biological kinship, without any moral authority, the panel concluded

> *that disputes about the morality of her decision to have an abortion should not deprive the woman of the legal authority to dispose of fetal remains. She still has a special connection with the fetus and she has a legitimate interest in its disposition and use. Furthermore, the dead fetus has no interests that the pregnant woman's donation would violate. In the final analysis, any mode of transfer other than maternal donation appears to raise more serious ethical problems. (DHHS/NIH, 1988:6)*

A concurring statement (written by John Robertson and signed by a majority of the panelists) disputed the guardianship model affirmed by the Bopp-Burtchaell dissent, contending that it "mistakenly assumes that a person who disposes of cadaveric remains acts as a guardian or

proxy for the deceased, who has no interests, rather than as a protector of their own interests in what happens to those remains" (Robertson, 1988:36). (Of course, where the deceased has expressed his or her wishes, then the situation is different.)

Although the panel accepted the structure of the UAGA (revised, 1987) as generally adequate, it recommended a modification in policy for the donation of fetal tissue in federally funded research. The UAGA allows either parent to donate fetal tissue unless the other parent objects. The panel concluded, however, that "the pregnant woman's consent should be *necessary* for donation—that is, the father should not be able to authorize the donation by himself, and the mother should always be asked before fetal tissue is used. In addition, her consent or donation should be *sufficient*, except where the procurement team knows of the father's objection to such donation" (DHHS/NIH, 1988:7). Affirming that there is no legal or ethical obligation to seek the father's permission, the panel nevertheless held that there is "a legal and ethical obligation not to use the tissue if it is known that he objects (unless the pregnancy resulted from rape or incest)" (DHHS/NIH, 1988:7). In its recommendations on federal funding of HFTTR, the panel also stressed the importance of compliance with state laws and noted that at least eight states have statutes that prohibit the experimental use of cadaveric fetal tissue from induced abortions (DHHS/NIH, 1988:13; Smith, 1988).

LIMITS ON DISCLOSURE OF INFORMATION AND DECISION MAKING

Several times during its deliberations the panel addressed questions of the disclosure of information, as well as the specificity of the woman's decision to donate. On the one hand, the panel concluded that no information about the donation and use of fetal tissue in research should be provided prior to the pregnant woman's decision to abort, *unless* she specifically requested that information (DHHS/NIH, 1988:3, 4). Donation, in contrast to informed consent in medicine and research, generally does not presuppose the disclosure of detailed information. Yet, in addition to the requirement of informed consent for the research subject, that is, the recipient of the transplant, the woman having the abortion and donating fetal tissue is herself a research subject insofar as she provides a medical history and undergoes tests relevant to the research transplant. Any research protocol reviewed by the institutional review board (IRB) in a given situation will therefore involve procedures and consent documents that pertain to the woman as a research subject, and the IRB must determine the adequacy of the information disclosed to her when she is considering "whether to consent to tests (e.g., for antibody to the human immunodeficiency virus) to determine the ac

ceptability of the fetal tissue for transplantation research" (DHHS/NIH, 1988:7). Within the model of stages of disclosure of information and decision making about the separate acts of abortion and donation, it is thus necessary to disclose information about tests to determine the acceptability of fetal tissue as part of the research protocol. Other issues include what to disclose to the pregnant woman about the test results.

For various reasons that have already been identified—the desire to separate the abortion decision from the donation decision, the desire to protect pregnant women from exploitation and coercion, and the desire to avoid fanning the flames of the abortion controversy—the panel recognized several limits on the pregnant woman's autonomy without restricting the abortion decision itself. In the UAGA there is no obligation to accept donated tissue and organs; hence, the woman's right to give fetal tissue does not engender an obligation on the part of anyone else to accept the gift. The pregnant woman has a right, the panel argued, to request and receive information about donation of fetal tissue prior to her abortion decision, but that information should not be disclosed to her as a matter of course if she does not request it. Here again, the rationale is to separate the two decisions to reduce the likelihood that knowledge of the possibility of donating will influence the decision to abort. In addition, the panel recommended that "the timing and method of abortion should not be influenced by the potential uses of fetal tissue for transplantation or medical research" (DHHS/NIH, 1988:4). In response to the assistant secretary's questions about potential pressure to modify the timing and method of abortion to secure older fetuses, the panel stressed that, according to the evidence it had received, there were no pressures for later abortions. It further insisted that, "to the extent that Federal sponsorship or funding is involved, no abortion should be put off to a later date nor should any abortion be performed by an alternate method entailing greater risk to the pregnant woman in order to supply more useful fetal materials for research" (DHHS/NIH, 1988:14).

Stressing the express donation model embodied in the UAGA, the panel's recommendations would allow the pregnant woman to choose whether to donate fetal tissue for research or some other purpose and to receive as much information as she needed regarding donation after she had decided to abort, without allowing her to know or to designate the recipient. By contrast, the 1989 report of Britain's Committee to Review the Guidance on the Research Use of Fetuses and Fetal Material (the so-called Polkinghorne report) recommended indeterminate donation to the extent of providing "no knowledge of what will actually happen to the fetus or fetal tissue"—to make it even less likely that the possibility of beneficial use of tissue will influence the woman's deci

sion to have an abortion—and not allowing her "to make any direction regarding the use of her fetus or fetal tissue" (p. 10). Reflecting differences in sociocultural context, the British report does not emphasize the disclosure of information to the pregnant woman to the same extent as the U.S. panel report does. Similarly, the U.S. panel recommended the disclosure of the source of the tissue—that is, that it came from a fetus or fetuses provided by induced abortion—so that the potential recipient of the transplant could choose not to participate; the British report recommended against such disclosure. However, both reports recommended disclosure of information about the tissue source to health care professionals.

OTHER ISSUES AND RECOMMENDATIONS

A few other issues and panel recommendations merit attention before we turn to other developments, including recent public policy responses. The panel insisted on procedures that would accord dead human fetuses "the same respect accorded other cadaveric human tissues entitled to respect" (DHHS/NIH, 1988:1).

Although the panel did not discuss the implications of this recommendation, the principle entails that the dead human fetus not be subjected to procedures that are undignified or that show disrespect toward "cadaveric human tissue." This position does not presuppose that the fetus is a full human being; instead it may rest on other convictions—for example, that the fetus is a potential human being and has symbolic significance even when dead, or that respect for human fetal tissue is appropriate to avoid offending those who view the fetus as a full or potential human being. At any rate, the principle of equal respect implies that if it is justifiable to use any "cadaveric human tissue" in transplantation research—for example, after accidents or homicides—then it is justifiable to use cadaveric fetal tissue after abortions.

Throughout its deliberations the panel recommended institutional procedures and arrangements to avoid conflicts of interest, that is, situations in which parties might have some incentive to encourage pregnant women to abort to provide fetal tissue. The panel concluded that concerns about the impact of the use of fetal tissue on the practices of abortion clinics could be "best addressed by strict adoption of a number of safeguards; safeguards that would eliminate or at least radically reduce profit motives and tendencies toward commercialization, and safeguards that would ensure the greatest possible separation between abortion procedures, facilities, and personnel on the one hand, and fetal-tissue research procedures, facilities and personnel on the other" (DHHS/NIH, 1988:10). These safeguards included the insistence, in

accord with current federal law and many state laws, that no fees be paid to the abortion clinic "for its efforts in procuring fetal tissue (other than expenses incurred in retrieving fetal tissue)" (DHHS/NIH, 1988:9; see also p. 10); in addition, however, the panel recognized that, in order "to prevent abortion clinics from making profits from fetal tissue donation, specific rules for what counts as a reasonable payment for retrieval expenses may be required" (DHHS/NIH, 1988:12). In accord with the spirit of the panel, other commentators have recommended additional precautions to separate the practices; for example, Annas and Elias (1989) argue that "to avoid any conflict of interest there should be no academic incentive (such as co-authorship of publications or grant support) or other incentive for the physician performing the abortion or anyone else involved in the woman's care, to obtain her agreement for the use of fetal tissue."

Another major set of issues centers on the justification of human fetal tissue transplantation *research*, particularly from the standpoint of potential recipients. According to federal regulations and common practice, ethically justified research must satisfy several criteria, including favorable benefit-risk ratios (Levine, 1986). Such benefit-risk analyses presuppose careful laboratory and animal studies before research involving human subjects can be justified. In response to Assistant Secretary Windom's question about whether animal studies justify HFTTR for certain diseases, the panel concluded that "there is sufficient evidence from animal experimentation to justify proceeding with human clinical trials in Parkinson's disease and juvenile diabetes," but not enough evidence from animal studies to justify proceeding with HFTTR for other diseases (DHHS/NIH, 1988:14; see also pp. 19–20). The panel did not have the research protocol that had been submitted to NIH and thus did not approve or disapprove a specific research protocol as a peer review process or institutional review board would have done.

OTHER DEVELOPMENTS AND PUBLIC POLICY RESPONSES

This case study has focused on the deliberations and recommendations of the HFTTR panel. The panel's report was submitted to the Director's Advisory Committee of NIH on December 14, 1988, with oral presentations by nine of the ten panel members who attended (another absent panel member's statement was entered into the record). The report of the Director's Advisory Committee, *Human Fetal Tissue Transplantation Research* (December 14, 1988), notes that the advisory committee members and NIH council representatives quickly concluded that the panel's report was "an impressive and skillfully crafted

document" that reflected "extensive and thoughtful work." "[G]iven the divisiveness underlying our society, on the issues related to the topic under consideration, the report represented a remarkable consensus" (Advisory Committee to the Director', NIH, 1988:4). After reviewing and discussing the panel's report, the advisory committee unanimously approved three recommendations:

- to accept the report and the recommendations of the panel as written;
- to recommend that the assistant secretary for health lift the moratorium on federal funding of human fetal tissue transplantation research utilizing tissue from induced abortions; and
- to accept current laws and regulations governing human fetal tissue research with the development of additional policy guidance as appropriate, to be prepared by NIH staff to implement the recommendations of the panel (Advisory Committee to the Director, NIH, 1988).

The panel's report and the advisory committee's report were not forwarded to DHHS until January 1989, just before the end of the Reagan administration, which took no action on the reports. After President Bush's inauguration, controversy developed over his nominee for secretary of health and human services, in part because of concerns about his stand on abortion and related issues, including HFTTR. Hearings on Louis Sullivan's nomination included attention to these matters, and during the hearings Sullivan commented that he had not read the two reports an HFTTR and could not respond until he had done so (Rich, 1989; Tolchin, 1989). The reports were not released to the public until April 1989.

Then, on November 2, 1989, in a letter to acting NIH director William F. Raub, Secretary Sullivan informed NIH of his decision to continue indefinitely "the moratorium on Federal funding of research in which human fetal tissue from induced abortions is transplanted into human recipients." Stressing his office's discretion in the matter, as well as the extensive review and public discussion, he identified several substantive considerations. First, the administration and Congress had made it clear that DHHS should not fund activities that encouraged or promoted abortion, and Sullivan was persuaded that "permitting the human fetal research at issue will increase the incidence of abortion across the country." He continued: "I am particularly convinced by those who point out that most women arrive at the abortion decision after much soul searching and uncertainty. Providing the additional rationalization of directly advancing the cause of human therapeutics cannot help but tilt some already vulnerable women toward a decision to have an abortion." In support of his position he notes that 18 of the

21 members of the panel agreed to begin their report with the statement that "[i]t is of moral relevance that human fetal tissue has been obtained from induced abortions." However, he did not examine the different meanings this statement about "moral relevance" had to the different panelists or consider the significance of the fact that the three dissenters from this part of the report were also opposed to HFTTR and dissented from the report as a whole.

Second, Secretary Sullivan doubted that the desired "strict wall" between the abortion decision and the donation decision could be erected, however clear it might be in theory, because it "may be necessary to consult pregnant women before the abortion is actually performed" to be able to utilize postmortem tissue promptly. This consultation could influence the woman's decision making process.

Third, Sullivan noted that if the research proved successful, there would be a demand for more fetal tissue. He seemed to suggest that there would be a subsequent demand for more abortions, but did not address the question of whether the current rate of abortions would be sufficient to provide the needed tissue.

Finally, he noted that HFTTR can be continued in the private sector to generate "whatever biomedical knowledge" might emerge. There has been some privately funded HFTTR—for example, during fall 1988, at the University of Colorado and Yale University, and it continues there and perhaps elsewhere in the United States as well as abroad; yet some people express the fear that without federal funding the field will not grow rapidly or attract the best researchers. In addition, Sullivan's acceptance of private HFTTR did not address the concern expressed by Judge Arlin Adams, chairman of the HFTTR panel, who opposes abortion except in very limited situations:

> *Without government funding there undoubtedly would be many efforts to use fetal tissue for medical research that would be completely unsupervised and not governed by any guidelines. Thus if the National Institutes of Health proceeds cautiously, and with carefully articulated safeguards and a program of periodic reviews, there would be much greater assurance that carefully crafted guidelines will be in place as an absolute condition to any research procedures. Such an arrangement would protect pregnant women and fetuses in a far more circumspect and intelligent manner than if the NIH did not participate in any way. (Adams, 1988.26–27)*

James Mason, assistant secretary for health, reiterated and further amplified the views of DHHS, as expressed by Secretary Sullivan. In particular, he averred that "if just one additional fetus were lost because of the allure of directly benefiting another life by the donation of fetal tissue, our department would still be against federal funding. . . .

However few or many more abortions result from this type of research cannot be erased or outweighed by the potential benefit of this research" (Mason, 1990:17). He stressed moral and ethical factors (mainly having to do with abortion) that had to be weighed with the potential benefits of the research and called for a common effort to "find alternatives to fetal tissue transplantation" and "explore other research paths that lead us to the same ends." After the announcement of the indefinite extension of the moratorium, some abortion opponents indicated that they would apply pressure to eliminate not only transplantation research but all federally funded research involving human fetal tissue (Kolata, 1989).

In view of the subsequent disregard by Secretary Sullivan of the panel's conclusions, some panelists have indicated that they should have pressed for stronger language—for example, in contending that HFTTR is not only "acceptable public policy" but also "ethically acceptable"—because the numerous efforts to find compromise language to gain the support of more panelists left the report vulnerable at points and subject to neglect, misuse, and misquotation. To take one instance, Assistant Secretary Mason claimed that the majority of the panelists indicated that "moral and ethical considerations were not central to their view of the issue" (Mason, 1990:17). Yet rather than denying the centrality of "moral and ethical considerations," the panelists in the majority arguably had a different view of the dictates of morality and ethics and offered a different balance of such considerations.

Critics have sharply challenged DHHS's indefinite extension of the moratorium. Thirty-two medical research and education organizations, including the American Medical Association, the Association of American Medical Colleges, and the American Academy of Pediatrics, wrote Secretary Sullivan on January 4, 1990: "It is clear to us that the potential for good to result from this research outweighs the concerns about the impact on the abortion rate in this country, concerns that are at best speculative. Continuing the moratorium ignores the suffering of millions of Americans" (Hilts, 1990). After reviewing some documents and requesting others, Congressman Ted Weiss (D-N.Y.) contends that DHHS has offered no documentation that HFTTR would increase the number of abortions. In addition, he notes, even a member of DHHS's Office of General Counsel conceded that an extension of the ban would have a "shaky legal base" unless it was made permanent in the proper way through public notice with public comment and then by establishing a rule (Hilts, 1990). "The so-called indefinite moratorium," Congressman Weiss continues, "is a thinly veiled scheme to ban Federal funds for fetal tissue transplant research while avoiding the public outrage and scientific and legal scrutiny that would result from establishing a per

manent ban. . . . I am hopeful Secretary Sullivan will be able to get beyond these abortion litmus tests to promote the crucial research that could be saving the lives of thousands of seriously ill Americans" (Hilts, 1990).

Similar themes emerged in the April 2, 1990, hearings on human fetal tissue research before the House Subcommittee on Health and the Environment of the Committee on Energy and Commerce, chaired by Congressman Henry Waxman. Following testimony from several members of the HFTTR panel, as well as by the assistant secretary for health, bioethicist John Fletcher accused the federal government of "moral recklessness" in the suppression and repression of several forms of research relating to the fetus and the embryo. He also noted the oddity of DHHS officials maintaining that it would be wrong for the federal government to fund HFTTR without condemning (and even apparently accepting) HFTTR funded through private sources.

CONCLUSION

In light of recent reports of the success of HFTTR for a Swedish (Lindvall, 1990) and a U.S. (Freed, 1990) patient with Parkinson's disease, the debate about the moral justifiability of the moratorium can be expected to continue. One former panelist, LeRoy Walters, has noted that the position taken by the panel, in contrast to the moratorium by DHHS, is in accord with the international ethical consensus on HFTTR using tissue from electively aborted fetuses. He observes that the recommendations of various committees or deliberative bodies around the world, which numbered at least nine by December 1988 and have been increased by several others since then, display "remarkable similarities." In fact, Walters says, there is "an impressive international consensus on the ethical standards that should govern the use of fetal tissue for research. The positions adopted in the panel's report are located squarely in the middle of this international consensus" (Walters, 1988; see also his testimony on April 2, 1990, before the Subcommittee on Health and the Environment). While conceding that there is no guarantee that such an international consensus is itself "ethically correct," Walters stresses that "we are less likely to make a serious moral mistake when numerous groups of conscientious men and women from around the world have sought to study the issue with great care and have reached virtually identical conclusions about appropriate public policy" (Walters, 1988). Within the United States, similar proposals, with minor variations, have emerged in the last two years from such groups as the Stanford University Medical Center Committee on Ethics (Greely et al., 1989) and the Councils on Scientific Affairs and on Ethical and Judicial Affairs of the American Medical Association (1990).

This case study has offered in passing several comparisons with other reports and actual or proposed policies in other countries, particularly the proposals of the Polkinghorne Committee in the United Kingdom in 1989. Several distinctive features of the social-political-cultural context in each nation account for differences in specific guidelines even within a strong international consensus on ethical standards. Obviously one major difference is the political strength of various groups that press certain moral visions or interests, such as the right-to-life movement in the United States. In addition, some concerns about HFTTR may be particularly appropriate in the United States because of special factors. First, many European countries have abortion laws that are more restrictive than those of the United States and thus may have less reason to fear the impact of HFTTR on abortion decision making and on the societal acceptance of abortion (Clendon, 1989). Second, there may be important differences in the commercialization and regulation of abortion clinics and of tissue procurement. For example, it could be argued that the HFTTR panel in the United States did not pay sufficient attention to actual institutional pressures (Annas and Elias, 1989), whereas the Polkinghorne report, which also recommended the separation of *decisions* regarding abortion and the use of fetal tissue, called for an intermediary as a mechanism of separation of the practice of abortion and the use of fetal tissue. (If there were more than one tissue bank, they would all function under a single intermediary organization.)

Sociocultural differences may lead to such variations in guidelines and approaches, even within a strong international consensus about the relevant ethical standards. One important question in the United States is whether, as some critics claim, public policy regarding HFTTR is being held hostage to the society's uneasiness about abortion, or whether the recommendations of the HFTTR panel or similar recommendations will be found to reflect an acceptable balance of ethical concern for fetuses, prior to and after their deaths; for pregnant women; for professionals and researchers; for patients who lack effective therapies and are potential beneficiaries of HFTTR; and for social integrity, including the democratic process. The debate is in part about how to proceed in a situation of doubt; thus, it also becomes a question of which side has the burden of proof when there is a lack of irrefutable evidence that it is possible to separate abortion decisions and practices sufficiently from decisions and practices regarding the use of fetal tissue following abortions. Because of the lack of irrefutable evidence, the panel recommended that the secretary of health and human services review the proposed guidelines at appropriate intervals. As of this writing, the moratorium continues to be defended by the secretary, and

Congress is considering legislation that would require a lifting of the ban. There is no doubt that this issue will continue to be argued on moral, ethical, legal, political, and medical grounds for some time.

EDITOR'S NOTE: A bill (H.R. 5661) that would lift the ban on federally approved fetal tissue transplantation research failed passage near the end of the 101st Congress. In January 1991, the American College of Obstetrics and Gynecology and the American Fertility Society announced they will form a national advisory board to monitor embryo and fetal tissue research in the absence of federal guidelines.

APPENDIX A

Appendix A is a March 1988 memorandum from the assistant secretary for health to the director of the National Institutes of Health. The memo lists 10 questions that should be addressed by a Human Fetal Tissue Transplantation Research Panel, once it is appointed and convened.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
National Institutes of Health

Memorandum

Date MAR 22 1988

From Assistant Secretary for Health

Subject Fetal Tissues in Research

To Director, National Institutes of Health

I have given careful thought to your request to perform an experiment calling for the implantation of human neural tissue from induced abortions into Parkinson's patients to ameliorate the symptoms of this disorder.

This proposal raises a number of questions--primarily ethical and legal--that have not been satisfactorily addressed, either within the Public Health Service or within society at large. Consequently, before making a decision on your proposal, I would like you to convene one or more special outside advisory committees that would examine comprehensively the use of human fetal tissue from induced abortions for transplantation and advise us on whether this kind of research should be performed, and, if so, under what circumstances.

Among other questions, I would like the advisory committee(s) to address the following:

1. Is an induced abortion of moral relevance to the decision to use human fetal tissue for research? Would the answer to this question provide any insight on whether and how this research should proceed?

2. Does the use of the fetal tissue in research encourage women to have an abortion that they might otherwise not undertake? If so, are there ways to minimize such encouragement?

3. As a legal matter, does the very process of obtaining informed consent from the pregnant woman constitute a prohibited "inducement" to terminate the pregnancy for the purposes of the research--thus precluding research of this sort, under HHS regulations?

4. Is maternal consent a sufficient condition for the use of the tissue, or should additional consent be obtained? If so, what should be the substance and who should be the source(s) of the consent, and what procedures should be implemented to obtain it?

B1

Page 2 - Dr. Wyngaarden

5. Should there be and could there be a prohibition on the donation of fetal tissue between family members, or friends and acquaintances? Would a prohibition on donation between family members jeopardize the likelihood of clinical success?

6. If transplantation using fetal tissue from induced abortions becomes more common, what impact is likely to occur on activities and procedures employed by abortion clinics? In particular, is the optimal or safest way to perform an abortion likely to be in conflict with preservation of the fetal tissue? Is there any way to ensure that induced abortions are not intentionally delayed in order to have a second trimester fetus for research and transplantation?

7. What actual steps are involved in procuring the tissue from the source to the researcher? Are there any payments involved? What types of payments in this situation, if any, would fall inside or outside the scope of the Hyde Amendment?

8. According to HHS regulations, research on dead fetuses must be conducted in compliance with State and local laws. A few States' enacted version of the Uniform Anatomical Gift Act contains restrictions on the research applications of dead fetal tissue after an induced abortion. In those States, do these restrictions apply to therapeutic transplantation of dead fetal tissue after an induced abortion? If so, what are the consequences for NIH-funded researchers in those States?

9. For those diseases for which transplantation using fetal tissue has been proposed, have enough animal studies been performed to justify proceeding to human transplants? Because induced abortions during the first trimester are less risky to the woman, have there been enough animal studies for each of those diseases to justify the reliance on the equivalent of the second trimester human fetus?

10. What is the likelihood that transplantation using fetal cell cultures will be successful? Will this obviate the need for fresh fetal tissue? In what time-frame might this occur?

B2

Page 3 - Dr. Wyngaarden

Based on the findings and recommendations of the advisory committee(s), I would like you to reconsider whether you would like to proceed with this kind of research, and, if so, whether you wish to make any changes, regulatory or otherwise, in your research review and implementation procedures for both extramural and intramural programs.

Pending the outcome of the advisory committee(s)' assessment and your subsequent review, I am withholding my approval of the proposed experiment, and future experiments, in which there is performed transplantation of human tissue from induced abortions. You will note that this does not include research using fetal tissues from spontaneous abortions or stillbirths. However, I would like the special advisory committee(s) to consider whether current research procedures are adequate for the appropriate ethical, legal and scientific use of tissue from these other sources.

I believe that greater input from outside professionals and also from the public will enhance protections for research participants and will help assure greater public confidence in our work.

Robert E. Windom, M.D.

APPENDIX B

Human Fetal Tissue Transplantation Research Panel

Arlin M. Adams *(Chair)*, Schnader, Harrison, Segal & Lewis, Philadelphia, Pennsylvania

Kenneth J. Ryan *(Chair, Scientific Issues)*, Chairman, Department of Obstetrics & Gynecology, Brigham and Women's Hospital, Boston, Massachusetts

LeRoy Walters *(Chair, Ethical and Legal Issues)*, Director, Center for Bioethics, Kennedy Institute of Ethics, Georgetown University, Washington, D.C.

J. David Bleich, Professor of Law, Cardoza Law School, New York, New York

James Bopp, Jr., Brames, McCormick, Bopp, and Abel, Terre Haute, Indiana

James T. Burtchaell, Professor of Theology, Department of Theology, University of Notre Dame, Notre Dame, Indiana

Robert C. Cefalo, University of North Carolina School of medicine, Chapel Hill, North Carolina

James F. Childress, Chairman, Department of Religious Studies, University of Virginia, Charlottesville, Virginia

K. Danner Clouser, Professor, Hershey Medical Center, Pennsylvania State University, Hershey, Pennsylvania

Dale Cowan, Hematologist/Oncologist, Marymount Hospital, Garfield Heights, Ohio

Jane L. Delgado, President and Chief Executive Officer, National Coalition of Hispanic and Human Services Organizations, Washington, D.C.

Bernadine Healy, Chairman, Research Institute, Cleveland Clinic Foundation, Cleveland, Ohio

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Ethics of Fetal Tissue Transplantation

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Now that the Clinton Administration has overturned the ban on federal funding for fetal tissue transplantation, old ethical issues renew their relevance and new ethical issues arise. Is fetal tissue transplantation necessary and beneficial? Are fetal rights violated by the use of fetal tissue in research? Is there a moral danger that the potential of fetal tissue donation will encourage elective abortions? Should pregnant women be allowed to designate specific fetal transplant recipients? What criteria should be used to select fetal tissue transplants? Whose consent should be required for the use of fetal tissue for transplantation? We review the current state of clinical research with fetal tissue transplantation, the legal history of fetal tissue research, the major arguments against the use of fetal tissue for transplantation, and the new post-moratorium ethical dilemmas. We include recommendations for guidelines to govern the medical treatment of fetal tissue in transplantation.

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Human fetal tissue transplantation is still experimental, and trials with animals and humans have shown limited success. But researchers and clinicians agree that, given social and legal support, fetal tissue transplants could soon promise unique therapy for dozens of crippling diseases with substantial morbidity and mortality. Clinical trials with human fetal tissue have already been conducted on patients with Parkinson's disease, insulin-dependent diabetes mellitus, the DiGeorge syndrome, severe combined immunodeficiency, aplastic anemia, acute myelogenous leukemia, thalassemia, Fabry's disease, the Hurler syndrome, and Gaucher's disease. Others have proposed that fetal tissue be used to treat Alzheimer's disease, congenital heart failure, congenital liver failure, congenital kidney failure, and a host of hematologic and endocrine abnormalities in adults and children. The patient population that could benefit from fetal tissue transplants is substantial.

Since *Roe versus Wade* legalized abortion in 1973, pregnant women and their developing fetuses have been at the center of one of the most heated public debates in American history. Scientific journals have steered clear of such politically charged controversy, and several federal panels have found vague language to evade moral stances on abortion. But the promise of fetal tissue therapy in a shifting political climate makes clear the need for opinions to be voiced frankly by the medical community.

We strongly favor the use of human fetal tissue for the purposes of medical therapy, and herein we discuss the current state of clinical research with fetal tissue transplantation, the legal history of fetal tissue research in the United States, the major arguments against fetal tissue transplantation, and a framework for solving ethical problems involving aborted fetuses. We conclude by proposing a set of ethical guidelines to govern medical uses of human fetal tissue.

Using Fetal Tissue for Transplantation

Fetal tissue transplantation may be able to overcome the failures of traditional medical and surgical therapy to ameliorate several diseases, most notably Parkinson's disease and insulin-dependent diabetes mellitus. Furthermore, the use of fetal tissue may be required to develop novel therapies for hematolymphoid diseases.

Medical and Surgical Alternatives

Medical alternatives to fetal tissue transplantation are currently being refined, but long-term cures remain elusive. Most persons with insulin-dependent diabetes currently use genetically engineered human insulin, combined with careful dietary management, to control blood glucose levels. Even with good glucose control, however, the disease progresses, and patients have a relatively early onset of peripheral neuropathy, nephropathy, retinopathy, and heart disease. Patients with Parkinson's disease derive some benefit from the drug levodopa, a congener of dopamine, but even with medication, they continue to ex-

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ABBREVIATIONS USED IN TEXT
NIH = National Institutes of Health
UAGA = Uniform Anatomical Gift Act

perience "on-off" episodes of neuromuscular control, and many young persons lose their ability to function at work and at home. Although multidrug trials with chemotherapy and radiotherapy hold promise for some hematolymphoid diseases, most of these diseases eventually resist medical treatment.

Surgical alternatives are overshadowed by unsatisfactory results and long-term requirements for immunosuppression. Some patients with Parkinson's disease have received autografts and allografts of adrenal medullary cells and xenografts of modified adrenal medullary cells from rodents and primates.[1] Many surgical protocols, however, particularly in the field of adrenal allografts, have been suspended in response to unpromising results.[2] Hematopoietic stem cell replacement is a possible therapy for some immunodeficiencies and hematologic cancers, but the research—much of which uses fetal tissue—is in its infancy.[3]

Although initially hopeful, pancreatic allograft and xenograft results provide little comfort for persons newly diagnosed with diabetes. And although the possibility of isolated islet cell xenografts is being actively pursued, no permanent success has yet been reported.[4] More than 3,000 persons with diabetes have received pancreas transplants during the past 26 years, and the most recent transplants have produced insulin-independent life-styles for 72% of the recipients. Unfortunately, all recipients require immunosuppressive medication, and the one-year mortality rate is about 8%.[5] Thus far, only persons with diabetes who have received kidney transplants and those who are severely impaired are considered for pancreas transplants. As a result, the long-term ability of these allografts to prevent the onset of the diabetic morbidity is untested.

Principles of Fetal Tissue Transplantation

Human fetal tissue is an attractive source of therapeutic transplants because it has two physiologic properties that make it more useful than adult or animal tissue. First, most fetal cells are hyperproliferative and multipotent, meaning that these donor cells are capable of quickly reversing the lost function of a host organ. Second, fetal cells may pose a low immunogenic threat to the cellular defenses of the host.[6,7] Current experiments with adult donor tissue are often limited by deficiencies in these properties.

Research on fetal tissue to develop medical therapy is not new. Fetal tissue research was responsible in the 1950s and 1960s for vaccines against polio and rubella, the treatment of Rh incompatibility, and the prenatal diagnosis of genetic diseases. But the use of fetal tissue as a means of medical therapy is new. Clinical trials with fetal neural, thymic, pancreatic, and hematopoietic tissue are underway internationally.

Fetal Tissue Transplantation in Humans

The only recorded successes with fetal tissue transplantation in humans are in treating Parkinson's disease[7-11] and a rare congenital disorder, DiGeorge syndrome.[12] The most accepted theory to explain Parkinson's disease attributes its cause to a relative deficiency of dopamine produced in the nigrostriatal region of a patient's brain. Operating on this theory since 1987, surgeons have transplanted dopamine-producing neural tissue from first-trimester abortuses into the brains of patients with Parkinson's disease. Results with 13 patients in three separate studies vary according to surgical technique and patient selection, but fetal tissue transplantation does improve self-assessed quality of life; it decreases the frequency and intensity of "freezing spells"—a characteristically disabling feature of the disease—and decreases the required dosage of levodopa.[8-10]

For more than 20 years patients with DiGeorge syndrome, an immunodeficiency resulting from the absence of thymus and parathyroid tissue at birth, have been known to respond well to transplants of fetal thymus tissue.[12]

Preliminary results with fetal tissue transplantation for other human diseases show little success. Fetal pancreatic tissue has been shown to reduce exogenous insulin requirements in humans with insulin-dependent diabetes, but only transiently.[13] Because fetal liver tissue is a robust source of pluripotent hematolymphoid cells, it has been used experimentally to treat hemophilia, severe combined immunodeficiency, aplastic anemia, and acute myelogenous leukemia. These treatments have produced minimal success, but most have been done late in the natural progression of the disease, after standard chemotherapeutic trials have failed.[10] In utero transplants to treat hematologic and immune deficiencies are being widely investigated in animals[14,15] and in humans.[16-18] Several medical and scientific organizations have concluded that fetal tissue transplantation will be a vital part of cellular therapy in years to come.[10]

Need for Tissue From Elective Abortions

During a 1991 Senate debate, the Bush Administration proposed an amendment that established a national network of tissue banks authorized to store only tissue from spontaneously aborted fetuses and ectopic pregnancies.[15] The tissue bank, administered through five national centers, cost $6 million to establish.[19] For logistical reasons, however, future success in human fetal tissue transplantation cannot depend on tissue from spontaneous abortions, stillbirths, and ectopic pregnancies. Unlike that from elective abortions, tissue from at least 60% of spontaneous abortions contains severe genetic defects. Even without genetic defects, a large percentage of these fetuses do not have enough differentiated tissue to be therapeutically useful. Of spontaneous abortions, only 3.8% (or about 28,000 fetuses) each year would provide tissue theoretically eligible for transplantation, but this figure includes many fetuses that are practically ineligible for transplantation because they died much earlier in utero or

because they were never karyotyped to rule out trisomy. Of ectopic pregnancies, 21% to 49% (18,000 to 43,000) are morphologically intact, but only 1% (880) are unassociated with tubal hemorrhage, a common cause of early organ death in fetuses.[20] The combined conservative total represents less than a third of the annual population diagnosed in the United States with Parkinson's disease and insulin-dependent diabetes mellitus. This low yield, combined with the burden of obtaining specimens from unscheduled events that often occur at home or in an emergency department, makes transplantable tissue from spontaneous abortions and ectopic pregnancies effectively inaccessible.

Legal History of Fetal Tissue Research

Although fetal tissue transplantation has been experimental in the United States since the 1930s, legal controversy over fetal tissue research did not arise until immediately after the Supreme Court's *Roe versus Wade* decision. On April 12, 1973, a 200-person protest organized by a Catholic girls' school persuaded a National Institutes of Health (NIH) official to voice publicly the government's opposition to the use of "live" fetal tissue for research. The next day, New York Representative Angelo Roncallo introduced legislation to ban all fetal tissue research in the United States.[21]

Political action on fetal tissue research remained dormant until March 1988, when Robert Windom, President Reagan's Assistant Secretary of Health and Human Services under Otis Bowen, imposed a moratorium on fetal tissue research for transplantation purposes, pending the recommendations of a 21-member NIH panel. After two days of public hearings and three months of deliberation, the panel concluded that funding human fetal tissue transplantation was acceptable public policy. Despite such institutional support for fetal tissue research, Secretary of Health and Human Services Louis Sullivan extended indefinitely the moratorium on federal funding of fetal tissue research for transplantation.

Separate measures to overturn the funding moratorium, appended to an NIH appropriations bill, passed in the House of Representatives in 1991 and in the Senate in 1992. Senate support was heavily influenced by personal appeals, including Republican Strom Thurmond's plea on behalf of his daughter, who has diabetes.[22] New legislation would have funded research on tissue donated from elective abortions, subject to clear evidence that "the decision to make the donation is made separately and independently of the decision to undergo the abortion."[23] But Senate filibustering at the end of the last congressional session in 1992 allowed the bill's demise.

Soon after taking office in 1993, President Clinton overturned by executive order the moratorium on federally funded fetal tissue transplantation. Since then, there has been a notable increase in grant applications to the NIH for proposals to use fetal tissue in experimental transplantation, and Congress is authorizing the Department of Health and Human Services to oversee the conduct of this research.

The Fetal Tissue Transplantation Debate

During the 1988 NIH panel hearings and during congressional debate concerning fetal tissue research, a common list of ethical questions was addressed:

- Is fetal tissue transplantation ethically acceptable? Should the integrity of a human fetus place it in a class entirely separate from that reserved for other biologic gifts, such as blood, kidneys, and hearts?
- Should fetal tissue acquired from elective abortions be exempted from research uses? Should a woman not be allowed to play contradictory roles as agency in a fetus's death and as proxy to authorize donation of the fetus's tissue?
- Must a pregnant woman give consent to allow her fetus's tissue to be used for research purposes?
- Should a woman be permitted to abort a fetus to provide transplantable tissue for a relative?
- Will fetal tissue transplantation indirectly encourage women to choose abortions? If so, is this effect ethically permissible?

It is not the task of ethical analysis to answer these questions definitively. Various polling organizations have already gauged popular opinion, and the results are not surprising. A survey of college students indicates support for federal funding of fetal tissue research and opposition to the idea of women designating specific fetal tissue transplant recipients.[24] Nor have centuries of ethical analysis created political consensus. Legislators, governors, judges, and the electorate may long continue to debate the wisdom of *Roe versus Wade*, the public funding of family counseling, and the public's access to experimental procedures. In 1989, the Stanford University Medical Center Committee on Ethics, composed of 48 representatives of the university community, agreed that human fetal tissue research, when subject to the legal rules of the Uniform Anatomical Gift Act (UAGA) and a prohibition against a woman's designating specific recipients of fetal tissue, is ethically acceptable.[25]

Our ethical analysis will suggest a responsible direction for public debate about fetal tissue transplantation, which operates under the assumption that in the prevailing legal climate of the United States, abortion performed under informed consent is ethically acceptable.

Is a Fetus a Person?

Whereas abortion may be ethically acceptable, the actual practice remains inherently distasteful to most persons. In fact, without such a prevalent distaste for abortion, this entire discussion would be moot. Abortions would be neutral events, and fetuses would be neutral products of those events, openly accessible to researchers and clinicians.

The equivocacy of personhood is a central reason for this distaste. When during gestation does a fetus become a person, with accompanying rights? How do we identify a fetus as dead or alive, viable or nonviable? Do the answers to these questions have any bearing on the

postabortion use of fetal tissue? These questions are best approached at three points during fetal existence:

- Personhood after fetal death is accepted by most ethicists and legal scholars as the easiest to assess.[26] Regardless of its antemortem status, a dead fetus claims the same rights as a dead person. As with any human cadaver, the closest relative or guardian of the deceased has whole authority over the disposition of the fetal cadaver.
- Personhood in utero, before viability, is difficult to assess ethically, largely because fetal viability is difficult to define medically. Medical judgment generally labels previable any fetus less than 24 weeks' gestational age (about 500 grams), estimated by ultrasonic measurement of the fetal anatomy. At this stage, it is generally agreed that, even with extraordinary medical treatment, fetal lungs are incapable of operating independently. Most states permit elective abortions to be done on fetuses under 20 weeks' gestational age. This definition was established, however, before the successes with intra-alveolar surfactant treatment and extracorporeal mechanical oxygenation, which now enhance the long-term survival of infants weighing less than 750 grams (26 weeks' gestation).
- Fetuses ex utero and alive create the greatest challenge to an ethical critique of fetal tissue transplantation. Abortion procedures depend on the gestational age at which they are done. During the first trimester (before 12 weeks), a fetus is removed by suction and curettage techniques. During the second trimester, a fetus can be delivered live after the induction of labor, or more commonly, the fetus can be dismembered in utero and the fetal parts manually extracted. The second-trimester procedures sometimes, although rarely, produce fetuses whose cardiovascular and brain-stem functions remain operative for several hours ex utero.[27] More than 90% of abortions performed in the United States are done during the first trimester,[28] and most current research with transplantation for Parkinson's disease and diabetes mellitus uses tissue from fetuses aborted during the first trimester.

Ethical problems exist only for those rare second-trimester abortions that produce whole, live fetuses. It must be assumed that during this time period, when the fetus ex utero is alive, it claims the concomitant rights of personhood. Strong ethical and legal principles argue against the use of tissue from fetuses during this period. Under the principles of the Nuremberg Code and the Helsinki Declaration, nontherapeutic experimentation without a subject's informed consent is unethical, particularly if that experimentation is harmful to the individual.[29] United States judicial precedent argues against the authority of parents or guardians to consent by proxy to the nontherapeutic use of a child's organs to save the life of another child.[26] (The state assumes the role of *parens patriae* to resolve a conflict of interest between the emotional needs of the guardians and the life-claiming needs of the child.) Although not absolute, the same legal principle can be used to argue against the donation of a kidney from a dying anencephalic infant.

It follows logically, therefore, that the transplantation of tissue from live fetuses ex utero should be prohibited. Tissue from second-trimester abortions should, however, be available for transplantation immediately after fetal death has been declared by a qualified physician. A woman should be allowed to consent to the use of tissue from a dead fetus during the antemortem period, and there is no ethical proscription against subsequently informing a researcher of the impending death.

Bad Science

Beyond the debate about fetal personhood, the following arguments against the use of fetal tissue for transplantation to living humans are commonly presented:

- The results of animal and human research trials have not been encouraging, medical alternatives to fetal tissue transplantation exist, and the potential benefits of such transplantation do not reduce mortality. A careful review of the literature by a British ethicist concludes that "the case for utilization of human foetal pancreas in transplantation is in no way strengthened by the results of animal experimentation."[27(p58)] Medical therapy for parkinsonism, diabetes, and hematologic disorders is available, and unlike heart-lung and kidney transplants from adult cadavers, fetal tissue transplants do not represent immediate, life-saving treatment.

Although the claims of possible benefits from fetal tissue transplantation are admittedly guarded, we should not prohibit continued research and clinical trials in this field. The Helsinki Declaration, which demands that successful trials in animals precede human trials of experimentation, allows clinicians and researchers to judge the meaning of the word "success." The most important element of an experimental trial is an effective process for affording the transplant recipient full and informed consent. Perhaps scientific critics of fetal tissue transplantation should be welcomed to review this informed consent process, but they should not ask for artificial means (such as a blanket moratorium) to slow the pace of clinical research.

- The scientific use of fetal tissue welcomes abortion as "good," a necessary precursor to advances in medical therapy. By extension, opponents claim, society would be supporting the institution of abortion. This runs directly against a prevailing American sentiment that prefers to condone abortion, not to afford it any independent admiration.

"Science, since people must do it, is a socially imbedded activity," writes Stephen Jay Gould in *The Mismeasure of Man*, a historical treatise that argues for social accountability in science.[30(p21)] Scientists and clinicians make implicit social judgments with every primate experiment, every drug toxicity screen, and every private research institution newly incorporated. There is no ethical proscription against American scientists implicitly supporting women's access to abortion procedures. Those researchers and physicians who object to abortion are under no obligations to participate in procedures associated with fetal tissue transplantation.

Encouraging Elective Abortions

According to the most-often-voiced argument against fetal tissue transplantation, the life-enhancing potential of the procedure may encourage more abortions. Opponents argue that by adding something "good" to a distasteful procedure, fetal tissue transplantation may encourage more women to opt for abortions. Worse yet, the marketability of fetal tissue may encourage indirect ways of increasing the abortion rate. Hypothetical slippery slopes run rich in this argument. Imagine the following plausible scenario:

In mid-1993, a phenomenally successful procedure to treat male-factor infertility requires the transplantation of testicular cells from fetal tissue of more than 14 weeks' gestation. (Elective abortion and infertility therapy share common properties: neither are funded by public insurance, and neither are recognized as life-threatening.) Less than half of all aborted fetuses are eligible to provide such tissue, and because of the approval by the Food and Drug Administration for mifepristone (RU 486), the incidence of elective abortions nationwide is declining. A shortage of tissue develops. Meanwhile, private medical corporations market the treatment to thousands of infertile men, creating an increased demand. Because of these pressures, the incidence of abortion increases.

The claims are threefold: that the abortion rate will increase, that an increasing abortion rate is wrong, and that the influences that will create this increasing abortion rate are wrong. The first claim is wildly speculative, but for the purposes of this ethical analysis, it may be conceded. The second claim has already been discussed: namely, that although abortion may be distasteful, its exercise in the United States is ethically acceptable. The third claim requires further consideration.

Fetal Tissue Donation and Decision-making Autonomy

To understand why the third claim of the argument is untenable, we must first define "influence." Faden and Beauchamp depict a graded continuum of influences on a patient's decision-making process.[31] The goal of their analysis is to identify what they call "substantially controlling influences" that unduly compromise autonomous decision making. At one end of this continuum is rational persuasion, the art of convincing the family of a febrile patient with mental status changes, for example, to provide consent for a lumbar puncture. Persuasion falls entirely within ethical boundaries because it is a noncontrolling influence. At the other end of the continuum is coercion, strictly defined as any irresistible threat that causes a person to do something they otherwise would not do. Coercion exists when a researcher threatens to fire an employee unless that employee participates as a research subject. Coercion is ethically impermissible.

The middle ground on the continuum is manipulation, which may or may not be "unduly controlling." The US Public Health Service was unethical when it unduly manipulated (some claim "exploited") economically deprived men to participate in the Tuskegee (Alabama) syphilis experiments by providing irresistible offers of free food, medication, and burial assistance.[32] A professor would be within ethical boundaries, however, in offering extracredit points to students who enroll as research subjects because the offer is both welcome and (under the provision perhaps that a "B" not be convertible to an "A") resistible.[31]

Certainly any financial reimbursement for fetal tissue donation is ethically unconscionable because it may substantially compromise a woman's decision-making autonomy. Although welcome, it may not be effectively resistible. The UAGA's existing prohibition against the sale of human organs should be extended to protect fetal tissue donation from such controlling influences.

Could the altruistic thought of fetal tissue transplantation impose a controlling influence on a pregnant woman's decision about abortion? If a family member with diabetes or Parkinson's disease stands to benefit from a fetal tissue transplant, a woman might find reason to abandon fundamental beliefs against abortion. This effect may be real, but it is not coercive because the option of abortion is freely resistible and nonthreatening. There is one scenario, however, that could foster undue manipulation. If the woman were allowed to designate a specific person as the recipient of the transplant, the option of abortion may become effectively irresistible. In the case of permitting designated recipients, fetal tissue transplantation may be considered a substantially controlling influence over a woman's decision-making autonomy.

There must be safeguards in the donation process. First, financial incentives for fetal tissue donation should be declared explicitly illegal. Second, a woman should not be allowed to designate a specific recipient or group of transplanted tissue for her aborted fetus's tissue.

Ethical Dilemmas

Now that the scientific support, the political reality, and the ethical acceptability of fetal tissue transplantation have been established, new ethical issues arise. The Department of Health and Human Services will soon be creating guidelines and "safeguards" governing the use of fetal tissue. Many new questions must be addressed: How should fetal tissue be procured? Which transplant recipients should be given preference, and which diseases should be given preference? What type of informed consent ought to be obtained? Who should be responsible for obtaining informed consent from the tissue donors?

Managing Fetal Tissue

Tissue from an aborted human fetus deserves the same respect and dignity afforded tissue from an adult cadaver. A fetus possesses moral integrity, unlike blood or a kidney, and as such should be respected as a donor, not as a gift. By this definition, all fetal tissue donated for scientific research may be governed by the same ethical principles that govern the use of cadaveric organs.[33] In more than 95% of cases, an adult trauma victim, like a deceased fetus, contributes no direct consent to authorize organ donation. Instead, the UAGA designates the closest

relative, usually the parents of the deceased, to act as proxy for such consent. As such, any fetus whose death is unavoidable, as in the cases of spontaneous abortions and ectopic pregnancies, should be treated as would the body of a deceased adult.

Likewise in "avoidable" cases of elective abortion, fetal cadavers should be afforded the same dignity, neither more nor less, as that of adult cadavers. Indeed, some suggest that fetuses from elective abortions deserve greater protection from research use than do adult cadavers. Nolan extends this argument to conclude that fetuses from elective abortions should be ineligible as sources of transplantable tissue.[34] She argues that any woman who acts as an "agency of death" of a relative should not be able to act also as a decision-making proxy for that relative's organ donation. The fetus, in this model, is a murder victim, not an accident victim. Therefore, she suggests, only tissue from spontaneous abortions and ectopic pregnancies should be used in research.

To answer this argument, we must first understand that it is based on a moral opposition to the abortion procedure itself. It assumes that abortion is murder and that affording any authority to the murderer is wrong. The prevailing legal climate, however, "acquits" a woman choosing abortion of the charge of murder. Against that simple premise, the argument cannot stand.

But even if we accept the assumption that the fetus is a murder victim, the argument against the use of elective abortuses fails. Murder victims, like accident victims, are eligible organ donors under the provisions of the UAGA. The only prohibition, then, would be against asking the "agency of death" for consent. If the woman were to be viewed as a murderer, authority for donating tissue would rest in the hands of the nearest surviving relative—the woman's husband, the fetus's father, the woman's child—or, if one is neither available nor competent, authority would rest on a court order. The result (that each abortion require a search for the appropriate consenting adult) is absurd, but it does not prohibit the use of tissue from elective abortions. Instead, it makes the process cumbersome for clinicians and medicolegal staff, and it unjustly alienates women.

The UAGA, which has been active in most states since 1985, dictates guidelines for the treatment of any donated human tissue, including the following:

- No monetary compensation or services, including medical services, should be exchanged for donor tissue. The construed purpose of this guideline for fetal tissue transplantation is to protect a woman from undue manipulation during her decision to terminate a pregnancy.
- Informed consent should be obtained from the closest competent donor family member. By law, this gives the woman and the child's father equal power to authorize consent.

Under these guidelines, donors are allowed to designate recipients of donated organs, and the handling of donated tissue is not discussed. With this in mind, we recommend two additions to the guidelines established by the UAGA, designed specifically to address the sensitive issues of abortion and fetal tissue donation:

- The donor and donor family should be disconnected from the process of choosing the transplant recipient. As previously discussed, this prevents unjust consequences for recipients and undue influence on the donor families.
- Donor tissue should be acquired discreetly and rapidly. The most recent review of the literature indicates that the therapeutic function of grafted dopaminergic cells is greatest when the donor tissue is fresh.[35] Nonetheless, the tissue deserves the respect in handling that would be afforded any human cadaver. We recommend that each clinical facility providing donor fetal tissue include in its code a provision for Institutional Review Board oversight of fetal tissue procurement.

Selecting Recipients

The field of fetal tissue transplantation has yet to face a daunting obstacle that for years has complicated the field of adult organ transplantation: the inadequate supply of needed tissue. Current projections estimate the yearly incidence of elective abortions at about 1.5 million,[28] and the maximum estimate for the Parkinson's disease population of the United States is just under 510,000.[36] Should current experiments become remarkably successful with Parkinson's disease, the supply of transplantable tissue should be adequate. Furthermore, many researchers suggest a future in which one aborted fetus may be used to create multiple cell lines that have the potential to treat hundreds of patients. Nonetheless, if new protocols with other diseases prove fetal tissue transplantation useful in the treatment of larger patient populations such as those with diabetes or leukemia, the problem of rationing fetal tissue may become real.

Given that recipient populations for fetal tissue therapy are largely hypothetical, creating criteria now to help allocate donor tissue in the future is premature. Useful themes exist, however, in the current systems for choosing recipients of pediatric and adult organs. The process of organ procurement and allocation is orchestrated by the National Organ Procurement and Transplantation Network, established by Congress in 1984. Criteria to exclude possible recipients are social and medical: advanced age, inability to pay, lack of psychosocial support, psychiatric illness predisposing to noncompliance with a strict medical regimen, incompatible blood type, systemic infection, degree of organ failure, and a list of other medical conditions that varies with the type of transplantation. Ad hoc amendments to these criteria are often made, based on subjective judgments of social appropriateness or of the degree of medical emergency.[37] The social criteria are clearly the most ethically problematic, but they have withstood more than a decade of debate in the bioethics literature. These criteria can be debated on the same grounds regardless of the origin of the donated tissue.

Anticipating the arrival of fetal tissue transplantation

as a therapeutic reality, we suggest that any recipient selection scheme should include the following:

- A federal mandate to the National Organ Procurement and Transplantation Network to create a national registry of possible fetal tissue recipients.
- An annual conference of fetal tissue researchers, physicians, and surgeons to determine medical exclusion criteria specific to each of the newly approved therapies.
- The inclusion of bioethicists, psychiatrists, legal experts, and organ recipients in the annual conference to participate in the creation of exclusion criteria that are nonmedical.
- A prospective study of all fetal tissue recipients to accumulate data that will further inform the annual conference.

Requiring Informed Consent

Because a human fetus is more than a vestigial organ from the female body, researchers should not be allowed to acquire fetal tissue without a woman's consent. Under UAGA regulations, the fetus should be treated as donor and the pregnant woman as "next of kin." As already explained, the act of abortion does not disqualify her as an appropriate proxy for decision making regarding donation.

Under these definitions, informed consent for using fetal tissue in transplantation should be obtained from a pregnant woman before she has an elective abortion. Noting that the UAGA's definition of "next of kin" includes the father, the NIH advisory committee in 1988 added that fetal tissue should not be used if the father objects, "except in cases of incest or rape."[38] It is unnecessary, both from an ethical perspective and from a practical perspective, for researchers or transplant surgeons to obtain this consent in person. The best requester is a good communicator and counselor. In the area of cadaveric organ transplantation, the requester is usually a primary care physician, a primary care nurse, an emergency department physician, or an experienced liaison person from a local organ procurement organization. Similarly, fetal tissue researchers may opt to provide informed consent information through either physicians or an organ procurement organization. Once consent is obtained, the tissue should be removed from the operating suite by an authorized representative of the fetal tissue transplant team.

Informed consent should be requested only in cases in which there is a reasonable chance that the fetal tissue will be used for transplantation purposes. Given the currently low demand for such tissue, it would be unreasonable to require that all women seeking abortions be counseled about fetal tissue transplantation.

Ethics of Persuasion

Could the demand for fetal tissue encourage indirect inducements to abortion? As explained earlier, the supply of fetal tissue from elective abortions exceeds the current demand. But even if the demand increases dramatically, the feared inducements to increase abortion rates may likely be unsuccessful. After ten years of legal requirements and millions of dollars in educational efforts, the attempt to increase organ donation rates of adult donors has been largely unsuccessful. It is unlikely that less direct attempts to increase abortion rates would be more successful.

Even if successful, there is nothing morally wrong with providing information about fetal tissue transplants to influence a woman's decision making. This is the sort of rational portrayal of information that Faden and Beauchamp call persuasion.[31] Photographs of bloody fetuses have strong persuasive power, but their issuance to pregnant women contemplating abortions is not morally wrong. Similarly, the potential that tissue extracted from fetuses may improve the lives of persons with Parkinson's disease offers persuasive information that should not be peremptorily excluded from a woman's decision-making process.

One recently proposed piece of legislation threatened to limit such free exchange of information. Congressional bill HR 2507 explicitly exhorted a woman to identify the influences on her choice to have an abortion to ensure that fetal tissue transplantation is not one of those influences. The bill's language required physicians to be participants in this scrutiny.[23] Women get pregnant for many reasons, but no one suggests the need to monitor every woman's motivations to get pregnant. No legislator seriously proposes that pregnant women seen in publicly funded maternal health clinics sign documents attesting that their decision to have a child is "separate and independent" of economic, medical, or other external influences. Extending the same argument, no legislator should seriously propose to scrutinize a woman's decision-making process to terminate her pregnancy.

If the need for fetal tissue becomes as great as the current need for cadaveric organs, state governments may consider expanding the required request legislation to include women seeking abortions as a mandated population for organ donation requests. Persuading women to donate fetal tissue is not only ethically permissible, it may prove to be ethically necessary.

Suggested Guidelines for Fetal Tissue Transplantation

Based on the analysis of the ethical challenges to the use of fetal tissue, we suggest that fetal tissue transplantation is an ethically appropriate activity when subject to the following stipulations:

- Fetal tissue derived from dead fetuses resulting from elective abortions should be included under the principles of the Uniform Anatomical Gift Act.
- Financial incentives to a donor's family, physicians, researchers, or any other party involved in the donation of fetal tissue should be prohibited.
- Women donating fetal tissue should not be permitted to designate specific recipients of that tissue.
- Informed consent specific to the use of fetal tissue for research and transplantation should be made available to all women whose aborted fetuses may be used for the purposes of transplantation.

• Each clinical facility providing donor fetal tissue should mandate in its code Institutional Review Board oversight of fetal tissue procurement.

• The National Organ Procurement and Transplantation Network should include fetal tissue transplant recipients in its national registry.

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HOLD FOR RELEASE
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BY WITNESS
March 2, 2016

Statement of
Lawrence Goldstein, Ph.D.
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Dept. of Neurosciences
Director, UC San Diego Stem Cell Program
Scientific Director, Sanford Consortium for Regenerative Medicine
Director, Sanford Stem Cell Clinical Center, UCSD School of Medicine

before the

Select Investigative Panel
Of the
Committee on Energy and Commerce
United States House of Representatives

Good morning Chairwoman Blackburn, Ranking Member Schakowsky, and other Members of the Committee.

Thank you for the opportunity to testify before you this morning about the important and lifesaving research being done with fetal cells and fetal tissue, and to briefly share three examples of this research, and the potential impact of this research.

Background

My Bachelor's degree in biology and genetics is from the University of California San Diego in 1976.

My Ph.D. in genetics is from the University of Washington in 1980.

I did postdoctoral work at the University of Colorado at Boulder and MIT and was a junior faculty member and then tenured professor at Harvard University until 1993.

I moved to the University of California San Diego in 1993 where

I am currently a distinguished professor in the department of Cellular and Molecular Medicine and the Department of Neuroscience.

I serve as Director of the UC San Diego stem cell program, Scientific Director of the Sanford Consortium for Regenerative Medicine and Director of the Stanford Stem Cell Clinical Center. I have received numerous honors and awards for my work, including election to the American Academy of Arts and Sciences.

I have been a practicing scientist for 40 years, most recently using all types of stem cells to understand and treat Alzheimer's disease, spinal cord injury, ALS, kidney and liver disease, and other terrible afflictions.

On behalf of myself and the International Society for Stem Cell Research and the American Society for Cell Biology, two distinguished scientific and medical organizations with membership of more than 10,000 scientists around the world and based on over four decades of biomedical research experience, it is my

privilege to provide you with up to date and state of the art information about the important value of fetal tissue and cell research.

Research

My message is simple: fetal tissue and cells that would otherwise be discarded play a vital role in modern cutting edge medical research. These fetal tissues and cells cannot be replaced by embryonic stem cells, reprogrammed stem cells, or adult stem cells. These other cell types do not make astrocytes with identical properties as those from fetal sources.

I'll give you three examples of vital cutting edge-state of the art medical research that depends upon the use of fetal tissue and cells that would otherwise be discarded: 1) Alzheimer’s disease; 2) spinal cord injury; and, 3) kidney generation.

In the first example, my lab uses human reprogrammed stem cells to develop cells in culture that have the behavior of Alzheimer's disease. This devastating disease afflicts millions of Americans and costs the United States billions of dollars a year in health care costs. This number does not fully reflect the very real and terrible personal costs that so many American families, friends, and colleagues face with this disease. We do not have a cure, nor is one obviously in sight; we must find a

way to successfully treat this terrible disease. In my own lab, we use Alzheimer's disease cells to understand why brain cells with Alzheimer's disease are abnormal and to try to develop drugs. A type of cell that is valuable in this work is called an astrocyte, which is a support cell type in the brain. We use fetal astrocytes, which are vital to these research investigations. These fetal astrocytes provide growth factors that keep nerve cells healthy and other factors that are not yet defined that help the neurons establish connections and maintain long-term growth and viability. Although we can make cells that are similar to astrocytes from stem cells, the fetal astrocytes are the "gold standard" to which we compare astrocytes made from stem cells and which we cannot use yet to replace the fetal astrocytes because they are not identical in capacity to the best of our current knowledge. The fetal astrocytes are vital to these investigations, which I think will help conquer the terrible scourge of Alzheimer's disease.

In a second example, in the Center that I direct, the Sanford Stem Cell Clinical Center, fetal neural stem cells are being used in clinical trials for spinal cord injury in human patients. These fetal neural stem cells have previously been shown to yield remarkable results in animals that have spinal cord injury. These fetal stem cells, when implanted at the site of a spinal cord injury in animals develop into new neurons that appear to function as relays across the site of the injury rendering

the animals able to function in a way that is superior to their performance before the injury. As a result of these investigations, we have FDA approval to test the fetal stem cells in human patients. Physicians and surgeons in my center have initiated an FDA-approved phase 1 clinical trial of these cells and have implanted them in four patients to date. These surgeries are very arduous and the human volunteers are courageous in the face of uncertainty about their future. The trial is a success thus far. We have learned that at a minimum the surgery is safe and the fetal cells are safe. We will track the patients over the next few years to observe what we are hopeful will be evidence of beneficial effect on the patients' paralysis. Our next goal is to advance this trial to cervical spinal cord injuries soon . We hope to see evidence of positive impact on these patients as time progresses over the next 3-5 years. This trial and others like it are vital to pushing medical science ahead in our attempts to cure spinal cord injury, which is a terrible affliction to patients and the families who care for them. These same fetal neural stem cells are also being used in NIH clinical trials at various sites around the country for another incurable and devastating disease called ALS or Lou Gehrig's disease.

In a third example, I chair the executive committee of a group of NIH-funded scientists who are working together to try to learn whether it is possible to build new kidneys from stem cells. The hoped-for building of new kidneys is significant

because 93,000 Americans are on waiting lists for kidney transplant. The goal of building a functional kidney is audacious, but one that I believe can be obtained with hard work, determination, and time. Fetal tissue that would otherwise be discarded is vital to the future of this investigation as it is only by examining this fetal tissue that it will be possible to determine the earliest biochemical signals that cells use to tell some cells to make kidneys and other cells to make other organs.

Our ability to examine the earliest stages of human development are vital to our understanding and our ability to treat many diseases in the future including diseases of pregnancy, diseases of the placenta, and diseases of children and adults. Development of many of these new therapies will rely on our learning and understanding of the proper developmental signals that cells use at the earliest stages of development. We must continue to use fetal tissue that would otherwise be discarded and that is a window into the early stages of human development. Without fetal tissue, vital research such as the examples I have shared with you will be slowed down that would otherwise lead to therapies and vaccines sooner in the future and which could literally be life changing for individuals and their families in the future.

Summary

Let me close by stating once again that in my opinion research with fetal tissue and cells that would otherwise be discarded is ethical, valuable, and vital to ongoing biomedical research projects. If we do not continue to use this tissue that is destined for discard, we forego the ability of researchers to continue to make timely and significant progress in mitigating if not eliminating devastating diseases like Alzheimer's and improving the quality of life of many people in the future.

I want to thank the Committee for allowing me the opportunity to share a researcher's perspective on the importance of fetal tissue and cells to biomedical research.

Chairwoman Blackburn, I would be pleased to respond to any questions you or the other Members of the Committee may have regarding my research.

One page summary of the testimony of Dr. Lawrence S. B. Goldstein to the Select Investigative Panel on Infant Lives Of the Committee on Energy and Commerce, United States House of Representatives

1) Dr. Lawrence S.B. Goldstein is a highly qualified scientist who is knowledgeable about the value of fetal tissue research.

2) Research with fetal tissue that would otherwise be discarded has great value in research on many different diseases including Alzheimers disease, spinal cord injury, ALS and others.

3) Research with fetal tissue that would otherwise be discarded may help us learn how to construct new organs from stem cells.

4) Research with fetal tissue that would otherwise be discarded cannot be replaced by research with other types of cells or with animals.

ACOG Statement In Support of Fetal Tissue Research

March 30, 2016

Washington, DC – Mark S. DeFrancesco, MD, MBA, President of the American Congress of Obstetricians and Gynecologists (ACOG), today released the following statement:

"Obstetrician-gynecologists are physicians who specialize in the care of women throughout their lives. We guide younger patients into healthy adulthood, we counsel them as they build their families, we assist them if they choose not to have children, and we help them to stay strong and well through their postmenopausal years.

"We recognize that decades of medical breakthroughs have resulted in lasting improvements in the lives of our patients and their families, and we celebrate our ability to not just treat, but in some cases, to actually prevent or even cure debilitating and life-threatening diseases.

"However, current attacks on fetal tissue research, part of an effort to oppose and disparage safe, legal abortion in this country, represent a significant setback in our Nation's approach to science and our patients' hope for future breakthroughs.

"Ob-gyns treat women battling various forms of cancer as well as diseases like Parkinson's or multiple sclerosis. Our patients may be caring for their own children with conditions that have poor prognoses, like cystic fibrosis. Scientific research has given us some tools that help us improve patient's lives and outcomes when battling these conditions, but there is more work to be done, and fetal tissue research may play an important role in tomorrow's breakthroughs.

"The current Zika virus outbreak shows that we must use the full potential of science, including fetal tissue research, if we hope to develop a vaccine or a medicine that will allow us to prevent serious birth defects and even deaths in the future. Already, scientists studying Zika have gathered strong evidence about the disease and its potential association with birth defects through fetal tissue analysis.

"Women affected by Zika virus are terrified about their own health and the health of their families. We must do everything we can to help them and protect more families faced with a Zika diagnosis during pregnancy, especially as this outbreak continues to grow.

"Unfortunately, some state and federal politicians are working hard to obstruct — or even criminalize — fetal tissue research, limiting the ability of scientists and researchers to develop new vaccines and medicines to prevent and treat disease.

"America's scientists and researchers have helped this country be a leader in medical advances, and our patients have benefited from these breakthroughs. This work benefits our communities and economy, as well. But by barring medical innovation, fetal tissue research bans will stymie U.S.-based medical progress, leaving us to rely on other countries to develop medicines for our own patients.

"Now, some in Congress want research institutions to hand over the names of individual researchers, doctors, and medical students engaged in this life-advancing research. This is an invasion of academic freedom, a serious government overreach, and an effort to intimidate scientists who have devoted their careers to helping patients and improving lives. This is simply politicians interfering with important medical science.

"We are at a crossroads. We can either look to the future and build upon a rich foundation of American leadership in health care, or we will hamstring our researchers, attack their reputations, and leave our patients to suffer. We are better than that.

"We urge politicians to stand up not only for fundamental American freedoms, but also for families who, without this research, will have very little hope for tomorrow's cures."

ACOG has signed onto a joint letter in support of fetal tissue research. That letter can be found here.

The American College of Obstetricians and Gynecologists (The College), a 501(c)(3) organization, is the nation's leading group of physicians providing health care for women. As a private, voluntary, nonprofit membership organization of approximately 58,000 members, The College strongly advocates for quality health care for women, maintains the highest standards of clinical practice and continuing education of its members, promotes patient education, and increases awareness among its members and the public of the changing issues facing women's health care. The American Congress of Obstetricians and Gynecologists (ACOG), a 501(c)(6) organization, is its companion organization. www.acog.org

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NEWS FEATURE

COURTESY OF LEONARD HAYFLICK

Leonard Hayflick, pictured in 1982, inspects WI-38 cells that he derived from aborted fetal lungs. The cells have been used to produce vaccines in use worldwide.

Cell division

In 1962, Leonard Hayflick created a cell strain from an aborted fetus. More than 50 years later, WI-38 remains a crucial, but controversial, source of cells.

BY MEREDITH WADMAN

The woman was four months pregnant, but she didn't want another child. In 1962, at a hospital in Sweden, she had a legal abortion.

The fetus — female, 20 centimetres long and wrapped in a sterile green cloth — was delivered to the Karolinska Institute in northwest Stockholm. There, the lungs were dissected, packed on ice and dispatched to the airport, where they were loaded onto a trans-atlantic flight. A few days later, Leonard Hayflick, an ambitious young microbiologist at the Wistar Institute for Anatomy and Biology in Philadelphia, Pennsylvania, unpacked that box.

Working with a pair of surgical scalpels, Hayflick minced the lungs — each about the size of an adult fingertip — then placed them in a flask with a mix of enzymes that fragmented them into individual cells. These he transferred into several flat-sided glass bottles, to which he added a nutrient broth. He laid the bottles on their sides in a 37 °C incubation room. The cells began to divide.

So began WI-38, a strain of cells that has arguably helped to save more lives than any other created by researchers. Many of the experimental cell lines available at that time, such as the famous HeLa line, had been grown from cancers or were otherwise genetically abnormal. WI-38 cells became the first 'normal' human cells available in virtually unlimited quantities to scientists and to industry and, as a result, have become the most extensively described and studied normal human cells available to this day.

Vaccines made using WI-38 cells have immunized hundreds of millions of people against rubella, rabies, adenovirus, polio, measles, chickenpox and shingles. In the 1960s and 1970s, the cells helped epidemiologists to

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Listen to a podcast about the WI-38 story at:
go.nature.com/nkoyah

identify viral culprits in disease outbreaks. Their normality has made them valuable control cells for comparison with diseased ones. And at the Wistar Institute, as in labs and universities around the world, they remain a leading tool for probing the secrets of cellular ageing and cancer.

"Here's a clump of cells that has had an enormous impact on human health," says Paul Offit, chief of the division of infectious diseases at the Children's Hospital of Philadelphia. "These cells from one fetus have no doubt saved the lives of millions of people."

Few people, however, know the troubled history of the cells — one that may offer lessons for modern researchers seeking to work with human tissues. Six years after deriving his famous strain, Hayflick made off with stocks of the cells and later started to charge for shipping them, prompting an epic legal battle with the US National Institutes of Health (NIH) in Bethesda, Maryland, about who owned the cells. That struggle nearly destroyed Hayflick's career and raised questions about whether and how scientists should profit from their inventions.

What's more, the WI-38 strain has helped to generate billions of dollars for companies that produce vaccines based on the cells, yet it seems that the parents of the fetus have earned nothing. That recalls the earlier development of the HeLa cell line, named after the woman whose tumour gave rise to the cells and chronicled in Rebecca Skloot's book *The Immortal Life of Henrietta Lacks* (Crown, 2010). As with HeLa, the WI-38 case highlights questions about if, and how, tissue donors should be compensated that are still urgently debated today. Last month, for example, some scientists in the United States found themselves barred from using new stem-cell lines derived from human embryos because women had been paid for the eggs used to make them (see *Nature* http://doi.org/mv2; 2013).

The story of WI-38, unlike that of HeLa, also has its own controversial twist because it was derived from an aborted fetus. For 40 years, anti-abortion activists have protested against the use of WI-38 and vaccines developed from it. "It's still a live issue," says Alta Charo, a professor of law and bioethics at the University of Wisconsin Law School in Madison. "We still have people who refuse to take these vaccines because of their origins in fetal tissue."

SEEKING CELLS

When Hayflick opened up that icy package from Sweden in 1962, he was working at the vanguard of virus research in the United States. At the time, the Wistar Institute was led by Hilary Koprowski, a polio-vaccine pioneer who hired Hayflick to run the centre's cell-culture laboratory and supply cells to researchers. But Hayflick also began investigating whether some human cancers might be caused by viruses. To do so, he needed a resource that did not yet exist: verifiably normal human cells that could be reliably grown in the lab. Fetal cells, he thought, were an ideal candidate, because they were less likely to have been exposed to viruses than adult cells.

Although abortions were technically illegal in Pennsylvania at the time, they were still performed when doctors said they were medically necessary. Hayflick says he was able to obtain fetuses straight from the operating room of the University of Pennsylvania Hospital across the street from Wistar. Unless the tissue was put to some use, he reasoned, "it was definitely going to end up in an incinerator". The University of Pennsylvania says that it is unable to find records to confirm the source of fetal tissues used by Hayflick.

Hayflick developed 25 different fetal-cell strains, numbered WI-1 to WI-25. But several months into the project, he began to notice something strange. Scientific orthodoxy held that cells in culture, properly treated, would replicate forever. But his oldest cell strains were beginning to replicate more slowly. Eventually, they stopped dividing altogether.

In 1961, Hayflick and his colleague Paul Moorhead published a paper[1] that would become one of the most cited publications in biology. Entitled 'The serial cultivation of human diploid cell strains', it showed that normal fetal cells stop replicating after about 50 population doublings. The paper launched a new field: the study of cellular ageing. And the wall that the cells hit — which was later found to arrive much earlier for adult cells, which have already divided many times[2] — became known as 'the Hayflick limit'.

Crucially, Hayflick and Moorhead also showed that the fetal cells remained viable after months in the freezer and that, once thawed, they would 'remember' how many replications they had been through and would pick up where they left off. "It's apparent," the authors wrote, "that by freezing cells at each subcultivation, or every few subcultivations, one could have cells available at any given time and in almost limitless numbers." What's more, the pair's cells turned out to be easy to infect with a broad range of human viruses, suggesting that they would be perfect vehicles in which to grow viruses for vaccines.

> *"These cells from one fetus have no doubt saved the lives of millions of people."*

Hayflick decided to derive a fetal cell strain that he hoped would become both a ubiquitous laboratory resource and a substrate for industrial-scale vaccine manufacturing. He had support: in February 1962, the National Cancer Institute awarded Wistar, with Hayflick as co-principal investigator, a contract "to produce, characterize, store and study human diploid cell strains and to distribute such cell strains to all qualified investigators".

SUCCESSFUL STRAIN

By this time, Hayflick had turned to a different source for his fetal tissues: Sven Gard, chairman of the department of virology at the Karolinska Institute in Sweden, where abortion was legal. In June 1962, Hayflick received the set of lungs that would give rise to WI-38. He cultured the cells for weeks, splitting them when they covered the bottom of a bottle, so that two bottles became four, four became eight and so on. By the time the original cell population had doubled nine times, there were hundreds of bottles.

On 31 July, in a marathon session for which he recruited a small army of technicians, Hayflick dispensed the cells into more than 800 tiny glass ampoules, sealing each one with a quick pass through the flame of a Bunsen burner. Later, he transferred the precious ampoules to a liquid-nitrogen freezer in the Wistar's basement.

A year later, Hayflick received information from Sweden assuring him that the mother of the fetus and her family were free of cancer and hereditary diseases, something vaccine manufacturers would want to know. Although there is some indication that the mother consented to use of the tissue, *Nature* does not know for sure that she did. Swedish law at the time did not require such consent and, says Niels Lynöe, professor of medical ethics at the Karolinska Institute, "research ethical awareness in Sweden as well as in the US was rather low", before the Helsinki declaration, a statement of human research ethics adopted by the World Medical Association in 1964. In Sweden, "research material like tissues from aborted fetuses were available and used for research without consent or the knowledge of patients for a long time", both before and after consent rules were tightened later in the 1960s, says Solveig Jülich, a historian of medicine at Stockholm University.

Armed with the ampoules, Hayflick now launched WI-38 on its

march around the globe. During his frequent flights abroad, he often toted a small liquid-nitrogen freezer bearing WI-38 ampoules. In this way, he hand-delivered the cells to colleagues in London, Moscow, Leningrad and Belgrade. He also mailed out hundreds of 'starter' cultures grown from the ampoules. Scientists were hungry for the cells in part because they were a cheap, plentiful model for studying the fundamental biology of normal human cells — and soon papers began to appear, probing everything from the cells' respiration[3] to their constituent fatty molecules[4].

WI-38 found a greater use in virology, where the ease of infecting the cells with a panoply of human viruses quickly made the strain an important virus-identification tool. In 1967, the cells became a workhorse in a World Health Organization survey of viruses causing lower respiratory tract infections in hospitalized children on four continents.

Hayflick also supplied WI-38 liberally to aspiring vaccine-makers. One was Stanley Plotkin, a Wistar scientist and a physician who had seen at first hand the effects of the huge rubella epidemic that swept the United Kingdom and the United States in the early 1960s. Rubella can be devastating to fetuses whose mothers are infected: those that are not killed *in utero* are frequently born blind, deaf, mentally disabled or with some combination of these conditions.

WISTAR INST.

Hilary Koprowski, director of the Wistar Institute, is inoculated by Stanley Plotkin with rabies vaccine developed using WI-38, in 1971.

Working at the Wistar, Plotkin grew rubella in WI-38 at 30 °C, cooler than body temperature, creating a weakened strain that still fired up the immune system enough to protect against future infections. Trials showed that his vaccine induced better immunity against rubella than competitors[5]. Plotkin's vaccine was licensed in Europe in 1970 and in the United States in 1979. A version made by the pharmaceutical company Merck, based in New Jersey, is today the only rubella vaccine available in the United States, and GlaxoSmithKline uses Plotkin's weakened virus in a rubella vaccine that it markets in Europe and Australia.

The rubella vaccine was only one of many made using WI-38. In the 1960s, a WI-38-based measles vaccine was licensed in the former Soviet Union and Koprowski developed a rabies vaccine using the cells. In the early 1970s, the pharmaceutical company Wyeth (now part of Pfizer) launched an oral adenovirus vaccine developed using WI-38 and Pfizer, based in New York, used WI-38 to make a vaccine against polio. Today, the cells are also used by Merck to make vaccines against chickenpox and the painful nerve infection shingles.

SENSE OF EXCLUSION

Despite his groundbreaking paper and the growing prominence of WI-38, Hayflick felt like a second-class citizen at the Wistar Institute. He was never promoted to a full member, and he believed that Koprowski, much as he publicly bragged about WI-38, saw him as more of a technician than a scientist. (Koprowski died last April.)

Hayflick's simmering sense of exclusion boiled over when one day, Hayflick says, he learned that Koprowski had offered a guaranteed supply of WI-38 to the British drug-maker Burroughs Wellcome (one of the companies that merged into GlaxoSmithKline), along with Hayflick's cell-culture technology for producing live polio vaccine[6], all in exchange for royalties to the institute. Hayflick says that he was shocked that Koprowski intended the institute to profit from WI-38 and believes that it had kept him in the dark.

Hayflick found a new job as a professor of medical microbiology at Stanford University in California, to start in July 1968. In January that year, he met to discuss the fate of the 370-odd remaining WI-38 ampoules with Koprowski and representatives from the NIH and the American Type Culture Collection (ATCC), then in Rockville, Maryland, a non-profit organization that distributes cell cultures. The participants agreed that Hayflick could take ten ampoules of WI-38 with him to Stanford, and that ten would stay at the Wistar. The rest would remain the property of the NIH's cancer institute and were to be transferred to the ATCC, which would handle distribution from that point on.

Hayflick was troubled by the plan, which he says he felt under pressure to sign. And he felt a sense of injustice. Companies, and the Wistar, he now believed, were profiting from cells he had created and handed to them freely. "To then have [them] descend on what I had struggled so hard to give value to, and try to take it for their own benefit," he says. "I think that an average person would be capable of understanding why I was — to put it mildly — concerned." The Wistar Institute says that it acted ethically in conducting research that led to the development of WI-38 and that it received royalties from licensed vaccines grown in WI-38 cells but not from licensing the cells.

At some point after that January meeting, Hayflick made a quiet trip to the Wistar basement and packed all the WI-38 ampoules into a portable, 30-litre liquid-nitrogen tank. In June 1968, he strapped the container into the back seat of his green Buick LeSabre next to two of his children, and motored to California. "I just absconded with the cells," Hayflick says with a wry smile.

Once in Stanford, Hayflick began charging for many of the WI-38 cultures that he was sending out to hundreds of scientists who were still asking for them. His fee was US$15 — the same amount charged by the ATCC for cell shipments — and he banked the money in an account he called 'Cell Culture Fund'. By May 1975, he had accrued more than $66,000.

Hayflick was determined, he says, to keep the funds in a separate account until some independent legal authority could determine who owned the cells. The issue didn't come up until the spring of 1975, when he was interviewed at the NIH as a candidate to direct its new National Institute on Aging. The NIH decided to turn to its Division of Management Survey and Review, an office that investigated allegations of mismanagement of NIH funds. It sent three accountants to Hayflick's Stanford lab, where they spent days going over records and assessing his inventory of WI-38.

Their report became public in March 1976, when the NIH provided it under the Freedom of Information Act (FOIA) to several journalists. Accounts of its contents soon appeared in *Science* and on the front page of *The New York Times*. "Within 24 hours my career was in the sewer," Hayflick says. The report said that Hayflick had sold "the property of the United States Government" and banked the money; that the WI-38 ampoules had been poorly accounted for; and that some ampoules were contaminated with bacteria. Hayflick strongly

disagrees with the report. He says that no legal decision gives the government title to WI-38; that he sequestered the funds received for preparing and shipping WI-38 in an account until ownership could be established; and that no evidence has ever been provided for the assertion of mismanagement. Hayflick explains that, contrary to common practice in 1962, he had not laced the cells with antibiotics at the outset because vaccine manufacturers feared allergic reactions to the drugs.

Shortly before the *Science* article[7] was published, Hayflick sued the NIH. He argued that the agency had violated the 1974 Privacy Act by making his name and the allegations against him available under the FOIA without including his rebuttal. He also sued for title to WI-38 and its proceeds. By then, Hayflick was also facing a criminal investigation: Stanford University had alerted local prosecutors that the case could be one of criminal theft of government property. (The prosecutors subsequently found no grounds for criminal investigation and dropped the case.) Meanwhile, some vaccine manufacturers, fearing that there would not be enough stock of WI-38 to meet future needs, switched much of their work to an alternative fetal cell strain, MRC-5.

Hayflick resigned from Stanford in February 1976 and was soon in an unemployment line collecting $104 a week. Not only was he jobless, he was without the cells that he described to *Science* that spring as "like my children". The NIH had taken them from his lab while he was at a conference the previous year.

CHANGING TIMES

Some months later, Hayflick landed a job across the San Francisco Bay at the Children's Hospital, Oakland, and sought to revive his research on ageing. In 1977, peer reviewers approved his application for a three-year NIH grant and, after a lengthy fight with the NIH to get both the funding and some WI-38 cells, in January 1981 he received six of the original ampoules of cells.

One month earlier, the Bayh–Dole Act had become law, giving institutions the right to claim title to inventions made using government funds, as long as they gave the inventors a piece of the royalties. Hayflick's invention predated the law, but the new mindset that Bayh–Dole represented made it harder for the government to justify the continued legal fight over WI-38, which by then had stretched on for nearly five years. In summer 1981, the Department of Justice wrote to Hayflick's lawyers, offering to settle the lawsuit out of court, and Hayflick assented. With both sides agreeing that the issues were in reasonable dispute, and neither side admitting liability, the settlement allowed Hayflick title to the six original WI-38 ampoules now in his possession, and to their progeny. The government would retain title to the 19 original ampoules in its hands. As for the proceeds from his sales of WI-38, which, with interest, had grown to around $90,000, Hayflick would keep it. He spent it all, he says, and more, to pay his lawyers; he has never profited financially from WI-38, he says.

Scientists, meanwhile, were continuing to benefit academically from the cells. By the mid-1980s, thanks to revolutionary new tools in molecular biology, WI-38 was helping them explore everything from gene expression in human leukaemias[8] to the effects of the just-cloned tumour necrosis factor[9], an important immune regulatory protein.

> ***"We still have people who refuse to take these vaccines because of their origins in fetal tissue."***

The cells have played "a very critical role in studying cellular senescence," adds Rugang Zhang, who works in this field at the Wistar Institute. That's because they so reliably stop replicating after about 50 divisions and because scientists have, over time, built up a wealth of knowledge about the reasons why. In the 1990s, for instance, WI-38 was used to discover the most widely used marker of cellular senescence[10]. More recently, Zhang's team used the cells to discover a pathway by which the complex of DNA and proteins known as chromatin controls cell proliferation[11].

But the controversies surrounding the cells have rumbled on. Back in July 1973, Hayflick received a call at home from a senior medical officer at NASA. Skylab 3 had taken off several hours earlier from the Kennedy Space Center in Florida, bound for the Space Station. The NASA physician was contending with anti-abortion demonstrators who were protesting about the presence aboard of WI-38 cells, which were going to be used to detect the effects of zero-gravity on cell growth and structure. Once Hayflick explained that the abortion from which the cells were derived had occurred legally in Sweden, the physician said that he would defuse the situation — but concerns among anti-abortionists about WI-38 have lasted to this day.

"Other vaccines are produced in a completely morally non-objectionable way. So why aren't we doing this with all vaccines?" says Debi Vinnedge, the executive director of Children of God for Life, a group based in Largo, Florida, that opposes the use of WI-38 in vaccine-making. In 2003, Vinnedge wrote to the Vatican asking for an official position on whether Catholics could ethically receive vaccines made using cells from aborted fetuses. She waited two years for an answer. The letter, when it came, concluded that where no alternative exists, it is "lawful" for parents to have their children immunized with vaccines made using WI-38 and MRC-5, to avoid serious risk to their own offspring and to the population as a whole.

Still, the Vatican wrote, faithful Catholics should "employ every lawful means in order to make life difficult for the pharmaceutical industries" that use such cells. Merck, a major producer of Plotkin's rubella vaccine, has been a perennial target of abortion opponents, who have pressed the issue at Merck's US shareholder meetings. (Merck said in a statement to *Nature* that "it would be exceedingly difficult, if at all possible, to develop and test an alternative", and emphasized the vaccine's long record of safety and effectiveness.) The irony of the protest is not lost on Plotkin. "I am fond of saying that rubella vaccine has prevented thousands more abortions than have ever been prevented by Catholic religionists," he says.

Profits from Merck's rubella vaccine represent a big slice of the billions of dollars that have been made from products that have involved the use of WI-38. Among the other companies that have made money from WI-38 are Barr Laboratories (now part of Teva Pharmaceuticals, based in Petach Tikva, Israel), which today makes the adenovirus vaccine given to all US military recruits, and Sigma Aldrich in St Louis,

LEONARD HAYFLICK

Some original glass ampoules of WI-38 cells, created in 1962.

NEWS FEATURE

RAMIN RAHIMIAN/GETTY IMAGES

Leonard Hayflick today at his house in Sea Ranch, California. "We all owe a moral debt to the tissue donors," he says.

Missouri, which charges $424 in the United States for a vial of the cells.

Legal experts say it is unlikely that the parents of the fetus, or their heirs, would have any legal grounds to demand compensation for tissue collected over 50 years ago. At the time that WI-38 was derived, use of tissue without consent was routine in the United States, as it was in Sweden. Under current rules, researchers supported by US government grants are free to make use of surgically removed tissue — including aborted tissue — that has been stripped of its identifiers, without consent. However, some states have stricter rules.

But, says Charo, "if we continue to debate it entirely in legal terms, it feels like we're missing the emotional centre of the story". It could be argued, she says, "that if somebody else is making a fortune off of this, they ought to share the wealth. It's not a legal judgment. It's a judgement about morality."

The scientists and academic institutions that have worked with WI-38 and that commented for this story say that they do not see their work on the cells as unethical, in part because of the standards that existed at the time the cell strain was created. It is unfair, say some, to examine past acts by today's more stringent ethical expectations. "At the time [the fetus] was obtained there was no issue in using discarded material," says Plotkin. "Retrospective ethics is easy but presumptuous." Most companies in this story declined to comment; GlaxoSmithKline says that it is committed to upholding high ethical standards.

Regarding the situation today, Scott Kominers, a research scholar at the Becker Friedman Institute at the University of Chicago, Illinois, argues that offering donors a share in future profits from their tissues could encourage them to donate and fuel medical progress[12]. "We think that if you offer some sort of value-based compensation you'd be likely to boost tissue supply," he says. But Steven Joffe, a paediatric oncologist who directs the ethics programme at Harvard's translational medicine centre in Boston, Massachusetts, is concerned that compensating donors may paradoxically decrease their willingness to donate tissues, by taking altruism out of the equation. What's more, he says, the one-to-one relationship of WI-38, or of HeLa, to a donor, is rare. Far more often, modern medical products — such as therapeutic proteins extracted from donated blood — come from many samples combined. In these cases, he says, "trying to account for all these multiple holders of rights to income streams would just bring science to a standstill".

If nothing else, the WI-38 story highlights the benefits of discussing the issues of compensation and consent with tissue donors at the outset. In the case of WI-38, suggests Charo, returning to the donor now, even with an offer of compensation, "may also be a way of reopening an experience that may for her have been painful. You have to be careful."

Hayflick argues that there are at least four stakeholders with title to WI-38 or any human cell culture: the tissue donors, the scientists whose work gave it value, the scientists' institution and the body that funded the work. "Like me", he adds, "hundreds of other scientists had their careers advanced using WI-38 and other human cell cultures so we all owe a moral debt to the tissue donors."

Now 85 and regarded as a grand old man of ageing research, Hayflick hung onto his ampoules of WI-38 for decades, keeping them for many years in the garage of his home in California. But in 2007, weary of monthly treks to collect fresh liquid nitrogen, he donated them to the Coriell Institute in Camden, New Jersey, which, he says, he trusts to bank them safely.

In the end, he says, letting the cells go was no more traumatic than launching his own five biological offspring into the world: "It was about time that my 'children' — now adults — should leave home." ■

Meredith Wadman *is* Nature*'s biomedical reporter in Washington DC.* SEE EDITORIAL P.407.

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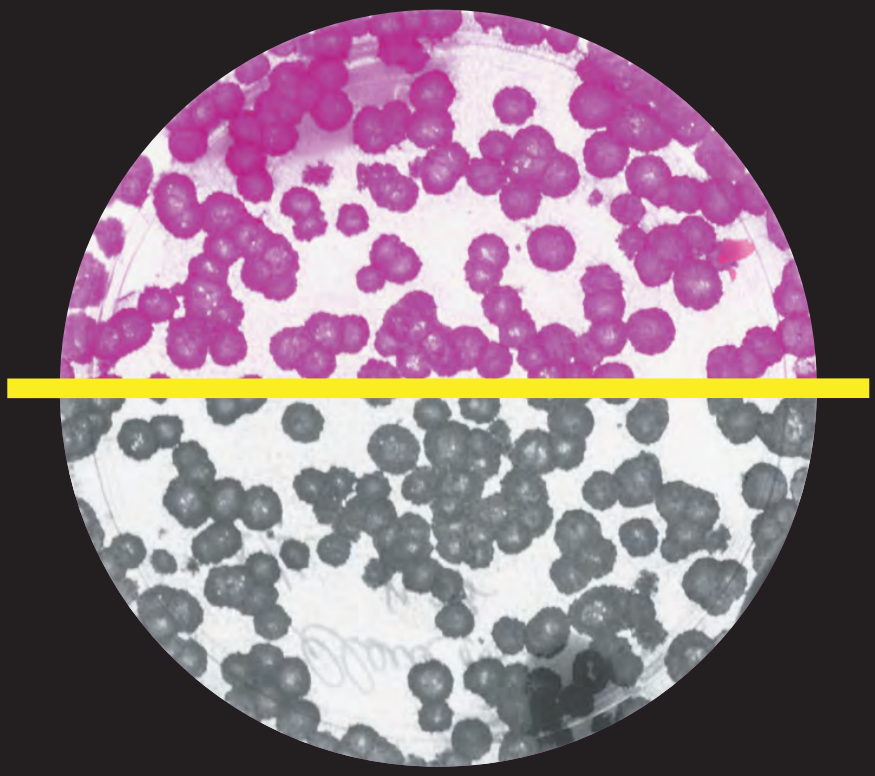
NEWS FEATURE



THE TRUTH ABOUT FETAL TISSUE RESEARCH

The use of aborted fetal tissue has sparked controversy in the United States, but many scientists say it is essential for studies of HIV, development and more.

BY MEREDITH WADMAN

Every month, Lishan Su receives a small test tube on ice from a company in California. In it is a piece of liver from a human fetus aborted at between 14 and 19 weeks of pregnancy.

Su and his staff at the University of North Carolina at Chapel Hill carefully grind the liver, centrifuge it and then extract and purify liver- and blood-forming stem cells. They inject the cells into the livers of newborn mice, and allow those mice to mature. The resulting animals are the only 'humanized' mice with both functioning human liver and immune cells and, for Su, they are invaluable in his work on hepatitis B and C, allowing him to probe how the viruses evade the human immune system and cause chronic liver diseases.

"Using fetal tissue is not an easy choice, but so far there is no better choice," says Su, who has tried, and failed, to make a humanized mouse with other techniques. "Many, many biomedical researchers depend on fetal tissue research to really save human lives," he says. "And I think many of them feel the same way."

MASSIMO BERGE/LIGHTHOUSE/SPL

An explosive climate has surrounded US research with fetal tissues since July, when an anti-abortion group called the Center for Medical Progress in Irvine, California, released covertly filmed videos in which senior physicians from the Planned Parenthood Federation of America bluntly and dispassionately discussed their harvesting of fetal organs from abortions for use in research. Planned Parenthood is a non-profit women's health provider that received US$528 million of government money in 2014, much of it in reimbursements for services ranging from contraception to cancer screenings, which it provides largely to poor women. Abortions, which are performed at about half of Planned Parenthood's 700 clinics, constitute 3% of its services. A handful of clinics in two states supply fetal tissue for research.

The videos provoked a furore that has intensified over the past few weeks. On 3 December, the Republican-led US Senate voted to strip Planned Parenthood of government funding. This is despite the fact that fetal tissue research is legal, the US National Institutes of Health (NIH) has been funding it for decades and President Obama is sure to veto the bill, should it reach his desk. A few days earlier, on 27 November, a gunman shot dead three people at a Planned Parenthood clinic in Colorado Springs, Colorado. In a post-arrest interview, the suspect is reported to have said "no more baby parts".

The episode has shone a spotlight on a little-discussed arm of biomedical research, raising the questions of why, how and how widely fetal tissue is used. To find out, *Nature* turned to an NIH database of research grants funded in 2014 to find those using fresh human fetal tissue, and in October contacted 18 researchers working with it. Su was one of only two who were willing to be interviewed. Most requests were declined or went unanswered; a public-affairs officer at one major Texas university refused to have a researcher speak to *Nature* to keep that person "safe".

The figures show that in 2014, the NIH funded 164 projects using the tissue, at a cost of $76 million. This is slightly less than half of what the agency spent on work with human embryonic stem cells (ES cells), which has also been highly controversial, and 0.27% of the $27.9 billion it spent on all research. (By comparison, the UK Medical Research Council spent 0.16% — £1.24 million ($1.9 million) — of its total spending on research on five projects involving fetal tissue in the 12 months up to 31 March 2015.) Analysis of the NIH projects shows that the tissue is used most heavily for research on infectious diseases, especially HIV/AIDS; in the study of retinal function and disease; and in studies of normal and anomalous fetal development (see 'Fetal tissue research by discipline').

> "USING FETAL TISSUE IS NOT AN EASY CHOICE, BUT SO FAR THERE IS NO BETTER CHOICE."

Opponents argue that the work is not necessary because other model systems and techniques can be used. "This is antiquated science," says David Prentice, the vice-president and research director at the Charlotte Lozier Institute, the research arm of the Susan B. Anthony List, which is an anti-abortion organization in Washington DC. "There are better and, frankly, more successful alternatives."

But supporters of the research counter that fetal tissue is legally obtained, that it would otherwise be destroyed, that such work has already led to major medical advances and that, if there were better alternatives, they would turn to them. "Fetal tissue is a flexible, less-differentiated tissue. It grows readily and adapts to new environments, allowing researchers to study basic biology or use it as a tool in a way that can't be replicated with adult tissue," says Carrie Wolinetz, the NIH's associate director for science policy.

"I get very frustrated when misinformed people go on about how it can all be done with computer models or cell cultures or stem cells or animals," says Paul Fowler, a reproductive biologist at the University of Aberdeen Institute of Medical Sciences, UK, who in January published a study using livers from aborted fetuses to probe the impacts of maternal smoking on liver development[1]. "In some areas, the human is absolutely dramatically different than rodents."

Some argue that the entire episode represents a thinly cloaked attempt to attack and limit access to abortion by eroding support and funding for Planned Parenthood. "People are talking about fetal tissue, but really what this discussion is about is abortion," says Shari Gelber, a specialist in maternal–fetal medicine at Weill-Cornell Medical College in New York City, who has argued for the value of the research.

LABORATORY LINES

Cell lines derived from aborted fetal tissue have been fairly commonplace in research and medicine since the creation in the 1960s of the WI-38 cell strain, which was derived at the Wistar Institute in Philadelphia, Pennsylvania, and MRC-5, which came from a Medical Research Council laboratory in London (see *Nature* **498,** 422–426; 2013). Viruses multiply readily in these cells, and they are used to manufacture many globally important vaccines, including those against measles, rubella, rabies, chicken pox, shingles and hepatitis A.

Companies have shipped at least 5.8 billion vaccines made with these two cell lines which, with others, have become standard laboratory tools in studies of ageing and drug toxicity. (Research with such lines is not covered by US regulations governing the use of fresh fetal cells and tissue nor captured in the NIH database.) In the past 25 years, fetal cell lines have been used in a roster of medical advances, including the production of a blockbuster arthritis drug and therapeutic proteins that fight cystic fibrosis and haemophilia.

But off-the-shelf fetal cell lines are of limited use for scientists because they do not faithfully mimic native tissue and represent only a subset of cell types: WI-38 and MRC-5, for example, were derived from fetal lungs. The lines can also accumulate mutations after replicating *in vitro* over time. And creating humanized mice such as Su's requires whole pieces of fetal organs to provide sufficient numbers of stem cells. For all of these reasons, researchers turn to fresh tissue.

In the United States, this is collected at medical centres and clinics that perform abortions under a patchwork of laws and regulations governing consent, tissue collection and transfer (see 'Fetal tissue and the law'). US law says that clinics can recover "reasonable payments" to offset the costs of providing the tissue, but it makes it a felony to profit from doing so. Planned Parenthood officials say that its clinics obtain full and informed consent from women choosing to donate fetal remains for research, and the organization announced in October that its clinics will no longer recover costs of $45–60 per specimen for collecting the tissue.

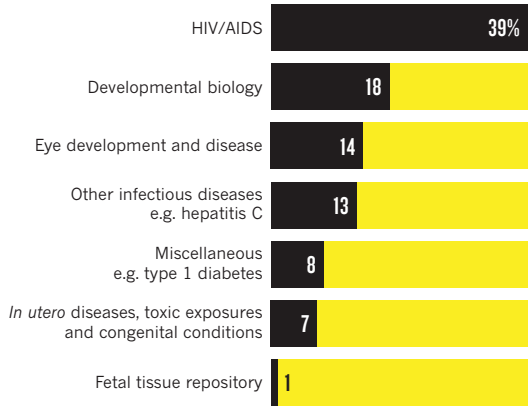
From the clinics, fetal tissue is then often passed to biological-research supply companies, which act as intermediaries and process the tissue before selling it to researchers. Su pays $830 for each sample of fetal liver tissue supplied to his lab by one of the most widely used suppliers, Advanced Bioscience Resources in Alameda, California.

HIV AND AIDS

The category of fetal tissue work that draws most NIH funding is the study of HIV and AIDS: it accounts for 64 of the 164 NIH grants. Researchers in this field have long struggled with the paucity of effective models for this uniquely human disease. The standard models, macaques, are expensive to breed, are infected with SIV instead of HIV and have immune responses that are different from those of people. The flexibility and adaptability of fetal tissue — and its richness as a

FETAL TISSUE RESEARCH BY DISCIPLINE

The US National Institutes of Health funded 164 projects using human fetal tissue in the 2014 fiscal year, in these research areas:



SOURCE: NIH

US REGULATION

Fetal tissue and the law

Regulations governing US-funded fetal tissue research, first issued in 1975, state that:

- The research must comply with all applicable US, state and local laws and regulations.
- If information associated with the fetal tissue allows it to be traced to a living individual, that person becomes a research subject and informed consent from the donor is required for its use.

(Laws in at least 40 states require informed consent from the woman even if the fetal tissue will be anonymized.)

Additional requirements from a 1993 US law:

- Providers may not transfer fetal tissue for profit, but can receive funds to cover 'reasonable payments', such as for processing, storage and transportation.
- Researchers may not acquire fetal tissue if they know that a pregnancy was initiated in order to provide that tissue for research.
- Violators of either provision above are subject to criminal penalties of up to ten years in prison, up to US$500,000 in fines, or both. These apply to both the tissue supplier and the tissue receiver in a transaction.

source of stem cells — has allowed the creation of a number of mice with humanized immune systems.

Prominent among these is the BLT (bone marrow–liver–thymus) mouse, which was created in 2006 (ref. 2). This model is made by destroying the animal's immune system and then surgically transplanting liver and thymus tissue fragments from a human fetus into the mouse. The immune system is further humanized with a bone-marrow transplant, using blood-forming stem cells from the same fetal liver. The animal enables studies of, for instance, immune responses that are key to developing an effective HIV vaccine. The mouse has "accelerated the study of HIV pathogenesis and novel approaches to harness anti-viral immunity to control HIV", reads a recent review by several NIH-funded scientists who are using the mouse[3].

The mouse has also helped to demonstrate that prophylactic drugs may prevent vaginal HIV infection — a strategy that is now in late-stage human trials. The animal is currently being used to examine how genital infection with herpes simplex virus alters immunity at the vaginal mucosa, making it easier for HIV to infect. In a similar vein, Su is now using his humanized mouse to examine the mechanisms by which hepatitis C and HIV co-infection can hasten liver disease.

There are drawbacks: the BLT mouse's average lifespan is relatively short, at only around 8.5 months, because the animals tend to develop cancers of the thymus. And the humanized immune system is not inherited, so the model must be created again and again — leading to the constant demand for fetal tissue that so disturbs abortion opponents.

HUMAN DEVELOPMENT

In some research areas, fetal tissue may, in time, be replaced by other materials and methods: alternative, flexible cell types, including human ES cells and induced pluripotent stem (iPS) cells, and organoids, which are lab-created cellular structures that resemble tissue from normal organs (see *Nature* **523,** 520–522; 2015). But there is one area in which, scientists say, fetal tissue is needed by definition: studies of early human development, and why it sometimes goes wrong.

"Human fetal tissue is likely never going to be replaced in some areas of research, particularly relative to fetal development," says Wolinetz. And the application of such work goes far beyond understanding developmental disorders such as congenital heart disease or other malformations, says Neil Hanley, an endocrinologist at the University of Manchester, UK. "For a wide range, now, of adult diseases and disorders, we know that they have their origins during very early human development," he says — type 2 diabetes and schizophrenia are both cases in point. "And unless you understand normal you're not going to understand abnormal."

The 30 developmental-biology grants involving fetal tissue that were awarded by the NIH in 2014 range from a study of the differentiation of myoblasts, which are the embryonic precursors of muscle cells, to several examinations of development of the urogenital tract — studies with relevance, for instance, to hypospadias, a common condition in which the urethra fails to close and the underside of the penis is incompletely formed. One project is creating a three-dimensional atlas of gene expression in the genital tubercle, the precursor of the penis. Another is probing gene activity in cells lining the fetal intestine to help explain excessive intestinal inflammation in premature babies. Hanley says that such studies are important, particularly because gene regulation — the finely tuned symphony that controls when and where genes are active — can vary strikingly between species, so findings in other animals often do not hold true in humans.

More than half of the 30 grants are for studies of brain development, and many of these projects are seeking advances in combating maladies such as autism, schizophrenia and Alzheimer's disease. Larry Goldstein, a neurobiologist at the University of California San Diego School of Medicine in La Jolla, uses cells called astrocytes from the brains of aborted fetuses to nourish neurons that he has derived from iPS cells and that have mutations associated with Alzheimer's disease. The astrocytes are thought to secrete factors that keep the neurons healthy in culture, and he uses the system to study the pathogenesis of the disease and to test potential drugs.

Goldstein hopes eventually to derive the astrocytes, too, from iPS cells. But "the human fetal astrocytes that we get at present are the gold standard that we use, and will use, to compare astrocytes that we make by differentiation", he says. He has also used neurons from aborted fetal brains to compare with the neurons made from iPS cells[4]. "As long as fetal tissue is available, this is a very valuable use of it," he says.

Another 23 of the NIH grants using fetal tissue involve eye development and disease. Damage to the retinal pigment epithelium (RPE), a single layer of cells at the back of the eye, has a key role in a

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The collection of aborted fetal tissue for use in research has prompted demonstrations for and against US health provider Planned Parenthood.

number of eye diseases, including age-related macular degeneration, the most common cause of blindness in adults in the developed world. The 2000s saw advances in ways to create cell cultures with RPE dissected from the eyes of fetuses, allowing scientists to study the function of these cells in a dish. And although some scientists have turned to stem cells to generate RPE, like Goldstein they continue to use fetal tissue as a benchmark of normal development and function.

Goldstein agreed to speak to *Nature*, he says, because "somebody has to speak up responsibly". He stressed that he and his colleagues think hard about the ethics of their work. "We are not happy about how the material became available, but we would not be willing to see it wasted and just thrown away."

Occasionally, fetal tissue is used for clinical work. Last year, a company called Neuralstem in Germantown, Maryland, in collaboration with scientists at the University of California, San Diego, launched a trial in which stem cells from fetal spinal cord were implanted to treat spinal-cord injuries. In May, researchers in the United Kingdom and Sweden launched a study in which dopaminergic neurons from aborted fetuses are transplanted into the brains of patients with Parkinson's disease (see *Nature* **510,** 195–196; 2014). Research with fetal tissue is less controversial in countries where abortion is more widely accepted.

UNCOMFORTABLE VIEWING

The Planned Parenthood videos caused even some supporters of fetal tissue research to feel uncomfortable. In one video, physician Deborah Nucatola, the group's senior director of medical services, describes how she crushes fetuses above and below key organs to preserve them intact for research. She also described turning a fetus into a breech presentation to deliver the head last, when the cervix is more dilated, thus preserving the brain.

This raised the question of whether physicians are altering abortion techniques to accommodate research requests, violating a widely held precept of research ethics. Arthur Caplan, a bioethicist at the New York University School of Medicine, dismisses the videos as "pure politics", but some of the footage "did get my eyebrow to arch", he says. "You can't use a different approach to the abortion to try to preserve something. Those are just no-no's."

Planned Parenthood spokeswoman Amanda Harrington says that the organization is not aware of any instances in which the method of an abortion has been changed to preserve organs. But, she adds, "if minor adjustments that have no bearing on the woman's health and safety are done when the woman has expressed a desire to donate tissue, that is entirely appropriate and ethical and legal". Women's health and safety, she says, "is always the number one priority".

The question for many scientists is what the fallout of the controversy will be. On the heels of the Colorado shootings, some Republicans in Congress backed off earlier attempts to defund Planned Parenthood, and President Obama is expected to veto any bill that does so. This means that the lasting damage of the videos may end up being inflicted not on Planned Parenthood's budget, but on science. Since July, four bills that would criminalize or otherwise restrict the research have been introduced in the US Congress, and lawmakers have launched similar efforts in a dozen state legislatures. (Missouri, Arizona and North Dakota already ban the research.)

Su felt the climate for his research grow colder when, on 1 October, a new North Carolina law was signed that makes it a felony to sell fetal tissue for any amount within the state. Su receives the tissue he uses from outside the state, but the message behind the new law concerns him. "I hope this current controversy, or possible congressional interventions, won't slow down biomedical research," he says. "The benefit is bigger than the drawback on this."

The controversy "absolutely puts fetal tissue research at risk", says Caplan. "Young scientists are unlikely to enter a field riven with controversy, where funding is uncertain and physical threats are a real possibility."

Caplan says that parallels could emerge with events in the early 2000s, when the use of human ES cells in US research became politically fraught. Then, tight federal regulations governing NIH funding of the research were adopted, but some states, including California and Massachusetts, responded by pouring money into the science all the same.

"To move ahead, the reality is that fetal tissue research need not be funded or permitted everywhere," Caplan says. "It needs to be allowed somewhere." ■

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CORRECTION

The News Feature 'The truth about fetal tissue research' (*Nature* **528,** 178–181; 2015) incorrectly stated that around 5.8 billion people have received vaccines made with the WI-38 and MRC-5 cell lines. In fact, companies have shipped some 5.8 billion vaccines made with these two cell lines.

The Washington Post

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Congress

In first hearing, GOP panel casts doubt on fetal tissue research

By Mike DeBonis March 2

Republicans on the special House panel investigating fetal tissue procurement and research practices aggressively questioned the morality and necessity of that research in the panel's first hearing Wednesday, while Democrats sought to portray the probe as a politically motivated witchhunt.

The Select Investigative Panel, created by Republican leaders last year following the release of undercover videos produced by anti-abortion activists, gaveled to order in an underground Capitol hearing room while, just across the street, the Supreme Court heard arguments in the most closely watched abortion case in 24 years.

Wednesday's hearing was set to explore the ethical implications of using fetal tissue in biomedical research but before the panel heard from six expert witnesses — four selected by Republicans and two by Democrats– members clashed over the series of document requests Republicans made to more than 30 entities. Those requests, made by subpoena in some cases, include demands for names of researchers, technicians and medical personnel involved in fetal tissue handling.

[*Dozens of groups targeted as House fetal tissue probe accelerates*]

Rep. Jan Schakowsky (D-Ill.), the panel's ranking Democrat, said the decision by chairwoman Marsha Blackburn (R-Tenn.) to subpoena the names was an "abuse of her position" that is "frankly reminiscent of

Sen. Joe McCarthy's abusive tactics." She noted the November shooting at a Colorado Planned Parenthood clinic, where the gunman used the phrase "no more baby parts" to explain his actions after killing three.

"Linking individual's names to an investigation that the Republicans describe as examining the 'harvesting of baby body parts' and the 'horrific practices' of abortion providers puts people in danger," she said. "Our words and our actions matter."

Blackburn replied that the panel is "entitled to the information," and a Democratic motion to quash the three subpoenas issued thus far was defeated on a party-line vote.

The panel emerged from the controversy created last year by undercover videos taken of Planned Parenthood officials talking about the use of fetal tissue, which anti-abortion activists alleged the officials were illegally attempting to sell. Conservative House members nearly ground the 2015 budget process to a halt – in the process ousting then-Speaker John Boehner (R-Ohio) – over their demands that federal funding be stripped from the group because it performs some abortions.

Several state investigations have found no wrongdoing by Planned Parenthood, and the House panel has not yet sought documents or testimony from the organization. However, the panel's brief has greatly expanded: Blackburn's own statements Wednesday, as well as the testimony of the four GOP-invited witnesses, appeared to be the beginnings of a case for broad new restrictions on the research use of aborted fetuses.

"There should be no doubt that the use of cadaveric fetal organs and tissue for research and clinical applications raises serious moral and ethical concerns, concerns that are heightened when the organs and tissue are obtained as the result of elective abortion," read the prepared testimony of one witness, Paige Comstock Cunningham of Trinity International University.

Another witness, Patrick Lee of the Franciscan University of Steubenville, testified that not only is it "unjust for the government to fund or encourage elective abortions" and to allow the use of fetal tissue resulting from those abortions, but that women who have abortions should have no option to donate their fetus: "Women who choose to have direct abortions by that act forfeit the moral standing needed for being a proxy decision-maker in regard to the disposition of their baby's remains."

Blackburn said in a Feb. 10 interview that the panel would take a broad look at the state of medical research, the practices of fetal tissue procurement, and the ethical dimensions at their intersection.

"It's time for us to sit down and look at the changes and what has happened with research and see what a way forward ought to be," she said. "When you go back and you look at the history of it, you realize, yeah, it's been a while since we have looked at this."

The effort could inject bioethics into politics e to a degree not seen in more than a decade, after President George W. Bush strictly limited federal funding for embryonic stem-cell research — a decision which emerged as a significant issue during his 2004 re-election campaign.

Blackburn suggested in the interview that recent medical advances are mostly due to research involving adult stem cells and that the panel's review might conclude that the use of fresh fetal tissue is not scientifically necessary.

Several of the Republican-invited witnesses on Wednesday cast doubt on the necessity of fetal tissue research. G. Kevin Donovan of the Georgetown University School of Medicine, for instance, said that tissue might be harvested from spontaneous miscarriages, thus avoiding the moral implications of using aborted fetuses. Kathleen M. Schmainda of the Medical College of Wisconsin said the research potential of fetal tissue experiments was "largely overexaggerated," noting that only 0.25 percent of the National Institutes of Health research budget funded fetal-tissue experiments. "This is not going to change the direction of science," she said.

Donovan told the panel that "not all scientific experimentation has been praiseworthy" and mentioned the medical experimentation of Nazi doctor Josef Mengele and the Tuskegee syphilis experiments.

"No one would want to associate our current scientific studies involving the human fetus with such egregious breaches of research ethics," he said.

Donovan was later pressed by Rep. Diana DeGette (D-Colo.) on whether he considered contemporary fetal tissue research to be morally equivalent to those infamous experiments.

"I think that we need to be very careful so that we don't do that," Donovan replied.

"Do you think that they are equal, yes or no?" DeGette asked.

"Maybe," Donovan said.

The witnesses invited by Democrats refuted the idea that fetal tissue is either unnecessary or ethically problematic.

That position also won support in a Tuesday letter to the panel from the American Academy of Pediatrics, which wrote that it "strongly supports continued federal funding for fetal tissue research" based on "the substantial historical and future potential benefit on child health."

Lawrence S.B. Goldstein of the University of California San Diego, who testified on behalf of the American Society for Cell Biology and the International Society for Stem Cell Research, prepared this testimony: "My message is simple: fetal tissue and cells that would otherwise be discarded play a vital role in modern cutting edge medical research. These fetal tissues and cells cannot be replaced by embryonic stem cells, reprogrammed stem cells, or adult stem cells."

Goldstein cited ongoing research into potential therapies for Alzheimer's disease and spinal cord injuries, as well as efforts to grow new kidneys: "We need all different types of cells to do research, because we don't know what is best."

While much of the hearing focused on the larger implications of that research, some Republicans concentrated on the particular practices of those handling that tissue — previewing what is likely to be an ongoing line of GOP inquiry.

Republicans highlighted several documents they obtained through their investigation, including an April 2014 email between undisclosed parties discussing a researcher's need for a "first trimester human embryo, preferably around 8 weeks, and up to 10 weeks gestation."

Rep. Diane Black (R-Tenn.) suggested the email was evidence "there effectively is an Amazon.com for human parts, including entire babies."

"This is not dignity," she said. "This is not respect for human life."

One of the Democratic witnesses, R. Alta Charo, a bioethics professor at the University of Wisconsin at Madison, said the language in the email was the "same kind of clinical, dispassionate language" typically used in medical research on human tissue.

The timing of Wednesday's hearing also emerged as a partisan issue. Not only did it coincide with the closely watched Supreme Court argument, but it also conflicted with a House hearing on the government's response to the Zika virus. Top government officials from the Centers for Disease Control and Prevention, the National Institutes of Health and the Department of Health and Human Services testified.

The Select Panel's Democrats asked Blackburn last month to reschedule the fetal tissue hearing so they could attend the hearing on Zika, which has been linked to infant microcephaly, a devastating birth defect.

In a letter to Blackburn, Rep. Jan Schakowsky (D-Ill.), the Select Panel's top Democrat, noted the Republican practice of referring to the committee as the "Select Panel on Infant Lives."

"Given the disproportionate and devastating impact of the virus on women and infants, having our members fully engaged and participating in congressional work on Zika should be a shared interest for all of us," Schakowsky wrote. "Indeed, it would be unfortunate if members of the Select Panel were unable to attend a hearing on a matter with such clear, negative impact on infants."

The hearing was not rescheduled.

Schakowsky asked Goldstein on Wednesday if new restrictions on fetal tissue research would delay a vaccine or cure for Zika or microcephaly.

Goldstein said any crackdown on the research would "absolutely delay" efforts to address Zika.

"If you want to understand the Zika virus, the most efficient place to start is with the fetal tissue that is infected," he said. "I think you have to go to the source if you want to understand what's going wrong."

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Ontogenic changes in CD95 expression on human leukocytes: prevalence of T-cells expressing activation markers and identification of $CD95^{-}CD45RO^{+}$ T-cells in the fetus

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Abstract

The ontogeny of the human immune system was studied by analyzing fetal and adult tissues for the presence of various lymphocyte populations and activation/maturation markers. CD95 (fas) was expressed in hematopoietic tissues during the final stages of development of monocytes, granulocytes, NK cells and T cells, but to a much lesser extent on B cells. In the periphery, CD95 expression declined on granulocytes and NK cells. CD95 was expressed at a higher level on $CD45RA^{+}$ peripheral T-cells in the fetus than in the adult. Contrary to the belief that most fetal T-cells are naïve or resting, a notable number of $CD45RO^{+}$ T-cells were observed as well as an unique $CD95^{-}CD45RO^{+}$ population. Activation markers CD25, CD122, CD69 and CD80 were also present on fetal T-cells. These findings indicate that in the initial weeks following thymic maturation, a high frequency of T-cells is activated in the periphery of the fetus.

Keywords: T cells; T-cell receptors; NK cells; B cells; Monocytes; Granulocytes; Liver; Thymus

1. Introduction

The human fetus is protected from most pathogens within the sterile environment of the uterus. Nonetheless, the cellular immune system begins its development early in gestation around the end of the first trimester. Reports suggest that T cells can be found in liver and peripheral blood as early as 7 and 9 weeks' gestation, respectively, although their overall numbers are very low [1,2]. Intrathymic $CD3^{+}$ T-cells can be readily identified at the 8th week of gestation [3,4] although the fetal

Abbreviations: BSA, bovine serum albumin; EDTA, ethylene diamine tetraacetic acid; FITC, fluorescein isothiocyanate; mAb(s), monoclonal antibodie(s); PBMC, peripheral blood mononuclear cells; PBS, phosphate buffered saline; PBS/BSA, washing buffer; PE, phycoerythrin; PerCP, peridinin chlorophyll; PI, propidium iodide; SP, single positive; TC, tricolor; TCR, T-cell receptor; UCB, umbilical cord blood.

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thymus is not anatomically completely mature until the 15th week of gestation [5]. Around this time, single positive (SP) $CD4^+CD8^-CD3^+$ and $CD4^-CD8^+CD3^+$ T cells begin to accumulate more rapidly in the periphery [4]. The purpose for the early development of lymphocytes is not known but may simply reflect the necessity for T-lymphopoiesis to keep pace with overall fetal development to assure the generation and proper selection of sufficient numbers of lymphocytes before birth. Moreover, the early development of T cells may also serve to protect the fetus from in utero infections or engraftment by maternal lymphocytes. Determining the functional capacity of fetal lymphocytes is key to defining a role for these cells in fetal immunity.

A limited number of studies have addressed the functional development of T cells from pre-term fetuses. Proliferation in response to allostimulation has been observed from fetal liver T-cells as young as 9 weeks' gestation [1,6–8]. However, cultured fetal T-cells showed some defects in cytotoxic responses which could be reversed by prestimulation with cytokine [7,9]. More on the functional capacity of fetal T-cells has been learned from analyses of T cells obtained from umbilical cord blood (UCB) at the time of birth. The T-cell repertoire appears fully formed at birth yet the repertoire appears to be composed of primarily naïve T-cells [10]. Whereas $CD45RO^+CD45RA^-$ memory T-cells are common in adult blood, UCB is primarily composed of $CD45RO^-CD45RA^+$ naive T-cells [11–15]. Other cell-surface markers important in the functioning of T cells, such as CD3 and CD28, are expressed at similar levels to adult cells, but signaling through these proteins is attenuated in UCB T-cells. Neonatal T-cells failed to increase CD25, CD154 and CD178 (Fas ligand) expression when stimulated through CD3 and CD28 [16]. Reduced proliferative responses of allostimulated UCB T-cells have also been noted [11,17–19]. Cord blood T-cells also have greatly reduced perforin expression [20]. Together with the observations of reduced CD178 expression, these findings suggest a reduced cytolytic capacity of neonatal T-cells similar to the findings on midgestation T-cells. Thus, despite T-lymphopoiesis beginning early in fetal life, some attenuation of T-cell function appears to occur in addition to the naïveté of the fetal immune system.

CD95 (fas) is an important regulator of homeostasis of the immune system. CD95 is expressed on some T cells and to varying degrees on all other leukocyte lineages. Its expression is increased with T-cell activation and CD95 expression is highest on $CD45RO^+$ T-cells [21]. Triggering of programmed cell death by CD95 activation, through interaction with CD178, leads to clearance of activated T-cells and thereby limits immune responses [22,23]. Neonatal T-cells express less CD95 than their adult counterparts [21,24]. Expression of CD95 is also low to negative on SP thymic cells from midgestation thymic tissues, although CD95 is expressed on immature T-cell progenitors [25]. Moreover, the expression of CD95 on T cells has been shown to increase with age up to 75 years, after which expression decreases somewhat [26]. These data suggest that CD95 expression increases with the maturation of the immune system. In this regard it is worth noting that CD95 expression can increase more rapidly in children infected by the human immunodeficiency virus [24].

In this study, it was our aim to gain a better understanding of the functional maturity of the fetal immune system by analyzing the expression of various cell surface markers on fetal T-cells as well as on other leukocyte populations. Expression of CD95 was analyzed on leukocytes harvested from peripheral blood, spleen, liver and bone marrow of midgestation fetuses and compared to CD95 expression on cells harvested from neonatal and adult tissues. Furthermore, various cell-surface markers, associated with activation, were analyzed on fetal, neonatal and adult T-cells. Our results suggest a higher level of T-cell activation in utero than would be predicted from previous studies of UCB T-cells.

2. Materials and methods

2.1. Isolation of human leukocytes from adult, neonatal and fetal tissues

Human tissues were obtained and studied under the approval of the Committee on Human Research at our institute. Male and female adult peripheral blood was

obtained from healthy volunteers ranging in age from 24 to 61 years. Neonatal UCB and fetal hematopoietic tissues were obtained with consent of the women prior to delivery or elective abortion. Neonatal blood (birth at 33 weeks' gestation to term) and some fetal tissues were obtained at our institute. Additional fetal tissues were obtained from Advanced Bioscience Resources Inc. (Alameda, CA). Fetal tissues were harvested shortly following the abortion and were transported to the laboratory in sterile containers held on ice. Experiments on adult bone marrow were performed at Ingenex, Inc. (Menlo Park, CA) in compliance with regulations issued by the state and federal governments. Fetal tissues ranged in gestational age from 15 to 24 weeks, as determined by the foot length of the fetus. Each experiment was performed on cells obtained from an individual specimen; tissues from different specimens were not pooled for analyses.

Adult peripheral blood was obtained by venipuncture. Approximately 7 ml of blood was drawn into a vacutainer tube containing ethylene diamine tetraacetic acid (EDTA). The blood was diluted to a total volume of 50 ml in PBS/BSA washing buffer consisting of phosphate buffered saline (PBS) containing 0.3% fraction-V ethanol-extracted bovine serum albumin (BSA) (Roche Applied Science, Indianapolis, IN) and 50 μg/ml gentamicin sulfate (Life Technologies, Grand Island, NY). The cells were pelleted by centrifugation and erythrocytes were depleted by chemical lyses using ACK lyses buffer, pH 7.2–7.4, consisting of 0.15 M NH_4Cl, 1.0 mM $KHCO_3$ and 0.1 mM Na_2 EDTA (Sigma Chemical Company, St Louis, MO). The cells were pelleted by a 7-min centrifugation approximately 1 min after the addition of the ACK lyses buffer. If lysis of the erythrocytes was incomplete, the procedure was repeated. Otherwise the cells were washed once in PBS/BSA and suspended in blocking buffer consisting of PBS with 5% normal mouse serum (Gemini Bio-Products, Inc., Woodland, CA) and 0.01% NaN_3. Alternatively, peripheral blood mononuclear cells (PBMC) were prepared by centrifugation of the blood at 600 × g for 25 min on a layer of 1.077 g/ml LymphoPrep (Life Technologies). The light-density cells were harvested and washed twice before being suspended in blocking buffer for staining.

PBMC were isolated from neonatal UCB by immunomagnetic bead depletion of $CD235a^+$ erythrocytes, performed as previously described for fetal liver cells [27], and density separation using 1.077 g/ml Nycoprep (Life Technologies). The isolation of light-density neonatal blood cells was performed in an analogous fashion to the procedure described for the adult PBMC. In some cases, freshly prepared PBMC from UCB were frozen in autologous plasma with 10% dimethyl sulfoxide (Sigma Chemical Co.) and were thawed shortly before phenotypic analysis.

Fetal blood leukocytes were harvested from umbilical cords, placental vessels and/or hearts obtained from elective abortions. Blood was harvested from the cords after first washing the cords with PBS/BSA and then resecting (0.5 cm) the ends with scissors. The washed cords were placed in on a clean culture dish and were cut in 2 cm pieces. Fifteen to forty millilitres of PBS/BSA were injected with a 28-gage insulin syringe (Becton Dickinson & Co., Franklin Lakes, NJ) into the three cord vessels to rinse the blood out of the vessels through the fresh cut surface. In some initial experiments, fetal UCB was squeezed out through the fresh cut end using forceps. Blood samples were filtered using 70 μ nylon-mesh cell strainers (BD Biosciences, San Jose, CA) as needed to remove clots or large cellular debris. For some fetal specimens fetal blood was obtained from the placenta by direct venopuncture of surface vessels near the placenta–umbilical cord junction. Placental blood was drawn into a syringe containing heparin. Fetal hearts were collected with the pericardial sack. The surface was cleaned with PBS/BSA to remove any contaminating maternal cells. The pericardial sack was then removed and the ends of the great vessels resected. In a clean dish, the heart was cut open from the great vessels down to the apex and the blood was rinsed out of the great vessels and chambers with PBS/BSA. Erythrocytes were depleted by chemical lysis using ACK lysis buffer or immunomagnetic bead depletion of $CD235a^+$ cells [27,28]. For some analyses of lymphocytes only, fetal PBMC were prepared using LymphoPrep as described above. Blood cells were washed and suspended in blocking buffer for staining.

Splenocytes were isolated by crushing the spleen with a glass pestle through a wire mesh cell strainer (Sigma Chemical Company) and rinsed with washing buffer. The cell suspension was passed through a 70 μ

nylon-mesh cell strainer and pelleted by centrifugation. Erythrocytes were depleted by chemical lysis using ACK lysis buffer or immunomagnetic bead depletion of CD235a$^+$ cells [27]. Alternatively, light-density splenocytes, depleted of erythrocytes and granulocytes, were isolated by centrifugation using LymphoPrep as described above. After either method, splenocytes were washed and suspended in blocking buffer for staining.

Fetal thymocytes were prepared for analysis by passage of the thymus through a cell strainer as described for the spleen samples. In order to remove erythrocytes and cellular debris, light-density thymocytes were harvested after centrifugation over a layer of 1.077 g/ml Nycoprep, as described above for the adult blood samples.

Light-density CD235a$^-$ fetal liver cells and fetal bone marrow cells were prepared by immunomagnetic-bead depletion and centrifugation over a layer of 1.077 g/ml Nycoprep as previously described [27].

2.2. Monoclonal antibodies

Fluorescein isothiocyanate (FITC), phycoerythrin (PE), allophycocyanin (APC) and peridinin chlorophyll (PerCP) labeled mAbs were purchased from BD Biosciences/BD PharMingen (www.bdbiosciences.com) recognizing the following antigens: CD3-FITC (SK7), CD8-FITC (SK1), CD10-FITC (W8E7), CD14-FITC (MΦP9), CD15-FITC (MMA), CD19-FITC (4G7 or SJ25C1), CD-19-PerCP (SJ25C1), CD45RA-APC (HI100), CD45RO-APC (UCHL1), CD45RO-PE (UCHL1), CD95-PE (DX2), CD122-PE (TU27), mouse IgG_1-FITC, mouse IgG_{2a}-FITC and mouse IgM-FITC. Anti-CD56-FITC and anti-CD56-PE (C5.9) were purchased from Exalpha Corporation (Boston, MA). Labeled antibodies recognizing CD4-tricolor (TC) (S3.5), CD14-FITC (TÜK4), CD15-FITC (V1MC6), CD25-PE (CD25-3G10), CD45-PE (HI30), mouse IgG_1-FITC, mouse IgG_1-PE, mouse IgG_{2a}-PE, mouse IgG_{2b}-FITC and mouse IgM-FITC were purchased from Caltag (Burlingame, CA). Conjugated mAb were also purchased from Beckman-Coulter (Miami, FL) recognizing the following antigens: CD3-phycoerythrin-cyanine 5 (PC5) (UCHT-1), CD14-PC5 (RM052), CD16-PC5 (3G8), CD45-PC5 (J33), CD45RA-FITC (ALB11), CD45RO-FITC (UCHL1), CD56-PC5 (N901), CD69-PC5 (TP1.55.3), CD80-PE (MAB104), CD127-PE (R34.34) and mouse IgG_1-PC5. Monoclonal antibodies labeled with PE recognizing T-cell receptor (TCR) α/β (BMA031) and TCR γ/δ (5A6.E9) were obtained from Endogen (Woburn, MA). A FITC-conjugated mAb against TCR α/β was obtained from T Cell Diagnostics, Inc. (Cambridge, MA). A kit containing a panel of FITC-, PE- and a mixture of FITC- and PE-conjugated mAb recognizing different TCR Vβ chains was purchased from Beckman-Coulter and was used according to the manufacturers recommendations.

2.3. Flow cytometric analysis of cell surface markers

Approximately 2×10^5 cells suspended in up to 200 μl blocking buffer were incubated in 96-well Costar V-bottom Plate (Corning Inc., Corning, NY) with saturating amounts of mAbs on ice for at least 30 min. Cells were washed twice with 250 μl PBS/BSA containing 0.01% NaN_3 (Sigma Chemical Co.). The washed cells were suspended in PBS/BSA containing 0.01% NaN_3 and 2 μg/ml propidium iodide (PI), purchased from Sigma Chemical Co. PI was used to mark dead cells, so that they could be excluded from the analysis. PI was omitted in 3-color analyses using PC5 or PerCP labeled mAbs. Flow cytometric analysis was performed using either a FACScan or a FACSCalibur flow cytometer (BD Biosciences). Analyses of results were performed using CellQuest software (BD Biosciences).

2.4. Data presentation and statistical analysis

The median results of multiple measurements done on individual tissue samples are reported to reduce the effects of outliers. Box plots are used to present the data, which show the 10th (lower bar), 25th (box bottom), 50th (median-bar in box), 75th (box top) and 90th (upper bar) percentiles. Circles in the box plots indicate outlying data points below the 10th and above the 90th percentiles. The significance of differences observed between fetal and adult cells was determined using an unpaired Student's *t*-test. Results were considered significant when $P \leq 0.05$.

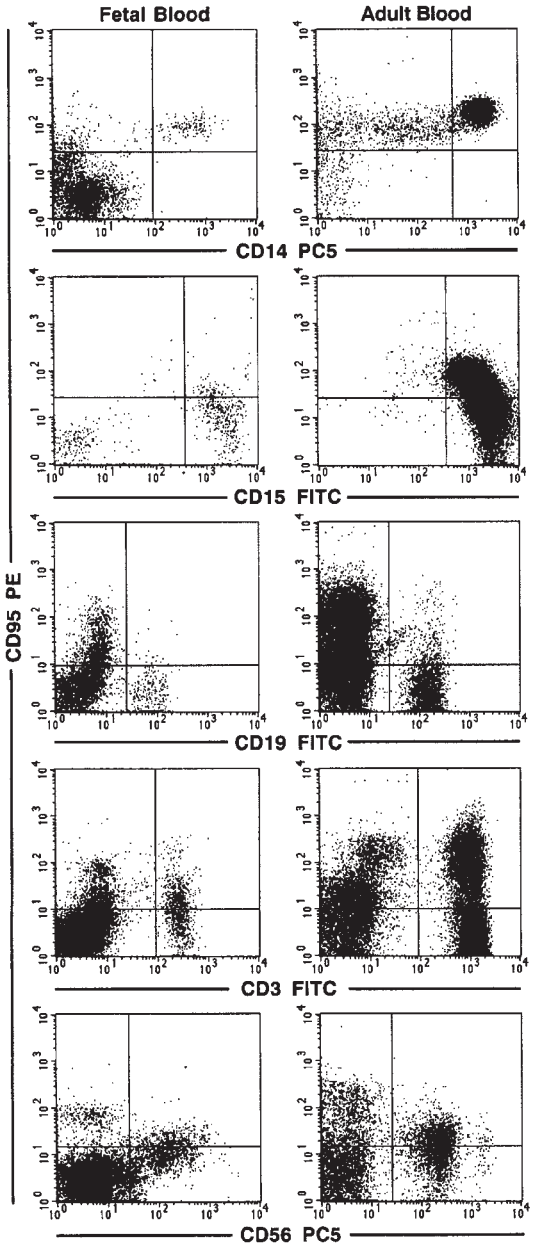

Fig. 1. Expression of CD95 by fetal and adult leukocytes. Representative data from analyses of fetal and adult peripheral-blood leukocytes are shown. The fetal leukocytes had a gestation age of 19 weeks. Adult peripheral blood was obtained from a 36 year old male. The five subsets of leukocytes were defined by the expression of their specific cell-surface antigen, as shown, as well as by their characteristic light-scatter profiles (not shown). $CD14^+$ monocytes as well as the 3 lymphocyte populations were defined as cells with a low to moderate forward-light scatter and a low side-light scatter. $CD15^+$ granulocytes were defined as cells with a high side-light scatter. Additionally, 3-color analyses further enabled the $CD19^+$ B cell population to be defined by their lack of CD14 expression (not shown), which helped to reduce non-specific background staining. $CD56^+$ NK cells were also defined by their lack of CD3 expression (not shown). Quadrants were drawn based on controls stained with mouse IgG1-PE, instead of CD95-PE, such that background staining was $\leq 2.2\%$ for the 2 myeloid populations and $\leq 0.9\%$ for the 3 lymphoid populations.

3. Results

3.1. Analysis of CD95 expression on fetal and adult leukocytes

Expression of CD95 was analyzed by flow cytometry on leukocyte populations found in fetal (blood, spleen, liver and bone marrow) and adult (blood and bone marrow) tissues. The gestational ages of the fetal samples ranged from 15 to 24 weeks. CD95 was expressed on at least some cells of each of the lineages analyzed in both fetal and adult tissues. Most circulating $CD14^+$ monocytes expressed CD95 at high levels (Fig. 1). In adult blood, a median 97.1% of monocytes expressed CD95. Likewise, a median 93.7% of fetal blood and 83.2% of fetal splenic monocytes showed CD95 expression (Fig. 2A). The levels of CD95 expressed on fetal and adult peripheral-blood monocytes also did not differ (Fig. 2B), although the fetal splenic monocytes had reduced levels of CD95 ($P = 0.053$). However, the reduced levels of CD95 in the spleen appeared to be the result of increased background staining, with non-specific isotype-matched control antibody, rather than reduced CD95 expression (data not shown). The expression of CD95 on the immature $CD14^+$ monocytes developing in hematopoietic tissues was also analyzed. Both in the fetal and adult bone-marrows, CD95 expression was apparent on cells expressing low and high levels of CD14 indicating that CD95 is already expressed at the time of CD14 acquisition (Fig. 3).

Few fetal $CD15^+$ granulocytes expressed CD95 (Fig. 1). In adult blood, a median 86.0% of granulocytes expressed CD95, but only 22.0% of fetal blood and 21.1% of fetal splenic granulocytes expressed CD95 (Fig. 2A). The decreased expression of CD95 in fetal tissues was significant compared to

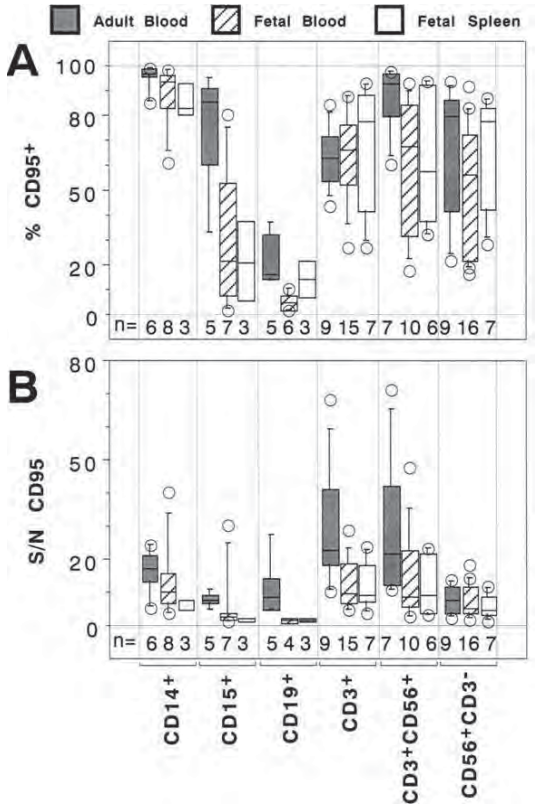

Fig. 2. Box plots of the frequency and intensity of CD95 expression on fetal and adult leukocytes. Leukocyte populations were defined by their phenotypic properties as described in Fig. 1. Box plots are shown of the percent of cells expressing CD95 (A) and the signal to noise (S/N) ratio for CD95 expression (B). The numbers (n) of tissue samples analyzed are indicated at the bottom of the box plots.

adult granulocytes ($P \leq 0.025$). The levels of CD95 expression on $CD15^+$ granulocytes was also significantly lower in the fetal spleen ($P = 0.006$), but did not differ between fetal and adult blood (Fig. 2B). CD95 expression appeared on those granulocytes with lower levels of CD15 expression as exemplified in Fig. 1. Furthermore, immature granulocytes in the fetal and adult bone-marrows uniformly expressed CD95 (Fig. 3). The immature $CD95^+CD15^{low}$ granulocytes were also enriched in the light-density fractions of fetal liver and neonatal UCB (data not shown), indicating that CD95 expression is a feature of young granulocytes that is decreased with maturation and increased CD15 expression.

The frequency of CD95 expression was decreased on $CD19^+$ B cells from fetal blood compared to adult blood ($P = 0.005$) (Fig. 2A). Although the level of CD95 expression was also decreased on fetal blood B-cells this difference was not significant (Fig. 2B). CD95 expression on fetal splenic B-cells did not differ significantly from adult B-cells. The overall modest levels of CD95 expressed on peripheral B-cells were also observed on B cells in the fetal and adult bone-marrows (Fig. 3). These results indicate a lack of CD95 expression on most immature B-cells and their immediate progenitors.

Both the frequency and levels of CD95 expression on $CD56^+CD3^-$ NK-cells was comparable between fetal and adult cells (Fig. 1). CD95 was expressed on a median 56.9–79.8% of fetal and adult NK cells (Fig. 2A). Immature NK cells, expressing low levels of CD56, found in the fetal liver and adult bone marrow expressed CD95 (Fig. 3). Thus, unlike the B cells, CD95 expression is a feature of maturing NK cells.

3.2. Expression of CD95 on fetal and adult T cells

A similar frequency of fetal and adult $CD3^+$ T-cells expressed CD95 (Figs. 1 and 2). However, the levels of CD95 expression on fetal blood and splenic T-cells were less than half those on adult T-cells ($P \leq 0.003$) (Fig. 2B). In general, fetal T-cells consisted of a predominant population of cells that expressed low levels of CD95 and a small subpopulation of T cells that expressed higher levels of CD95 (Fig. 1). Adult T-cells, in contrast, tended to be polarized into two subsets consisting of either $CD95^+$ or $CD95^-$ cells.

The frequency and intensity of CD95 expressed by adult $CD4^+$ T cells were previously shown by Miyawaki et al. to be higher than for $CD8^+$ T cells [21]. Our analysis of adult T-cells confirmed these findings. On the contrary, analyses of fetal blood and splenic T-cells did not indicate any significant difference in the frequency of CD95 expression by $CD4^+$ and $CD8^+$ T-cells (data not shown). However, the intensity of CD95 expressed by fetal $CD4^+$ T-cells was modestly higher than by fetal $CD8^+$ T-cells. The signal to noise (S/N) ratio for CD95 expression was 28% and 68% higher for $CD4^+$ T-cells than for $CD8^+$ T-cells from blood and spleen, respectively (data not shown). These differences did not reach significance by paired analysis ($P = 0.071$ for blood and 0.137 for

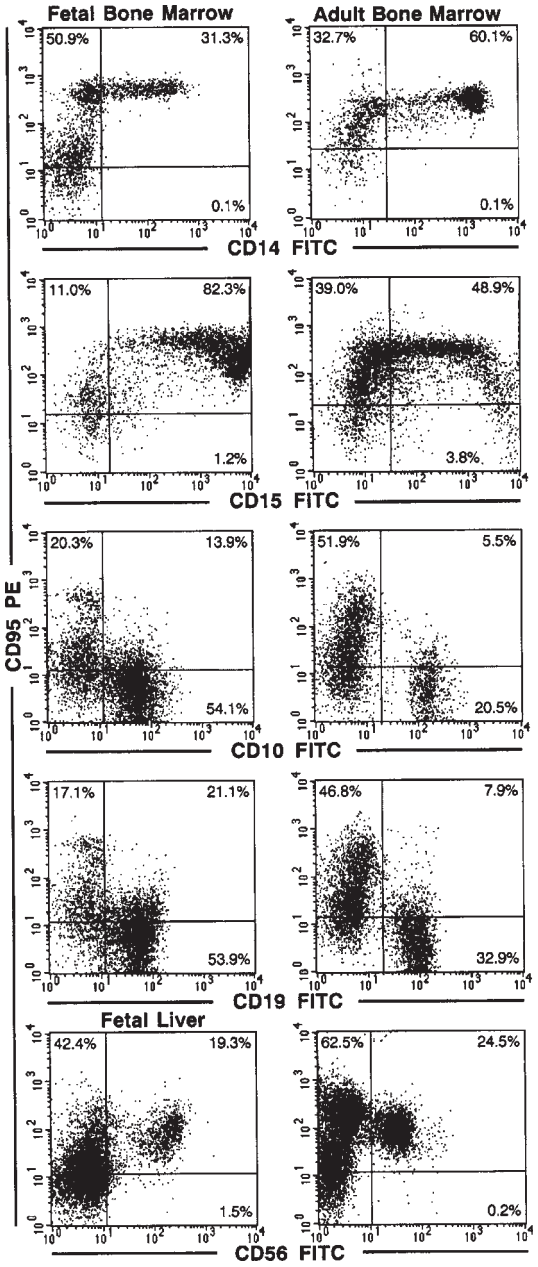

Fig. 3. Expression of CD95 on immature monocytes, granulocytes, B cells and NK cells. Fetal bone marrow, or fetal liver (left column) and adult bone marrow (right column) were analyzed for the expression of CD95 and the indicated leukocyte markers. All tissues were enriched for immature leukocytes by isolation of light-density $CD235a^-$ cells. Additionally, the leukocyte populations of interests were enriched for display by gating on their respective characteristic light-scatter profiles as described in Fig. 1. Quadrants were drawn based on controls, such that background staining in the upper right quadrant was ≤2.4% for the 2 myeloid populations and ≤1.1% for the 3 lymphoid populations.

spleen). For comparison, the S/N ratio for CD95 expression on adult $CD4^+$ T-cells was 125% higher than on $CD8^+$ T-cells.

Three-color analyses of CD3, CD4 and CD8 expression were performed on fetal blood and spleen samples ranging in age from 16 to 24 weeks' gestation. Although there were no significant differences in the ratio of CD4 to CD8 SP T-cells between fetal and adult samples, the younger fetal specimens had a lower ratio than older fetal specimens (data not shown). In three fetal samples younger than 19 weeks' gestation the CD4/CD8 ratio ranged from 0.46 to 1.8. In samples between 19 and 24 weeks had ratios that ranged from 2.0 to 2.7, comparable to ratios observed from adult blood.

The tendency towards higher CD95 expression on $CD4^+$ T-cells was also observed on SP T-cells in the fetal thymus (Fig. 4A). Fetal thymi of 15, 19 and 22 weeks' gestation were analyzed and CD95 was found to be on 1.9-fold more CD4 SP thymocytes than on CD8 SP thymocytes ($P = 0.057$, paired comparison). Low expression of CD95 was also observed on DP thymocytes. Double negative (DN) thymocytes were up to 83.5% $CD95^+$ ($n = 3$). DN thymocytes include $CD3^-$ T-cell progenitors, $CD3^+$ immature T-cells and cells of various other lineages. Nonetheless, the majority of CD95 expression in the fetal thymus was on cells expressing high levels of CD3 as seen in Fig. 4B. To determine whether CD95 is expressed by T cells shortly before emigration from the thymus we analyzed $CD3^+CD45RA^+$ and $CD3^+CD45RO^-$ thymocytes [29–31]. There was CD95 expression on both of these overlapping subpopulations of thymocytes, indicating that CD95 is expressed at low levels on T cells that emerge from the thymus.

3.3. Expression of CD45 isoforms by fetal and adult T cells

The high frequency of CD95 expression on fetal T cells was unexpected considering published findings indicating low expression of this protein on neonatal T

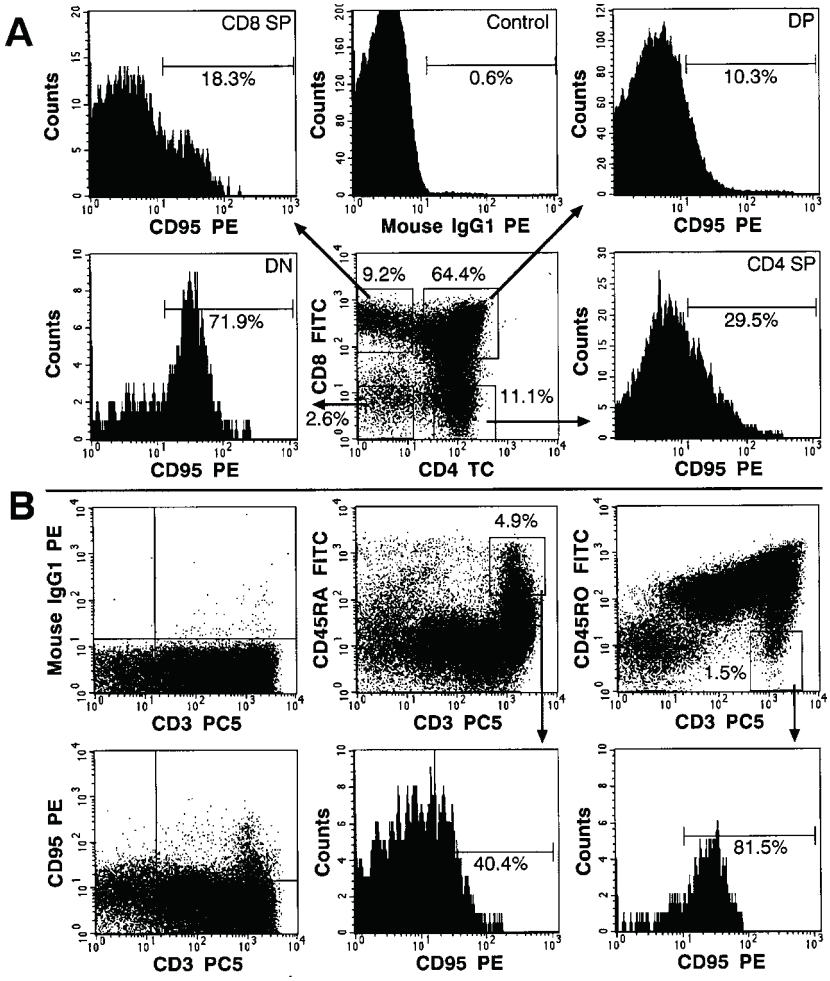

Fig. 4. Expression of CD95 during T-cell development in the fetal thymus. Expression of CD95 on DN, DP and SP thymocytes is shown in (A). Co-expression of CD3 and CD95 as well as the level of CD95 expression on $CD3^+CD45RA^+$ and $CD3^+CD45RO^-$ thymocytes is shown in (B). Representative results are shown from a 15 weeks' gestation thymus.

cells. Since CD95 expression on adult T cells is predominantly on $CD45RO^+$ T cells [21], we examined the expression of CD45RA and CD45RO on fetal, neonatal and adult T cells (Figs. 5 and 6A). Previous findings have indicated a higher frequency of $CD45RO^+CD45RA^-$ T-cells in the fetus than the in the neonate [32], thus possibly accounting for the higher rate of CD95 expression in the fetus. The $CD45RO^+CD45RA^-$ subset represented a median of 11.3% and 15.5% of T cells in the fetal blood and spleen, respectively, which was significantly higher than the median 1.5% in UCB obtained from full term newborns ($P = 0.031$ for blood and < 0.001 for spleen) (Fig. 6A). Although, the frequency of fetal $CD45RO^+CD45RA^-$ T-cells was reduced compared to the adult ($P = 0.046$ for blood and 0.072 for spleen) (Fig. 6A). Both fetal blood and spleen also had significantly reduced numbers of $CD45RO^+CD45RA^+$ T-cells compared to adults, whereas $CD45RO^-CD45RA^+$ T-cells were more prevalent in the fetus than in the adult ($P \leq 0.028$) (Fig. 6A). The majority of T cells in UCB were

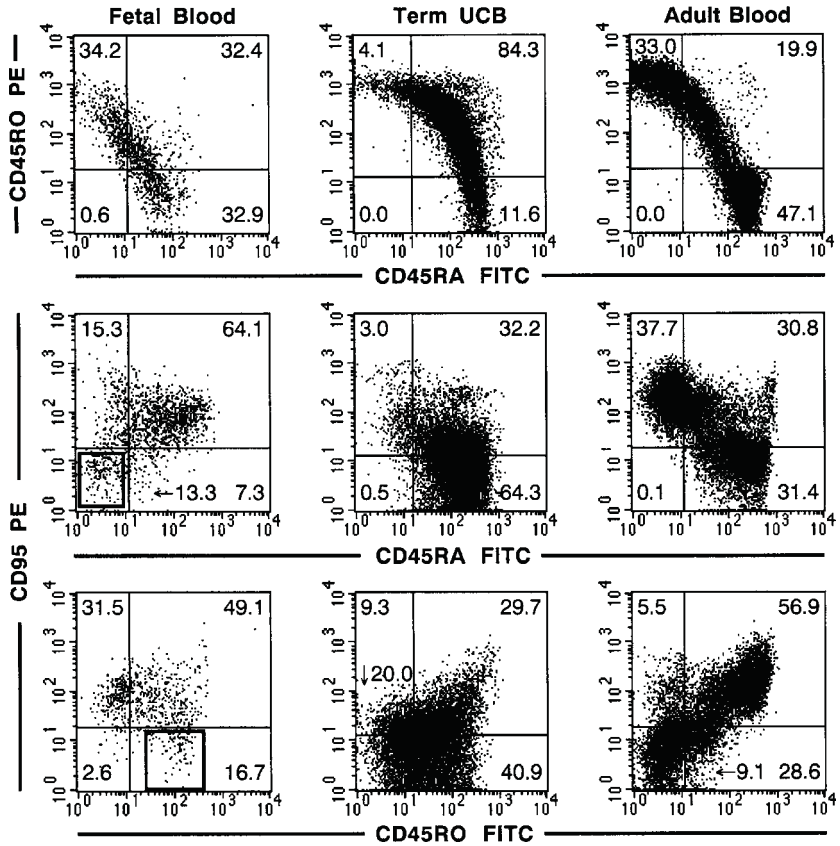

Fig. 5. Expression of CD45RA, CD45RO and CD95 by fetal, neonatal and adult T-cells. 3-color analyses were performed by staining blood cells with CD3-PC5 and the indicated mAbs. Events shown are gated on $CD3^+$ cells with low forward- and side-light scatters. The gestational ages of the fetal blood samples where 20 weeks for the top dot plot and 16 weeks for the lower two dot plots. The single UCB sample was obtained from a full-term delivery (approximately 40 weeks' gestation). Adult blood was obtained from a 29 year individual (top dot plot) and 37 year individual (middle and bottom dot plots). Numbers represent the percentage of events in the corresponding quadrants. The fetal $CD95^-CD45RO^+$/$CD95^-CD45RA^-$ T-cell population is highlighted by rectangular regions.

$CD45RO^+CD45RA^+$ ($P = 0.033$ versus adult blood), whereas the $CD45RO^-CD45RA^+$ subpopulation was similarly represented in UCB compared to adult blood. Thus, the naive $CD45RO^-CD45RA^+$ T-cell subset is enriched in the fetus, but a notable number of $CD45RO^+CD45RA^-$ T-cells are present in the fetal circulation, more so than at the time of birth.

CD95 expression was detected on both $CD45RA^+$ and $CD45RO^+$ fetal T-cells, but differences between fetal and adult T cells were apparent (Figs. 5 and 6B). The median frequency of fetal $CD45RA^+$ T-cells that expressed CD95 was 62.0% in the blood and 85.4% in the spleen (Fig. 6B). The median frequencies of CD95 expression on adult and neonatal $CD45RA^+$ T-cells were significantly lower at 45.1% and 37.1%, respectively ($P = 0.012$ for both comparisons). Most adult $CD45RO^+$ T-cells expressed CD95 (median 89.1%), as previously described [21]. However, CD95 expression was reduced on $CD45RO^+$ T-cells from fetal blood (median 59.7%), fetal spleen (median 72.8%) and UCB (median 54.9%). These differences in CD95 expression compared to adult $CD45RO^+$ T-cells were significant ($P \leq 0.009$). Moreover, examination of the pattern of CD95 expression on fetal T-cells revealed a subpopulation of $CD45RO^+CD45RA^-$ T-cells that was

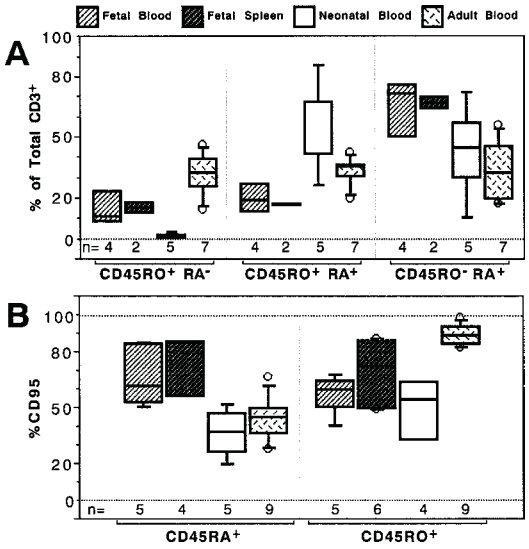

Fig. 6. Expression of CD45 subtypes and CD95 by fetal, neonatal and adult T cells. The percentages of $CD45RO^+CD45RA^-$, $CD45RO^+CD45RA^+$ and $CD45RO^-CD45RA^+$ T-cells in fetal tissues, UCB and adult blood are shown in (A). The percentages of $CD45RA^+CD3^+$ and $CD45RO^+CD3^+$ T cells that expressed CD95 are shown in (B). The numbers (*n*) of tissue samples analyzed are indicated at the bottom of the box plots.

$CD95^-$ (Fig. 5, boxed regions). These cells were best defined by their lack of CD45RA staining rather than their expression of CD45RO. This is because many $CD45RO^+$ cells can also express CD45RA, whereas all $CD45RA^-$ cells are $CD45RO^+$. The $CD95^-CD45RO^+CD45RA^-$ T-cell population was not present to any appreciable degree in either term UCB or adult peripheral blood.

3.4. Cytokine receptors and activation markers expression by fetal and adult T-cells

The expression of CD95 and CD45RO by fetal T-cells suggests the possibility that a sizable proportion of fetal T-cells have undergone activation. To support this hypothesis, we analyzed the expression of various cytokine receptors and other cell-surface markers associated with T-cell growth and activation (Table 1). Components of the IL-2 receptor complex were analyzed, which indicated that CD25 was expressed on a similar portion of fetal T-cells as on adult T-cells. In contrast, CD25 was significantly reduced on neonatal T-cells, particularly on the $CD45RO^+$ subset. CD122 was expressed on a significantly higher number of fetal T-cells than on either neonatal or adult T-cells. The α-chain subunit of the IL-7 receptor, CD127, was widely expressed on T-cells from all sources, but was significantly reduced on the $CD45RO^+$ subset of fetal T-cells. T cells in UCB expressed higher levels of CD127 compared to fetal or adult T-cells. CD132, the common γ-chain subunit of the IL-2, IL-4, IL-7, IL-9 and IL-15 receptors, was

Table 1
Expression of cytokine receptors and various activation markers on fetal, neonatal and adult $CD3^+$ T-cells

Marker	Total $CD3^+$ T-cells			$CD45RO^+CD3^+$ T-cells			$CD45RO^-CD3^+$ T-cells		
	Fetal	Neonatal	Adult	Fetal	Neonatal	Adult	Fetal	Neonatal	Adult
CD25	11.0[a]	3.4[b]	14.8	17.7	5.4[b]	22.2	3.8	2.6	3.4
CD122	14.3[a,b]	0.4	1.9	16.2[a,b]	0.7	2.2	11.5[a,b]	0.3[b]	2.0
CD127	77.8[a]	97.5[b]	84.3	67.5[a,b]	82.4	84.8	84.3[a]	100[b]	80.6
CD132	99.6	95.3[b]	100	92.5	96.3	98.4	100[a]	96.5	100
CD56	9.9	4.3	9.7	8.2	5.7	11.5	9.6	3.7	6.2
CD69	21.0[b]	12.5	10.7	ND	ND	ND	ND	ND	ND
CD80	3.7	0	0.3	5.2	0	0.6	0.6	0	0
TCR α/β	80.2[a]	97.6[b]	82.6	ND	ND	ND	ND	ND	ND
TCR γ/δ	17.3[a,b]	2.9[b]	8.2	ND	ND	ND	ND	ND	ND

Light-density cells isolated from fetal spleens and PBMC isolated from UCB and adult blood were analyzed for the expression of CD3, CD45RO and the indicated marker. T cells were defined by their expression of CD3 and by a low forward- and side-light scatter profile. Values represent the median level of expression observed on five fetal, four neonatal and six adult samples. ND = Not determined.

[a] $P \leq 0.05$ versus neonatal T-cells.

[b] $P \leq 0.05$ versus adult T-cells.

expressed on nearly all T-cells at any stage of ontogeny. The markers CD69 and CD80 are expressed on T cells that have become activated [33–35]. The frequency of fetal T-cells expressing these markers was higher than in the adult or neonate. CD56, which is expressed by a subpopulation of cytotoxic T-cells [36], was expressed at similar levels in the fetus and adult, but was approximately half as abundant in the neonate. A significantly greater frequency of fetal T-cells were found to express γ/δ chains of the T-cell receptor.

3.5. Repertoire of TCR Vβ chain expression by fetal T-cells and thymocytes

The TCR Vβ chain repertoire expressed by fetal T-cells was studied to determine the diversity of TCR expression in the emerging immune system. Vβ chain expression was analyzed on splenic $CD3^+$ cells ranging in age from 16 to 24 weeks' gestation (Fig. 7A). A diverse repertoire was observed with the mean percent expression of each Vβ chain falling within the range of expression observed on adult specimens, as reported by the manufacturer of the test reagents. Moreover, two subsets of fetal splenic T-cells, $CD45RA^-$ ($CD45RO^+$) and $CD45RA^+$, were examined and both displayed diversity in Vβ chain expression similar to as described above, except for the following differences: The $CD45RA^-$ subset had a higher representation of Vβ11 ($P < 0.05$, $n = 3$) and Vβ5.1 ($P = 0.075$) and lower representation of Vβ14, Vβ16 and Vβ21.3 ($P < 0.05$, $n = 3$). The possibility that the $CD45RA^-$ T-cells in the spleen are thymocytes that have not gained CD45RA expression before exiting the thymus was examined by comparing the expression of Vβ chains on splenic and thymic

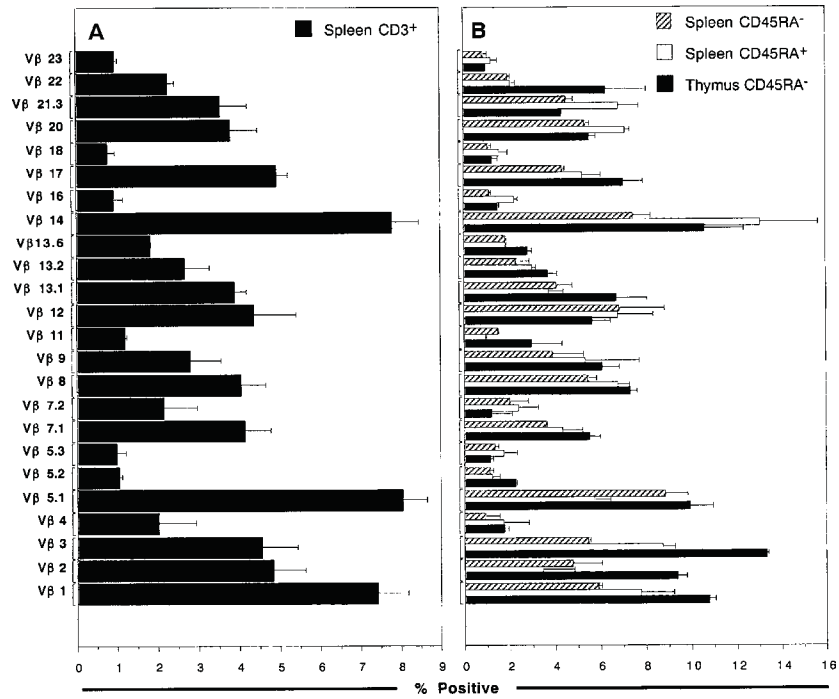

Fig. 7. Expression of TCR Vβ chains by fetal splenic T-cells and thymocytes. TCR Vβ chain expression was analyzed by 4-color flow cytometry. T cells were identified by their expression of high levels of CD3 and by their low light scatter profile. Vβ chain expression was analyzed from a cohort of 6 spleens ranging in gestation age from 16 to 24 weeks (A). Two of these spleens, of 19 and 22 weeks' gestation, were analyzed for Vβ chain expression on T-cells subdivided based on the expression of CD45RA (B). Thymocytes from these same fetal specimens were also analyzed and were gated using the same region as used to define the corresponding splenic $CD3^+CD45RA^-$ population. Results are presented as the mean ± SE.

$CD45RA^{-}CD3^{+}$ cells (Fig. 7B). Besides wide-ranging similarity and some non-significant dissimilarities, there were notable significant differences between the thymic and splenic T-cells. Mainly, a lower representation of Vβ 1, Vβ 3, Vβ 5.2 and Vβ 13.6 ($P \leq 0.05$, $n = 2$) was observed on the splenic T-cells. These differences indicate that the splenic $CD45RA^{-}$ T-cells are not an exact match to the corresponding thymic population.

4. Discussion

The maturity of the human fetal immune system was analyzed from the perspective of CD95 expression as well as a number of additional cell-surface markers associated with T-cell activation and growth (Fig. 8). Most knowledge regarding fetal T-cells has come from the analyses of neonatal T-cells obtained from UCB. Studies have shown neonatal T-cells to be comprised of primarily $CD45RA^{+}$ naive/resting T-cells [11–15] that express low levels of the activation marker CD95 [21,24]. In contrast, our examination of midgestation fetal tissues indicates that the frequency of T cells that express CD95 in these tissues is comparable to that of adult T-cells. However, the levels of CD95 expression are reduced on fetal T-cells. Although fetal T-cells were predominantly $CD45RO^{-}CD45RA^{+}$ T-cells, $CD45RO^{+}CD45RA^{-}$ T-cells were present in the blood of midgestation fetuses, more so than at full term. Furthermore, a number of cell-surface markers associated with T-cell activation, were also observed on fetal T-cells at levels similar or higher than in the adult. These data indicate a, heretofore, unappreciated level of activation of peripheral T-cells circulating in the immediate weeks following thymic development in the human fetus.

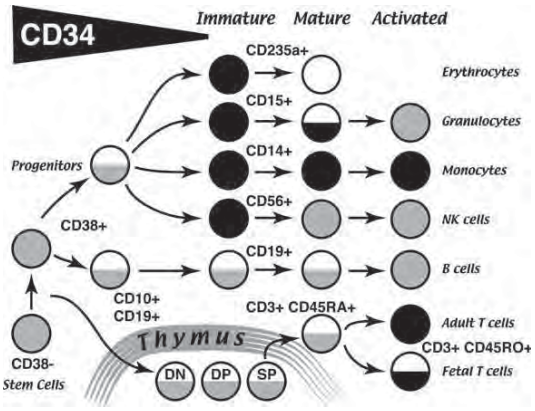

Fig. 8. Proposed expression of CD95 on human hematopoietic cells throughout ontogeny. The expression of CD95 at various stages of hematopoiesis ($CD34^{+}$ cells, black triangle), maturation and activation is indicated by shading. Black circles represent relatively high levels of CD95 expression, gray circles represent intermediate expression and open circles represent a lack of CD95 expression. Filled circles indicate that most cells of the indicated population express CD95, whereas semi-circles represent CD95 expression by a subpopulation of cells. The schema was developed from the data presented in this study as well as previously published reports [25,27,50–53].

Byrne et al. have reported a higher frequency of $CD45RO^{+}CD45RA^{-}$ T-cells in the midgestation fetus compared to full-term neonates [32]. Our findings confirm this observation and extend them by describing a subset of $CD45RO^{+}CD45RA^{-}$ T-cells in the fetus that lacks CD95 expression (Fig. 8). We are unaware of any previous description of a $CD95^{-}CD45RO^{+}CD45RA^{-}$ subpopulation of T cells, and we did not observe this population in postnatal blood. Nearly all adult $CD45RO^{+}CD45RA^{-}$ T-cells are known to express CD95 at high levels [21]. Indeed, the higher frequency of $CD45RO^{+}CD45RA^{-}$ T-cells in adults is a contributing factor to the higher levels of CD95 expression observed on adult versus fetal T-cells. The role of the $CD95^{-}CD45RO^{+}CD45RA^{-}$ T-cell subset in the developing immune system is presently unclear. The expression of CD45RO by these cells suggests that they may have been previously activated. Although there are some reports that suggest exposure of the fetus to external antigens can occur [37], the prevalence of the $CD45RO^{+}$ population of T cells could mean that these cells are being exposed to and subsequently responding to autologous antigens. We speculate that a developmentally early wave of activation of autoreactive T-cells may be an important step in the establishment of suppressor T-cell populations and peripheral tolerance. Indeed, the decreased expression of CD95 on these cells would be counter to the hypothetical removal of fetal autoreactive T-cells by a CD95-mediated apoptotic mechanism [32]. However, the loss of CD95 expression may still be associated with the removal

of these cells since there is evidence that signaling through CD95 may support T-cell growth rather than apoptosis in some circumstances [38,39].

A broader analysis of T-cell markers further supports our conclusion that the midgestation fetus contains a notable number of activated T-cells. Although a previous study failed to identify any $CD56^+$ natural cytotoxic T-cells in the fetus [40], we observed a similar number of $CD56^+$ T-cells in the fetus as in the adult. About 17% of fetal T-cells expressed the γ/δ TCR which was higher than in the neonate and adult, consistent with previous findings [41]. CD69, an activation antigen expressed early in T-cell activation [33], was expressed at nearly twice the frequency on fetal T-cells as on neonatal and adult T-cells. CD80 is a stimulatory molecule for T cells expressed by various leukocytes, which can be expressed on some T cells during the later phase of activation [34,35]. CD80 was expressed on fetal T-cells, in particular $CD45RO^+$ T cells, also at a higher frequency than in the neonate and adult. T-cell activation also results in upregulation of the α and β subunits of the IL-2 receptor, CD25 and CD122, respectively. Both components of the IL-2 receptor were found on fetal T-cells, with a notably higher number of $CD122^+$ T-cells in the fetus compared to the adult. Very little CD25 and CD122 expression was observed on neonatal T-cells. The expression of CD25 and CD122 by fetal T-cells suggests these cells may be activated, although it is possible that some of these cells represent $CD4^+$ suppressor/regulatory T-cells [42]. This regulatory subset of T cells has been described in UCB and is characterized in part by CD25 and CD122 expression [43]. IL-7 plays a critical role in the maintenance of the naïve T-cell pool through interaction with its receptor, CD127/CD132 [44]. After T-cell activation, CD127 expression is lost and, as such, is another indication that T cells have been stimulated [45]. We observed $CD127^-$ T-cells in both the fetus as well as in the adult, although most T cells in both cases express CD127. Indeed, there was a higher portion of $CD45RO^+$ T-cells that lacked CD127 expression in the fetus than in the adult. Moreover, CD127 was notably higher on neonatal T-cells compared to both fetal and adult T-cells. In total, these findings are consistent with a higher level of T-cell activation in the midgestation fetus than at term.

The abundant expression of CD95 by peripheral T-cells in the fetus prompted us to analyze the expression of CD95 on developing T-cells in the thymus (Fig. 8). CD95 expression in the fetal thymus was predominantly found on T-cells that had already begun to express high levels of CD3, although the majority of DP and SP T-cells did not express CD95. Most DN thymocytes expressed CD95. Our findings are consistent with those of Jenkins et al. who observed CD95 expression on T-cell progenitors, but found very little expression on mature $CD3^+$ SP thymocytes. These investigators also demonstrated that the thymic cells are resistant to CD95-mediated apoptosis [25]. We wished to further elucidate the degree of CD95 expression on mature thymic T-cells set to enter the circulation. Most developing T-cells in the thymus express CD45RO, which is expressed in an inverse relationship to CD45RA. Before exiting the thymus, T cells are known to down-regulate CD45RO expression and become $CD45RA^+$ [29–31]. Examination of CD95 expression on thymic $CD45RO^-$ and $CD45RA^+$ T-cells indicated that most T cells entering the periphery are $CD95^+$, consistent with the expression of CD95 observed on peripheral $CD45RA^+$ T-cells. Since adult $CD45RA^+$ T-cells, which are less likely to be recent thymic emigrants, expressed less CD95 it is likely that CD95 expression is reduced on naïve T-cells with time spent in the circulation.

There at least two additional potential explanations, besides (auto)antigen-specific activation, for the presence of T-cells in the fetal circulation with an activated phenotype. One possibility is that the markers associated with activation are expressed because of T-cell growth, associated with rapid expansion of the peripheral pool of T cells, rather than specific activation by antigen. Another possibility is that the $CD45RO^+$ T-cells in the fetal circulation are recent thymic emigrants that emerged from the thymus before changing to the $CD45RA^+$ phenotype. In attempt to distinguish these possibilities, the Vβ chain repertoire was analyzed on fetal T-cells. A diverse repertoire, comparable to that of adults, was observed as early a 16 weeks gestation. It is worth mention that methods more sensitive to minor sequence differences have shown reduced diversity within the Vβ chain families of late-gestation fetal and some neonatal blood samples [46,47], which

presumably is true for early mid-gestation T-cells as well. Our results also demonstrated diversity within the $CD45RA^-$ ($CD45RO^+$) subset of fetal T-cells indicating that this subset is not derived from the activation and expansion of one or a few T-cell clones. Differences in Vβ chain expression between splenic and thymic $CD45RA^-$ T-cells suggest that the splenic cells are not recent emigrants from the thymus, although further experiments are required to bolster this conclusion. There were also some differences in Vβ chain expression between splenic $CD45RA^-$ and $CD45RA^+$ T-cells, which may indicate selective expansion of T cell clones. However, further study is required to distinguish the possible reasons for the expression of activation markers on fetal T-cells.

We further examined if CD95 expression can be viewed as a marker of activation or maturation for leukocyte lineages other than T-cells (Fig. 8). CD95 was expressed on immature cells of all lineages and was down-regulated with maturation, except in the case of monocytes which expressed CD95 even in the sterile fetal environment. In contrast, granulocytes reduced their expression of CD95 after entering the circulation. Likewise, CD95 expression was decreased or lost on NK cells in the circulation, possibly due to a lack of growth or activation stimulus, although increased CD95 expression is correlated with in vitro activation of NK cells [48,49]. B cells expressed less CD95 than most other lineages during their development in the fetal or adult bone-marrow. Most $CD19^+$ and $CD10^+$ cells in hematopoietic tissues did not express CD95 and expression on circulating fetal B-cells was low and decreased compared to the adult. Miyawaki et al. first described similar results for UCB and adult peripheral blood B-cells [21]. CD95 expression on B cells correlates with increased functional differentiation and is, thus, likely low on fetal B-cells owing to their lack of stimulation and hormonal suppression. These findings show a diverse and variable expression of CD95 in the development of hematopoietic cells, indicating that CD95 expression alone is not a reliable marker of maturational status or activation.

Continued research into the development and functional status of the human fetal immune system should lead to new insights into the steps required in the development of the immune system and the establishment of peripheral tolerance towards autologous antigens. These insights may lead to better therapies for immune compromised patients and transplant patients. Efforts at fetal gene or cellular therapy would also benefit greatly from a clearer understanding of the functional capacity of the immune system at various stages of development.

Acknowledgements

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WOMEN'S HEALTH
Policy Report

MENU

IN THE NEWS

CDC issues new Zika guidance; state, federal efforts targeting fetal tissue donation could thwart Zika research

MARCH 29, 2016

CDC on Friday issued **guidance** advising men and women who have been exposed to the Zika virus to delay pregnancy, the ***New York Times*** reports (Tavernise, *New York Times*, 3/25).

Background

The Zika virus is a mosquito-borne disease that has spread across Latin America over the past year. Researchers recently learned that Zika can also be transmitted through sexual activity. The virus is not easily diagnosed, and it does not have a cure or vaccine. It also might be linked to the birth defect microcephaly, a condition in which an infant is born with an abnormally small head and brain. The condition is fatal for some infants, while others experience permanent disabilities.

Officials in Brazil and Honduras have issued guidance recommending that women avoid pregnancy. El Salvador's recommendation is that women not get pregnant until 2018. However, many countries in Latin America restrict access to contraception and often ban abortion. In addition, women have been advised to protect themselves against mosquitos, but insect repellant can be unaffordable for low-income women.

The World Health Organization has declared the outbreak and its suspected link to a congenital condition in infants a public health emergency of international concern. Separately, the United Nations High Commissioner for Human Rights issued a **statement** directing nations affected by the Zika virus to remove bans on access to reproductive health care services (***Woman's Health Policy Report***, 2/18).

In previous guidance, CDC said women who are pregnant should abstain from sex or use condoms during vaginal, anal or oral sex with male sexual partners who have traveled to a country affected by the Zika virus. CDC also advised pregnant women not to visit affected countries and said women who are trying to become pregnant should talk with their physicians before visiting those locations. In addition, the agency recommended that all pregnant women -- even those without symptoms -- should be tested within two to 12 weeks of returning from an area affected by the virus (***Women's Health Policy Report***, 2/8).

Latest advisory

CDC last week said a woman infected with Zika or displaying symptoms of the virus should delay attempts to conceive for at least eight weeks after she first presented with symptoms. Men who have been infected or present with symptoms should wait at least six months after the initial symptoms appear before having sex without protection, the agency said.

CDC also advised that men and women who have traveled to Zika-infected regions but who have not been infected or displayed symptoms should postpone trying to conceive by eight weeks. In addition, the agency recommended that people who live in Zika-infected regions discuss the risks of a Zika infection with their physicians. CDC did not advise such women to postpone pregnancy.

Denise Jamieson -- leader of the pregnancy and birth defects team in CDC's Zika response efforts -- said, "We're learning more every day, and evidence of a link between Zika and a spectrum of birth outcomes is becoming stronger and stronger" (*New York Times*, 3/25).

Advisory spotlights danger in Puerto Rico

CDC on Friday also underscored the risk women in Puerto Rico face of contracting the virus. Researchers said about 138,000 Puerto Rican women who do not want to become pregnant are unable to access effective contraception, which exposes them to unintended pregnancy and possible Zika infection. In Puerto Rico, according to the ***Washington Post***, roughly two-thirds of pregnancies are unintended.

The *Post* reports that Zika is spreading more quickly in Puerto Rico than in any other U.S. territory. Overall, officials have confirmed 261 cases of Zika infection in the territory, 24 of which involved pregnant women (Sun, *Washington Post*, 3/25).

Laws targeting fetal tissue donation could restrict Zika research

In related news, medical researchers say federal and state efforts in the United States to prohibit or restrict fetal tissue donation could hinder research into the Zika virus, ***Politico*** reports.

According to *Politico*, Arizona, **Florida**, **Indiana**, North Dakota, Ohio and South Dakota are among the 18 states that are considering or have passed measures targeting fetal tissue donation or banning fetal tissue research. *Politico* reports that Florida, the latest state to pass such legislation, is one of the states most at risk of the virus. Moreover, the Florida regulations also could limit non-Zika research, such as HIV research being conducted at several universities in the state.

At the federal level, conservative lawmakers in a House subcommittee investigating abortion providers recently **issued** 17 subpoenas seeking identifying information about people involved in abortion care and fetal tissue research, drawing criticism from liberal lawmakers who say such information could expose individuals to antiabortion-rights violence.

Efforts could thwart Zika research

According to *Politico*, the "clearest evidence yet" of a link between the Zika virus and fetal anomalies came from research conducted on fetal tissue resulting from an abortion. In that research, scientists found that brain damage in fetuses exposed to the Zika virus resulted from the virus, rather than from the reaction of the woman's placenta to the virus.

CDC has not issued an official statement on how measures targeting fetal tissue research might affect efforts to learn about the virus. However, CDC did recently release guidance urging the donation of fetal and infant tissue for Zika research. According to *Politico*, researchers might require the tissue to discern how the virus affects fetal development and how they might develop tests and treatments for infection.

Patrick Ramsey, an obstetrician at the University of Texas Health Science Center in San Antonio, said, "Basically the only insights we've had so far on Zika is with patients who have either lost a pregnancy or had miscarriages." He added, "This is a situation where the vaccine is going to have to protect" the woman and fetus, so "[f]etal tissue is going to be needed to look at the effects."

Separately, Georges Benjamin, executive director of the American Public Health Association, said, "I think if we're serious about making sure that babies are not affected by the Zika virus, we need to know all we can, and we learn a lot from fetal tissue, as we do with other human tissues."

Alta Charo, a bioethicist at the University of Wisconsin, added, "Given the uncertainty around the effects of exposure while pregnant, halting fetal tissue research might slow efforts to prevent those effects or at least let women know if chances are high or low of serious birth defects."

Robert Golden -- dean of the University of Wisconsin School of Medicine and Public Health, who helped defeat a state initiative to prohibit fetal tissue research last year -- said, "With the horrors of the Zika virus and its almost certain spread to Florida, to me it's unfathomable that anyone there would want to restrict this research ... And this in turn

might actually lead more women to choose abortions, out of fear of terrible birth outcomes" (Norman, *Politico*, 3/27).

Brazil seizes medication abortion

In other related news, the Canadian abortion-rights group Women on Web has temporarily stopped providing medication abortion to women in Brazil after learning that the Brazilian government has been confiscating the drugs, the ***Los Angeles Times*** reports (Simmons/Rigby, *Los Angeles Times*, 3/27).

Women on Web offers advice and medication for women seeking abortion care in countries where the procedure is banned, such as Brazil (*Women's Health Policy Report*, 2/18). The group said it received 9,500 emails in 2015 from women seeking medication abortion, primarily from Brazil, and another 10,400 emails from Spanish-speaking countries in the Americas. According to Women on Web, the demand for medication abortion has increased as the Zika virus has spread.

The group has been providing medication abortion at no cost to women in Brazil and other Zika-affected countries since Feb. 1. However, Women on Web announced that it was suspending services for Brazil after learning that only two of several dozen medication abortion packages mailed to women in the country had reached their destination. According to the group, the Brazilian government has confiscated 95 percent of the packages. Officials with the Brazilian government confirmed the seizures.

Women on Web is recommending that, if possible, women should arrange to have the medication abortion packages delivered to P.O. boxes in neighboring countries. However, according to the *Los Angeles Times*, such a strategy is out of reach for most low-income women.

Leticia Zenevich, a spokesperson for Women on Web, called the situation "very tragic."

Abortion-rights advocates in the country also have voiced concerns that women unable to access medication abortion will seek out unsafe abortion care. Sonia Coelho, a spokesperson for the National Campaign for the Legalization of Abortion, said, "We have a situation here in Brazil in which women are having clandestine abortions, and in which women are dying." She added, "This brings consequences ... particularly for [low-income] women and black women, who lack the means to have an abortion in a safer place" (*Los Angeles Times*, 3/27).

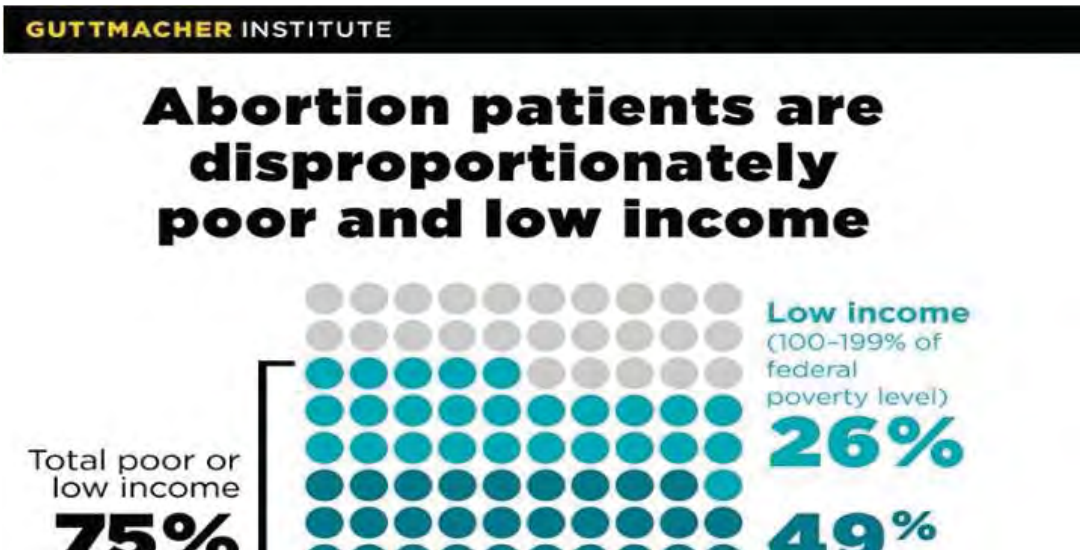
VIDEO ROUND UP

The *Wichita Eagle* spotlights an abortion clinic set to open in Oklahoma City this summer.

Watch the video »

See All

DATAPOINTS



In this infographic, the Guttmacher Institute highlights research showing how an increasing proportion of women who obtain abortion care in the United States are lower-income.

Read more »

See All

AT A GLANCE

"A woman's ability to end her pregnancy too often depends on where she lives, her age and how much money is in her pocket."

— Marcela Howell of In Our Own Voice: National Black Women's Reproductive Justice Agenda, discussing ongoing disparities in women's access to abortion care on the 43rd anniversary of *Roe v. Wade.*

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FUNDING

Project Listing by Category

RESEARCH, CONDITION, AND DISEASE CATEGORIZATION PROCESS RCDC

BACK

Click the column headings to sort project listings.

EXPORT

Category	FY	Funding IC	Project Number	Sub Project #	Project Title	PI Name	Org Name	State / Country	Amount
Human Fetal Tissue	2014	NIAID	1K22AI102769-01		Development of Vectored ImmunoProphylaxis as a strategy against HIV	BALAZS, ALEJANDRO	MASSACHUSETTS GENERAL HOSPITAL	MA	$156,632
Human Fetal Tissue	2014	NIAID	5R01AI097012-03		Mode of action of a new Tat HIV-1 inhibitor	VALENTE, SUSANA	SCRIPPS FLORIDA	FL	$678,760
Human Fetal Tissue	2014	NIAID	5R01AI095097-03		HIV co-infection and HCV-induced liver fibrosis in vivo	SU, LISHAN	UNIV OF NORTH CAROLINA CHAPEL HILL	NC	$370,000
Human Fetal Tissue	2014	NIAID	5R01AI051463-10		Repair of HCMV-Induced DNA Damage in Infected Cells	FORTUNATO, ELIZABETH	UNIVERSITY OF IDAHO	ID	$319,424
Human Fetal Tissue	2014	NEI	5R01EY018755-16		Herpes Simplex Virus Egress from Cells and Spread into Neuronal Axons	JOHNSON, DAVID	OREGON HEALTH & SCIENCE UNIVERSITY	OR	$446,321
Human Fetal Tissue	2014	NEI	5R01EY022936-02		Humoral Immunity, Astrocyte Injury, and Demyelination in Neuromyelitis Optica	BENNETT, JEFFREY	UNIVERSITY OF COLORADO DENVER	CO	$379,137
Human Fetal Tissue	2014	NIAMS	5R37AR042455-22		Maternal Autoantibodies: Pathogenesis of Neonatal Lupus	BUYON, JILL	NEW YORK UNIVERSITY SCHOOL OF MEDICINE	NY	$358,798
Human Fetal Tissue	2014	NEI	5R01EY022079-03		Defining the molecular mechanisms underlying human RPE plasticity	TEMPLE, SALLY	REGENERATIVE RESEARCH FOUNDATION	NY	$432,376
Human Fetal Tissue	2014	NIAID	5R21AI105847-02		Immune evasion in a humanized mouse model of HHV-6 infection	HUDSON, AMY	MEDICAL COLLEGE OF WISCONSIN	WI	$257,579
Human Fetal Tissue	2014	NIDDK	5R01DK092456-03		Human Endocrine Cell Development	WELLS, JAMES	CINCINNATI CHILDRENS HOSP MED CTR	OH	$455,040
Human Fetal Tissue	2014	NICHD	1R01HD078561-01		Development of Brain Connectivity in Human Fetus, Newborn, and Toddler Ages	TAKAHASHI OKI, EMI	CHILDREN'S HOSPITAL CORPORATION	MA	$379,162
Human Fetal Tissue	2014	NEI	1R01EY024045-01		3D retina-RPE constructs for vision restoration in new rat retinal degeneration m	KEIRSTEAD, HANS	UNIVERSITY OF CALIFORNIA-IRVINE	CA	$385,730
Human Fetal Tissue	2014	NIAID	5P01AI104715-02	5790	Optimizing CD8+ T Cell Vaccine Responses Against HIV	ALLEN, TODD	MASSACHUSETTS GENERAL HOSPITAL	MA	$393,756
Human Fetal Tissue	2014	NIAID	5P01AI104715-02	5798	Optimizing Antibody Vaccines Against HIV	SCHIEF, WILLIAM	MASSACHUSETTS GENERAL HOSPITAL	MA	$875,378
Human Fetal Tissue	2014	NIAID	5P01AI104715-02	5800	Animal and Laboratory Core	ALLEN, TODD	MASSACHUSETTS GENERAL HOSPITAL	MA	$728,637
Human Fetal Tissue	2014	NIAID	5P01AI100148-02	7194	Human Antibodies to HIV	NUSSENZWEIG, MICHEL	CALIFORNIA INSTITUTE OF TECHNOLOGY	CA	$336,786
Human Fetal Tissue	2014	NIAID	5P01AI100148-02	7195	Fc effector function in bNAbs	RAVETCH, JEFFREY	CALIFORNIA INSTITUTE OF TECHNOLOGY	CA	$947,985
Human Fetal Tissue	2014	NIAID	5P01AI100148-02	7199	Animal Services	NUSSENZWEIG, MICHEL	CALIFORNIA INSTITUTE OF TECHNOLOGY	CA	$362,222
Human Fetal Tissue	2014	NIMH	1K99MH102357-01		Genetic Influences on Human Cortical Development	STEIN, JASON	UNIVERSITY OF CALIFORNIA LOS ANGELES	CA	$117,990
Human Fetal Tissue	2014	NIAID	5R44AI102396-03		Therapeutic Antibodies for CMV	KAUVAR, LAWRENCE	TRELLIS BIOSCIENCE, LLC	CA	$990,935
Human Fetal Tissue	2014	NIAID	5R01AI064569-08		Role of CD47 in xenograft rejection by macrophages	YANG, YONG-GUANG	COLUMBIA UNIVERSITY HEALTH SCIENCES	NY	$364,541
Human Fetal Tissue	2014	NIMH	5R01MH099555-02		Phenotyping Astrocytes in Human Neurodevelopmental Disorders	BARRES, BEN	STANFORD UNIVERSITY	CA	$386,750
Human Fetal Tissue	2014	NIAID	5P30AI028697-25	7320	Humanized Mouse Chimera Core	KITCHEN, SCOTT	UNIVERSITY OF CALIFORNIA LOS ANGELES	CA	$136,054
Human Fetal Tissue	2014	NIAID	5P30AI028697-25	7321	Gene and Cellular Therapy Core	AN, DONG SUNG	UNIVERSITY OF CALIFORNIA LOS ANGELES	CA	$111,435

Categorical Spending - Project Listing - NIH Research Portfolio Online Reporting Tools (RePORT)

Human Fetal Tissue	2014	NIDA	2R01DA023999-06		Origin of Cortical Species-specific Distinctions.	RAKIC, PASKO	YALE UNIVERSITY	CT	$729,725
Human Fetal Tissue	2014	NIMH	1R01MH100914-01A1		Genomic mosaicism in developing human brain	VACCARINO, FLORA	YALE UNIVERSITY	CT	$796,238
Human Fetal Tissue	2014	NICHD	5P01HD029587-19	7045	PROJECT II - CLINICALLY-SAFE NMDAR ANTAGONISTS PREVENT NEUROTOXICITY	LIPTON, STUART	SANFORD-BURNHAM MEDICAL RESEARCH INSTIT	CA	$402,170
Human Fetal Tissue	2014	NICHD	5P01HD029587-19	7046	PROJECT III - GENETIC APPROACH TO EXCITATORY TRANSMISSION	NAKANISHI, NOBUKI	SANFORD-BURNHAM MEDICAL RESEARCH INSTIT	CA	$372,898
Human Fetal Tissue	2014	NICHD	5P01HD029587-19	7048	CORE B - NEUROSCIENCE RESEARCH CORE	ZHANG, DONGXIAN	SANFORD-BURNHAM MEDICAL RESEARCH INSTIT	CA	$238,881
Human Fetal Tissue	2014	NIAID	5R01AI020459-31		Varicella-Zoster Virus: T Cell/Skin Tropism & Immunity	ARVIN, ANN	STANFORD UNIVERSITY	CA	$438,199
Human Fetal Tissue	2014	NIAID	5P01AI099783-03	7518	In Vivo Model Core	AKKINA, RAMESH	SCRIPPS RESEARCH INSTITUTE	CA	$316,625
Human Fetal Tissue	2014	NIAID	5R01AI100121-03		Transitional and Naive CD4 T cells and B cells in Infant Vaccine Responses	LEWIS, DAVID	STANFORD UNIVERSITY	CA	$361,083
Human Fetal Tissue	2014	NIAID	5R01AI099284-03		Hepatitis C antivirals: Mechanism of action, combination efficacy and resistance	RICE, CHARLES	ROCKEFELLER UNIVERSITY	NY	$735,361
Human Fetal Tissue	2014	NIAID	5R44AI082799-05		Novel Methylenecyclopropane Analogues as Anti-Human Herpesvirus 6 and 8 Agents	BOWLIN, TERRY	MICROBIOTIX, INC	MA	$1,000,000
Human Fetal Tissue	2014	NINDS	5R01NS075998-04		Stem Cells of the Developing Human Neocortex	KRIEGSTEIN, ARNOLD	UNIVERSITY OF CALIFORNIA, SAN FRANCISCO	CA	$334,590
Human Fetal Tissue	2014	NEI	5R01EY009357-20		Vasculogenesis and hyperoxia in the developing retina.	LUTTY, GERARD	JOHNS HOPKINS UNIVERSITY	MD	$463,016
Human Fetal Tissue	2014	NEI	5R01EY017011-09		Endothelial Transmigration in Neovascular Age-related Macular Degeneration	HARTNETT, MARY ELIZABETH	UNIVERSITY OF UTAH	UT	$365,050
Human Fetal Tissue	2014	NEI	5R01EY016151-08		Birth and Death of Choriocapillaris.	LUTTY, GERARD	JOHNS HOPKINS UNIVERSITY	MD	$455,094
Human Fetal Tissue	2014	NINDS	5R21NS081447-02		Identification of Immune modulators associated with JC virus replication	GORDON, JENNIFER	TEMPLE UNIV OF THE COMMONWEALTH	PA	$231,660
Human Fetal Tissue	2014	NIAID	1R21AI110149-01		HIV-specific nucleases to reservoir cells	CANNON, PAULA	UNIVERSITY OF SOUTHERN CALIFORNIA	CA	$205,208
Human Fetal Tissue	2014	NIAID	1U19AI109784-01	8866	Modeling DENV Infection and PRINT-NP Based DENV Vaccines in Humanized Mice	TING, JENNY	UNIV OF NORTH CAROLINA CHAPEL HILL	NC	$563,944
Human Fetal Tissue	2014	NIAID	5R01AI072613-08		Identification and characterization of cellular factors involved in HCV entry	RICE, CHARLES	ROCKEFELLER UNIVERSITY	NY	$546,673
Human Fetal Tissue	2014	NIAID	1R01AI102825-01A1		HIV Cure with CCr5 (-) Human IPS Hematopoietic Stem Cells	LEVY, JAY	UNIVERSITY OF CALIFORNIA, SAN FRANCISCO	CA	$613,068
Human Fetal Tissue	2014	NIAID	1R01AI110297-01		Hematopoietic stem/progenitor cell reservoirs	CHEN, IRVIN	UNIVERSITY OF CALIFORNIA LOS ANGELES	CA	$385,000
Human Fetal Tissue	2014	NIAID	1R21AI110306-01		Targeting Type I Interferon Immune Activation to Control HIV Infection in vivo	KITCHEN, SCOTT	UNIVERSITY OF CALIFORNIA LOS ANGELES	CA	$231,000
Human Fetal Tissue	2014	NIAID	5R01AI087470-05		C5a as an Anti-HIV Microbicidal Candidate	GALLAY, PHILIPPE	SCRIPPS RESEARCH INSTITUTE	CA	$470,003
Human Fetal Tissue	2014	NIAID	5R01AI101192-03		Neuroimmune regulation of neurotropic JC virus by SF2/ASF in glial cells	SARIYER, ILKER	TEMPLE UNIV OF THE COMMONWEALTH	PA	$382,500
Human Fetal Tissue	2014	NIAID	5P01AI046629-14	5661	EBV and Heterologous Alloimmunity in Humanized Mice	SELIN, LIISA	UNIV OF MASSACHUSETTS MED SCH WORCESTER	MA	$483,023
Human Fetal Tissue	2014	NIAID	5P01AI046629-14	5662	Virology and Technology Core	BREHM, MICHAEL	UNIV OF MASSACHUSETTS MED SCH WORCESTER	MA	$137,760
Human Fetal Tissue	2014	NIAID	5P01AI046629-14	5663	Mouse and Transplantation Core	GREINER, DALE	UNIV OF MASSACHUSETTS MED SCH WORCESTER	MA	$145,117
Human Fetal Tissue	2014	NIAID	5R21AI108259-02		HIV-Induced Immune Activation in Humanized MIce	SWAMY, MANJUNATH	TEXAS TECH UNIVERSITY HEALTH SCIS CENTER	TX	$226,500
Human Fetal Tissue	2014	NIAID	5R01AI100845-03		Modeling Next Generation HIV PrEP in Humanized Mice	AKKINA, RAMESH	COLORADO STATE UNIVERSITY	CO	$674,697
Human Fetal Tissue	2014	NEI	5R01EY015240-10		Retinal iron transport in health and disease	DUNAIEF, JOSHUA	UNIVERSITY OF PENNSYLVANIA	PA	$618,434
Human Fetal Tissue	2014	NIAID	5R01AI026806-20		Plasmacytoid Dendritic Cells in HIV pathogenesis	FITZGERALD-BOCARSLY, PATRICIA	RBHS-NEW JERSEY MEDICAL SCHOOL	NJ	$393,525
Human Fetal Tissue	2014	NIAID	5R01AI102546-03		Varicella zoster virus: molecular controls of cell fusion-dependent pathogenesis	ARVIN, ANN	STANFORD UNIVERSITY	CA	$392,725
Human Fetal Tissue	2014	NIAID	5R21AI108398-02		Heat shock protein 90 and HIV persistence	STODDART, CHERYL	UNIVERSITY OF CALIFORNIA, SAN FRANCISCO	CA	$296,396
Human Fetal Tissue	2014	NIDDK	5K08DK093705-03		Epigenetic regulation of BCL11A in the hemoglobin switch	BAUER, DANIEL	CHILDREN'S HOSPITAL CORPORATION	MA	$124,675
Human Fetal Tissue	2014	NIAID	5R33AI088595-05		Exploring the Role of Vif Antagonists in Preventing Sexual HIV Transmission	STEVENSON, MARIO	UNIVERSITY OF MIAMI SCHOOL OF MEDICINE	FL	$413,403
Human Fetal Tissue	2014	NIAMS	5R03AR062763-02		Decellularized Stem Cell Matrix Rejuvenates Human Cells from Herniated Discs	PEI, MING	WEST VIRGINIA UNIVERSITY	WV	$74,000
Human Fetal Tissue	2014	NIAID	5R01AI102816-04		Interferon Effects on HIV Transmission in Human Models	LIEBERMAN, JUDY	CHILDREN'S HOSPITAL CORPORATION	MA	$822,004
Human Fetal Tissue	2014	NIA	5P50AG016573-15	6918	ASTROCYTE-RELATED MOLECULAR MECHANISMS UNDERLYING ALTERED NEURONAL PLASTICITY IN	BUSCIGLIO, JORGE	UNIVERSITY OF CALIFORNIA-IRVINE	CA	$224,584

Human Fetal Tissue	2014	NIDCR	1R01DE024188-01		Neuronal regulation of salivary stem cells	KNOX, SARAH	UNIVERSITY OF CALIFORNIA, SAN FRANCISCO	CA	$403,338
Human Fetal Tissue	2014	NIMH	1U01MH103365-01		Gene regulatory elements and transcriptome in iPSCs and embryonic human cortex	VACCARINO, FLORA	YALE UNIVERSITY	CT	$650,001
Human Fetal Tissue	2014	NICHD	5R24HD000836-50		LABORATORY OF DEVELOPMENTAL BIOLOGY	GLASS, IAN	UNIVERSITY OF WASHINGTON	WA	$668,537
Human Fetal Tissue	2014	NEI	5R01EY019320-05		Alternative Pathway of Complement Activation in Age-Related Macular Degeneration	ROHRER, BAERBEL	MEDICAL UNIVERSITY OF SOUTH CAROLINA	SC	$311,183
Human Fetal Tissue	2014	NINDS	5R01NS034239-20		Neuroprotective Immunity and HIV Dementia	GENDELMAN, HOWARD	UNIVERSITY OF NEBRASKA MEDICAL CENTER	NE	$367,537
Human Fetal Tissue	2014	NIAID	1R21AI111042-01		Role of Reactive Oxygen Species in Nipah Virus Pathogenesis	VALBUENA, GUSTAVO	UNIVERSITY OF TEXAS MEDICAL BR GALVESTON	TX	$193,698
Human Fetal Tissue	2014	NIAID	5R01AI096138-04		Next Generation Pre-exposure Prophylaxis	GARCIA-MARTINEZ, J. VICTOR	UNIV OF NORTH CAROLINA CHAPEL HILL	NC	$705,599
Human Fetal Tissue	2014	NHLBI	1U01HL122700-01		Biorepository for Investigation of Neonatal Diseases of Lung-Normal (BRINDL-NL)	PRYHUBER, GLORIA	UNIVERSITY OF ROCHESTER	NY	$406,822
Human Fetal Tissue	2014	NIAID	5R01AI065309-11		Impact of HSV-2 on Female Genital Tract Mucosal Immunity & HIV Infection	HEROLD, BETSY	ALBERT EINSTEIN COLLEGE OF MEDICINE	NY	$656,261
Human Fetal Tissue	2014	NEI	5R01EY019065-05		The Mechanism of the Outer Blood-Retina Barrier Breakdown	ABLONCZY, ZSOLT	MEDICAL UNIVERSITY OF SOUTH CAROLINA	SC	$346,920
Human Fetal Tissue	2014	NIDDK	5F32DK095539-03		Cell intrinsic immunopathology of Type I diabetes in humanized mice	DANZL, NICHOLE	COLUMBIA UNIVERSITY HEALTH SCIENCES	NY	$58,946
Human Fetal Tissue	2014	NIMH	5R01MH065151-13		BBB Protection in HIV Infection: Barrier-shielding effects of PARP inhibition	PERSIDSKY, YURI	TEMPLE UNIV OF THE COMMONWEALTH	PA	$458,846
Human Fetal Tissue	2014	NIAMS	5R01AR060317-04		C6ORF32, AN HDAC6-BINDING PROTEIN THAT REGULATES MYOBLAST DIFFERENTIATION	GUSSONI, EMANUELA	CHILDREN'S HOSPITAL CORPORATION	MA	$383,670
Human Fetal Tissue	2014	NIAID	5R21AI107587-02		Stx-mediated disease and immunomodulatory effectors of enterohemorrhagic E.coli	LEONG, JOHN	TUFTS UNIVERSITY BOSTON	MA	$170,625
Human Fetal Tissue	2014	NIDDK	5R01DK071111-07		Transplantation of Endothelial Cells	GUPTA, SANJEEV	ALBERT EINSTEIN COLLEGE OF MEDICINE	NY	$438,260
Human Fetal Tissue	2014	NIAID	2P30AI060354-11	6449	Humanized Mouse Core	TAGER, ANDREW	HARVARD UNIVERSITY	MA	$195,898
Human Fetal Tissue	2014	NICHD	2P30AI060354-11	6449	Humanized Mouse Core	TAGER, ANDREW	HARVARD UNIVERSITY	MA	$195,898
Human Fetal Tissue	2014	NINDS	5R01NS075345-04		Molecular Regulation of Human Glial Progenitor Cell-Based Remyelination	GOLDMAN, STEVEN	UNIVERSITY OF ROCHESTER	NY	$334,588
Human Fetal Tissue	2014	NEI	2R01EY014685-11A1		The Molecular Genetics of High Myopia	YOUNG, TERRI	DUKE UNIVERSITY	NC	$701,571
Human Fetal Tissue	2014	NICHD	5R37HD021341-30		A Program of Research in Population Cytogenetics	HASSOLD, TERRY	WASHINGTON STATE UNIVERSITY	WA	$566,040
Human Fetal Tissue	2014	NIAID	5R01AI070010-09		Targeting HIV Reservoirs in vitro and in vivo	ZACK, JEROME	UNIVERSITY OF CALIFORNIA LOS ANGELES	CA	$385,000
Human Fetal Tissue	2014	NIAID	5R01AI100652-03		Genetic protection of hematopoietic stem cells for stable HIV control	AN, DONG SUNG	UNIVERSITY OF CALIFORNIA LOS ANGELES	CA	$385,000
Human Fetal Tissue	2014	NEI	5R21EY023812-02		AMD THERAPY: A Screen for Molecules that Promote RPE Survival and Differentiation	ZACK, DONALD	JOHNS HOPKINS UNIVERSITY	MD	$238,140
Human Fetal Tissue	2014	NIAID	5R01AI077460-07		Cytokine regulation of JC virus latency and reactivation	WHITE, MARTYN	TEMPLE UNIV OF THE COMMONWEALTH	PA	$351,000
Human Fetal Tissue	2014	NEI	2R01EY012042-13A1		RPE Lactate Transporters: A Role in Retinal Survival	PHILP, NANCY	THOMAS JEFFERSON UNIVERSITY	PA	$514,923
Human Fetal Tissue	2014	NIAID	1R01AI111789-01		Harnessing type 1 IFN-stimulated antiviral mechanisms for HIV vaccine design	HAHN, BEATRICE	UNIVERSITY OF PENNSYLVANIA	PA	$217,200
Human Fetal Tissue	2014	NIAID	1R01AI111809-01		Boosting cell-intrinsic innate immune recognition of HIV-1 by dendritic cells	LUBAN, JEREMY	UNIV OF MASSACHUSETTS MED SCH WORCESTER	MA	$602,424
Human Fetal Tissue	2014	NIAID	1R01AI111860-01		T-cell-mediated targeting of therapeutics to HIV reservoirs	IRVINE, DARRELL	MASSACHUSETTS INSTITUTE OF TECHNOLOGY	MA	$436,887
Human Fetal Tissue	2014	NIAID	1R01AI111891-01		Multi-Species Mechanisms of Drug Bio-distribution in HIV Tissue Reservoirs	KASHUBA, ANGELA	UNIV OF NORTH CAROLINA CHAPEL HILL	NC	$808,479
Human Fetal Tissue	2014	NIAID	1R01AI111899-01		Plug & Purge: In Vivo Targeting of Active HIV Reservoirs That Persist Despite ART	GARCIA-MARTINEZ, J. VICTOR	UNIV OF NORTH CAROLINA CHAPEL HILL	NC	$486,481
Human Fetal Tissue	2014	NIAID	1R01AI111862-01		Improve the safety of an efficacious live-attenuated HIV-1 vaccine through unnatu	GUO, JIANTAO	UNIVERSITY OF NEBRASKA LINCOLN	NE	$485,765
Human Fetal Tissue	2014	NIAID	5R01AI073146-07		Prevention of HIV Acquisition by Long-acting Antiretroviral PrEP	GARCIA-MARTINEZ, J. VICTOR	UNIV OF NORTH CAROLINA CHAPEL HILL	NC	$633,949
Human Fetal Tissue	2014	NIAID	1R01AI111936-01		Inflammation and HIV risk: understanding partial Tenofovir efficacy in CAPRISA004	PASSMORE, JO-ANN	CENTRE/AIDS PROGRAMME/RES/SOUTH AFRICA	SO AFR	$460,080
Human Fetal Tissue	2014	NIAID	5U19AI096113-04	8210	BLT Model of latency and eradication	GARCIA-MARTINEZ, J. VICTOR	UNIV OF NORTH CAROLINA CHAPEL HILL	NC	$309,569
Human Fetal Tissue	2014	NIAID	5U19AI096113-04	8211	Eradication of HIV reservoirs in vivo	ZACK, JEROME	UNIVERSITY OF CALIFORNIA LOS ANGELES	CA	$358,721
Human Fetal Tissue	2014	NIAID	1R21AI109410-01A1		A new humanized mouse model of chronic hepatitis B	ROBEK, MICHAEL	YALE UNIVERSITY	CT	$206,767
Human Fetal Tissue	2014	NIA	5R01AG026094-09		The Sir2-p53-IGF link in mammalian life-span control	CHINI, EDUARDO	MAYO CLINIC ROCHESTER	MN	$353,963
Human Fetal Tissue	2014	NEI	5F32EY023911-02		Molecular patterning and specification of the fovea during retinal development.	MUNDELL, NATHAN	HARVARD MEDICAL SCHOOL	MA	$55,094

Categorical Spending - Project Listing - NIH Research Portfolio Online Reporting Tools (RePORT)

Human Fetal Tissue	2014	NIAID	5R33AI088601-04		TARGETED siRNA DELIVERY AS AN ANTI-HIV MICROBICIDE	DYKXHOORN, DEREK	UNIVERSITY OF MIAMI SCHOOL OF MEDICINE	FL	$405,350
Human Fetal Tissue	2014	NIAID	5R01AI097052-02		Migratory Properties of HIV-infected T cells in vivo	MEMPEL, THORSTEN	MASSACHUSETTS GENERAL HOSPITAL	MA	$772,503
Human Fetal Tissue	2014	NIDDK	5P01DK088760-04	6457	Reprogramming iPS Cells with Exogenous and Endogenous Transcription Factor Genes	KAN, YUET	UNIVERSITY OF CALIFORNIA, SAN FRANCISCO	CA	$381,220
Human Fetal Tissue	2014	NIDDK	5P01DK088760-04	6458	Correction of ^-globin Mutations in Human Somatic and iPS Cells	GRUENERT, DIETER	UNIVERSITY OF CALIFORNIA, SAN FRANCISCO	CA	$303,041
Human Fetal Tissue	2014	NIDDK	5P01DK088760-04	6459	Generation of Hematopoietic Stem Cells from Induced Pluripotent Stem Cells	MUENCH, MARCUS	BLOOD SYSTEMS RESEARCH INSTITUTE	CA	$263,598
Human Fetal Tissue	2014	NIDDK	5P01DK088760-04	6461	Cell and Molecular Biology Core	GRUENERT, DIETER	UNIVERSITY OF CALIFORNIA, SAN FRANCISCO	CA	$171,582
Human Fetal Tissue	2014	NIDDK	5P01DK088760-04	6462	Cell Transplantation and Analysis Core	MUENCH, MARCUS	BLOOD SYSTEMS RESEARCH INSTITUTE	CA	$180,242
Human Fetal Tissue	2014	NIAID	5R21AI106472-02		Impact of HIV infection on anti-tumor CD8 responses in vivo	VATAKIS, DIMITRIOS	UNIVERSITY OF CALIFORNIA LOS ANGELES	CA	$231,000
Human Fetal Tissue	2014	NICHD	5R01HD071920-02		Comparative Effectiveness of Pregnancy Failure Management Regimens (Pre-Fai-R)	SCHREIBER, COURTNEY	UNIVERSITY OF PENNSYLVANIA	PA	$552,064
Human Fetal Tissue	2014	NEI	5R01EY016182-09		Prenatal Development of Visual System	USREY, W	UNIVERSITY OF CALIFORNIA AT DAVIS	CA	$372,037
Human Fetal Tissue	2014	NEI	5K08EY022670-03		Micro-RNAs in the Sclera: Role in Ocular Growth, and Implications for Myopia	METLAPALLY, RAVIKANTH	UNIVERSITY OF CALIFORNIA BERKELEY	CA	$165,426
Human Fetal Tissue	2014	NIAID	5R01AI111595-02		Generation and Function of NK Cell Memory	VON ANDRIAN, ULRICH	HARVARD MEDICAL SCHOOL	MA	$834,830
Human Fetal Tissue	2014	NIAAA	5U01AA016501-09		PRENATAL ALCOHOL IN SUDDEN INFANT DEATH SYNDROME AND STILLBIRTH (PASS)	ODENDAAL, HENDRIK	STELLENBOSCH UNIVERSITY TYGERBERG CAMPUS	SO AFR	$969,106
Human Fetal Tissue	2014	NEI	5R01EY022044-03		Unfolded Protein Response in Glaucoma Pathogenesis	KUEHN, MARKUS	UNIVERSITY OF IOWA	IA	$369,950
Human Fetal Tissue	2014	NEI	5R01EY008538-24		RETINA: REVERSED POLARITY AND MORPHOGENESIS OF RPE	RODRIGUEZ-BOULAN, ENRIQUE	WEILL MEDICAL COLL OF CORNELL UNIV	NY	$591,990
Human Fetal Tissue	2014	NIDDK	5P01DK033506-29	8693	Bacterial-Enterocyte "Cross-Talk": in the Developing Intestine	WALKER, W	MASSACHUSETTS GENERAL HOSPITAL	MA	$288,146
Human Fetal Tissue	2014	NIDDK	5P01DK033506-29	5102	Xenograft and Isograft Core	WALKER, W	MASSACHUSETTS GENERAL HOSPITAL	MA	$338,449
Human Fetal Tissue	2014	NIAID	1R21AI112321-01		Retrogenic humanized mice for the study of T1D	GREINER, DALE	UNIV OF MASSACHUSETTS MED SCH WORCESTER	MA	$271,354
Human Fetal Tissue	2014	NIDA	5R21DA036423-02		Modeling Neural Injury Effects of Methamphetamine Metabolism by CYP2D6 in HIV	CHERNER, MARIANA	UNIVERSITY OF CALIFORNIA SAN DIEGO	CA	$232,500
Human Fetal Tissue	2014	NIAID	1R21AI112375-01		T follicular regulatory cells, a potential HIV reservoir.	UITTENBOGAART, CHRISTEL	UNIVERSITY OF CALIFORNIA LOS ANGELES	CA	$231,000
Human Fetal Tissue	2014	NIAID	1R01AI112443-01		In vivo genomic editing of hematopoietic cells for HIV resistance	KUMAR, PRITI	YALE UNIVERSITY	CT	$250,000
Human Fetal Tissue	2014	NIAID	2R01AI029329-24A1		Enhancing the Intracellular Functioning of anti-HV RNAS	ROSSI, JOHN	CITY OF HOPE/BECKMAN RESEARCH INSTITUTE	CA	$654,174
Human Fetal Tissue	2014	NIAID	2R01AI076059-07A1		Elimination of HIV using HERV specific T cells	NIXON, DOUGLAS	GEORGE WASHINGTON UNIVERSITY	DC	$484,540
Human Fetal Tissue	2014	RMAP	5PN2EY018241-10		NDC for the Optical Control of Biological Function	ISACOFF, EHUD	UNIVERSITY OF CALIFORNIA BERKELEY	CA	$4,877,000
Human Fetal Tissue	2014	NIAID	1R01AI112493-01		Learning from attenuated CMV how to broaden HIV-specific T cell responses	LE GALL, SYLVIE	MASSACHUSETTS GENERAL HOSPITAL	MA	$531,382
Human Fetal Tissue	2014	NIAID	1F30AI112487-01		Investigating graft-versus-host clearance of HIV-infected cells in vivo	TSAI, PERRY	UNIV OF NORTH CAROLINA CHAPEL HILL	NC	$33,436
Human Fetal Tissue	2014	NIDDK	5U01DK094479-05		High resolution mapping of lower urinary tract innervation during development	KEAST, JANET	UNIVERSITY OF MELBOURNE	AUSTRA	$153,900
Human Fetal Tissue	2014	NIDDK	5U01DK094523-04		3D imaging and deep sequencing of gene expression in the genital tubercle	COHN, MARTIN	UNIVERSITY OF FLORIDA	FL	$294,465
Human Fetal Tissue	2014	NIDDK	5U01DK094526-05		GUDMAP2 - Production of Mouse Strains for Gene Anatomy of the Lower Urinary Tract	MCMAHON, ANDREW	UNIVERSITY OF SOUTHERN CALIFORNIA	CA	$336,200
Human Fetal Tissue	2014	NIDDK	5U01DK094530-04		Generating molecular markers that selectively label urothelial sub-populations	MENDELSOHN, CATHY	COLUMBIA UNIVERSITY HEALTH SCIENCES	NY	$268,800
Human Fetal Tissue	2014	NIMH	5K99MH101252-02		Foxp2 regulation of sex specific transcriptional pathways and brain development	BOWERS, JERALD	UNIVERSITY OF MARYLAND BALTIMORE	MD	$88,128
Human Fetal Tissue	2014	NIAID	1R01MH104147-01		Novel Kinase and Nanoformulated Protease Inhibitors for Eradication of CNS HIV-1	GELBARD, HARRIS	UNIVERSITY OF ROCHESTER	NY	$473,852
Human Fetal Tissue	2014	NINDS	1R01MH104147-01		Novel Kinase and Nanoformulated Protease Inhibitors for Eradication of CNS HIV-1	GELBARD, HARRIS	UNIVERSITY OF ROCHESTER	NY	$200,000
Human Fetal Tissue	2014	NEI	5K08EY023609-02		Role in Myopia Development of Retinal Pigment Epithelium - A New Therapeutic Targ	ZHANG, YAN	UNIVERSITY OF CALIFORNIA BERKELEY	CA	$149,679
Human Fetal Tissue	2014	NIAID	1R21AI110343-01A1		Functional Assessment of CTL Anergy in HIV Infection	YANG, OTTO	UNIVERSITY OF CALIFORNIA LOS ANGELES	CA	$231,000
Human Fetal Tissue	2014	NIA	5R01AG043540-02		SMART HAND	GENDELMAN, HOWARD	UNIVERSITY OF NEBRASKA MEDICAL CENTER	NE	$625,779
Human Fetal Tissue	2014	NIAID	1P01AI112521-01	5417	P1: Differentiation of Antiviral Effector and Memory T Cell Subsets	VON ANDRIAN, ULRICH	HARVARD MEDICAL SCHOOL	MA	$349,462
Human Fetal Tissue	2014	NIAID	1P01AI112521-01	5419	P3: Chemokine-Mediated T Cell Trafficking in HIV Transmission and Immune Response	LUSTER, ANDREW	MASSACHUSETTS GENERAL HOSPITAL	MA	$590,638

Human Fetal Tissue	2014	NINDS	1P01NS083513-01A1	5642	Project 2: Contribution of the 3rd trimester fetal subventricular zone to human	KRIEGSTEIN, ARNOLD	UNIVERSITY OF CALIFORNIA, SAN FRANCISCO	CA	$252,697
Human Fetal Tissue	2014	NINDS	1P01NS083513-01A1	5644	CORE B: Neuropathology Core	HUANG, ERIC	UNIVERSITY OF CALIFORNIA, SAN FRANCISCO	CA	$325,872
Human Fetal Tissue	2014	NIDDK	1R01DK100854-01A1		Modeling genetic modifiers of hematopoiesis with induced pluripotent stem cells	CHOU, STELLA	CHILDREN'S HOSP OF PHILADELPHIA	PA	$365,400
Human Fetal Tissue	2014	NINDS	1K99NS088572-01		Molecular and Cellular Mechanisms of Miller-Dieker Syndrome	BERSHTEYN, MARINA	UNIVERSITY OF CALIFORNIA, SAN FRANCISCO	CA	$88,020
Human Fetal Tissue	2014	NIAID	1U19AI113048-01	6465	Project 1: Pharmacokinetics of Combination Antiretroviral Intravaginal Rings	HENDRIX, CRAIG	OAK CREST INSTITUTE OF SCIENCE	CA	$584,012
Human Fetal Tissue	2014	NIAID	1U19AI113048-01	6466	Project 2: Safety Evaluation of Combination Antiretroviral Intravaginal Rings	BAUM, MARC	OAK CREST INSTITUTE OF SCIENCE	CA	$727,419
Human Fetal Tissue	2014	NIAID	1U19AI113048-01	6467	Project 3: Anti-HIV/SHIV Efficacy of Combination Antiretroviral Intravaginal Ring	PYLES, RICHARD	OAK CREST INSTITUTE OF SCIENCE	CA	$865,518
Human Fetal Tissue	2014	NINDS	1R21NS085508-01A1		GABAergic neurogenesis in humans and the effect of prematurity	BALLABH, PRAVEEN	NEW YORK MEDICAL COLLEGE	NY	$241,500
Human Fetal Tissue	2014	NICHD	2R01HD058047-06A1		Understanding epigenetic remodeling in primordial germ cells	CLARK, AMANDER	UNIVERSITY OF CALIFORNIA LOS ANGELES	CA	$319,550
Human Fetal Tissue	2014	NIAID	1R21AI114433-01		Gene engineering using CRISPR/Cas9 mutagenesis to eliminate latent HIV-1	CHEN, IRVIN	UNIVERSITY OF CALIFORNIA LOS ANGELES	CA	$231,000
Human Fetal Tissue	2014	NIAID	1R21AI112486-01A1		Oral Induction of Mucosal and Systemic Antibodies Against HIV-1 gp41 MPER	DEAN, GREGG	COLORADO STATE UNIVERSITY	CO	$223,050
Human Fetal Tissue	2014	NEI	1U01MH105989-01		Mapping the Developing Human Neocortex by Massively Parallel Single Cell Analysis	KRIEGSTEIN, ARNOLD	UNIVERSITY OF CALIFORNIA, SAN FRANCISCO	CA	$1,605,807
Human Fetal Tissue	2014	NIMH	1U01MH105989-01		Mapping the Developing Human Neocortex by Massively Parallel Single Cell Analysis	KRIEGSTEIN, ARNOLD	UNIVERSITY OF CALIFORNIA, SAN FRANCISCO	CA	$1,605,807
Human Fetal Tissue	2014	NIMH	1U01MH105972-01		A Novel Approach for Cell-Type Classification and Connectivity in the Human Brain	SESTAN, NENAD	YALE UNIVERSITY	CT	$1,892,843
Human Fetal Tissue	2014	NEI	1U01MH105991-01		Defining cell types, lineage, and connectivity in developing human fetal cortex	GESCHWIND, DANIEL	UNIVERSITY OF CALIFORNIA LOS ANGELES	CA	$875,397
Human Fetal Tissue	2014	NIMH	1U01MH105991-01		Defining cell types, lineage, and connectivity in developing human fetal cortex	GESCHWIND, DANIEL	UNIVERSITY OF CALIFORNIA LOS ANGELES	CA	$875,397
Human Fetal Tissue	2014	NIMH	1F30MH106261-01		Do Astrocytes Cause Neurodevelopmental Disorders?	SLOAN, STEVEN	STANFORD UNIVERSITY	CA	$34,842
Human Fetal Tissue	2014	NIDDK	1U54DK104309-01	7667	The Genetic Origins and Complications of Urinary Tract Abnormalities	MENDELSOHN, CATHY	COLUMBIA UNIVERSITY HEALTH SCIENCES	NY	$366,571
Human Fetal Tissue	2014	NIAID	1R21AI116191-01		Lineage marking in humanized mice to reveal HIV-1 reservoirs	CHEN, BENJAMIN	ICAHN SCHOOL OF MEDICINE AT MOUNT SINAI	NY	$210,841
Human Fetal Tissue	2014	NIAID	2R56AI077414-06A1		Restoring anti-viral immunity during HTLV-associated neuroinflammatory disease	JAIN, POOJA	DREXEL UNIVERSITY	PA	$473,229
Human Fetal Tissue	2014	NEI	3R01EY018755-16S1		Herpes Simplex Virus Egress from Cells and Spread into Neuronal Axons	JOHNSON, DAVID	OREGON HEALTH & SCIENCE UNIVERSITY	OR	$56,213
Human Fetal Tissue	2014	NEI	1ZIAEY000419-11		Human Retinal Pigment Epithelial Physiology	MILLER, SHELDON	NIH		$1,146,810
Human Fetal Tissue	2014	NEI	1ZIAEY000456-07		Animal models of eye diseases	MILLER, SHELDON	NIH		$746,757
Human Fetal Tissue	2014	NEI	1ZIAEY000481-06		The treatment of uveitic cystoid macular edema with topical Interferon gamma	MILLER, SHELDON	NIH		$140,623
Human Fetal Tissue	2014	NEI	1ZIAEY000513-03		Immune-related mechanisms in the pathogenic processes of retinal degeneration	GERY, IGAL	NIH		$557,643
Human Fetal Tissue	2014	NIAID	1ZIAAI000538-27		HIV-Receptor Interactions and Related Anti-HIV Strategies	BERGER, EDWARD	NIH		$809,592
Human Fetal Tissue	2014	NIAID	1ZIAAI001141-04		HIV Infection in Humanized Mice	HASENKRUG, KIM	NIH		$376,655

RETURN TO TOP

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Novel humanized mouse models for HIV research

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Abstract

There are few models where HIV pathogenesis, particularly gut-associated lymphoid tissue (GALT) $CD4^+$ T cell depletion, can be studied and where potential clinical interventions against HIV disease can be evaluated. HIV cannot be studied in normal mice due to the limited species tropism of the virus. Through the pioneering efforts of many investigators, humanized mice are now routinely utilized to rapidly advance the field of HIV research. It is important to recognize that not all humanized mice models are equal and their strengths and weaknesses must be taken into consideration in order to obtain information that is most relevant to the human condition. This review distinguishes the major humanization protocols and highlights each model's recent contributions to HIV research, including mucosal transmission, GALT pathogenesis and the evaluation of novel therapeutic and prevention approaches to potentially treat HIV disease and prevent the further spread of AIDS.

Introduction

The involvement of mice in medical research has resulted in incalculable benefits to human health. Yet their application has been constrained because mice are not susceptible to certain human-specific pathogens like HIV, CMV, EBV, HCV, among others. Early after the identification of HIV as the causative agent for AIDS, mouse cells were shown to be unable to support HIV replication [1]. Despite this obstacle, the potential benefits of a small animal model for HIV/AIDS research encouraged continued attempts to study this disease in mice and to develop mice susceptible to HIV infection [2]. The cumulative result of these efforts has been the development of mice that exhibit relevant human phenotype(s) and that are designated "humanized mice". To date, transgenic mice genetically altered to express a variety of human proteins involved in different aspects of the HIV live cycle do not fully support HIV replication in vivo [2]. Therefore, alternative approaches to humanize immunodeficient mice have been developed that generally are referred to as severe combined immunodeficient-human mice (SCID-hu) [3, 4]. Unlike transgenic mice, SCID-hu mice are not genetically manipulated to express human proteins. Rather, SCID-hu mice are generated when human cells and/or tissues are placed into immunodeficient mice. Novel humanization strategies using human hematopoietic stem cells (HSC) and the recent development of several new immunodeficient strains of mice have led to development of new models that closely recapitulate key features of HIV disease. Specifically, these humanized mice harbor in situ generated human hematopoietic cells that differentiate into virtually all the cells relevant to different aspects of the HIV infection process in humans. The pathological effects of HIV infection in the intestines have been extensively studied in recent years. The perturbation of the gut-associated lymphoid tissue (GALT) early in HIV

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infection is now considered as a potentially important determinant of disease progression [5]. This effector mucosal site has been shown to be profoundly affected by HIV/SIV infection within the first few weeks of transmission in humans or macaques, respectively [6]. Thus, the GALT is a key tissue to examine for the presence of relevant human cells in humanized mice. Presented here is a brief account of the original SCID-hu models in HIV research followed by a detailed review of the newest iterations of “humanized mice” and their contributions to the study of HIV transmission, treatment and pathogenesis.

SCID-hu mouse models for HIV research

Different strains of immunodeficient mice are used to develop SCID-hu models. For the most part they are devoid of functional mouse T or B lymphocytes but with varying levels of residual immune function: SCID mice, exhibit essentially a complete innate immune system along with mouse natural killer cell activity; NOD/SCID mice, are similar to SCID but with much less mouse natural killer cell function; both $Rag2^{-/-}IL2R\gamma c^{-/-}$ (DKO) mice and $NOD/SCID\text{-}IL2R\gamma c^{(-/-)}$ (NOG) mice have no B or T cells and essentially no mouse natural killer cell activity [7]. SCID-hu PBL mice are generated when human peripheral blood lymphocytes are injected intraperitonealy into SCID mice [1]. The SCID-hu PBL model (including NOD/SCID-hu PBL mice) is characterized by a transient repopulation of the host with mature human lymphocytes; there are no HSC providing renewal capacity. Fully differentiated functional human B and T cells are present in SCID-hu PBL mice over a period of weeks, but both the B and T lymphocyte repertoires are severely limited [8, 9]. This humanization approach contrasts with SCID-hu thy/liv mice which are generated by implanting human fetal liver and thymus tissue under the kidney capsule of SCID mice [10]. In the SCID-hu thy/liv model there is an abundance of human thymocytes. However, virtually all human cells are confined to the thymic organoid that develops after implantation, except for in the spleen where low levels (<1%) of human T cells (and rarely human B cells) can be found [10]. Thus, SCID-hu thy/liv mice do not have significant systemic repopulation with human T cells and are virtually devoid of human B cells, monocytes/macrophages and dendritic cells.

In the nearly two decades since these two models were described their use has resulted in many advances in HIV research. SCID-hu PBL mice are susceptible to HIV-1 infection and they have contributed to HIV research on topics ranging from viral cytopathic effects to potential vaccine approaches [4]. In these mice, the intraperitonealy injected human PBL being targeted for HIV-1 infection are not present in the mouse vaginal cavity in any significant numbers; however, SCID-hu PBL mice do have “low and variable” susceptibility to vaginal transmission of cell-associated HIV-1 when the mice are pretreated with progestin to thin their vaginal epithelium [11]. This model has been used with limited success to evaluate the potential of topical microbicides for preventing vaginal HIV-1 transmission [12, 13], but due to the lack of target cells in the vaginal mucosa there remains some uncertainty regarding how these findings relate to human vaginal transmission [14]. SCID-hu thy/liv mice are not susceptible to mucosal HIV-1 infection but are infected when virus is injected directly into the thymic organoid – the organ to which pathological analyses are limited. The SCID-hu thy/liv model has been very useful in understanding the effects of HIV on thymopoeisis, including the depletion of $CD4^+CD8^+$ thymocytes [15] and in the pre-clinical evaluation of antiretroviral therapies [16]. Neither of these two models has demonstrated humanization of the gut mucosa, so neither rectal transmission nor the effects of HIV-1 infection on human cells in the GALT can be evaluated using these models.

Recent developments in humanized mice for HIV research

New humanization protocols that overcome the major limitations of the original SCID-hu models described above have been developed that facilitate the implementation of novel experimental approaches aimed at addressing key issues of HIV/AIDS research. These new protocols yield humanized mice exhibiting in situ development of long lasting robust systemic levels of human cells relevant to HIV infection, including T cells [7], offering significant benefits to HIV investigators (Table 1). Thus, HIV research in humanized mice has entered a new era that has opened new and exciting avenues of investigation. Key potential applications for the use of humanized mice in HIV research include: a) understanding HIV transmission; b) determining the molecular basis of HIV pathogenesis (including in GALT); c) evaluation of novel therapeutic strategies; d) development of anti-latency therapy; and e) pre-clinical evaluation of novel prevention modalities (including vaccines and microbicides). Three different new generation humanized mouse systems have been used to study HIV. The common aspect of these new humanization protocols is the transplantation of human HSC into one of the three immunodeficient mouse strains described above. One key difference that must be noted is the fact that human T cells are generated in the mouse thymus in both the humanized Rag2$^{-/-}$IL2Rγc$^{-/-}$ and NOD/SCID-IL2Rγc$^{-/-}$ systems, whereas in the BLT model human T cells are generated in the context of a fully functional human thymus. These systems also differ in several other aspects that are summarized in the following paragraphs. A synopsis is shown in Table 2.

Humanized Rag2$^{-/-}$IL2Rγc$^{-/-}$ mice

Traggiai, et al. described a humanization protocol whereby neonatal Rag2$^{-/-}$IL2Rγc$^{-/-}$ mice are transplanted intrahepatically with human CD34^{+} HSC [17]. In Rag2$^{-/-}$IL2Rγc$^{-/-}$ mice CD34^{+} cells develop into human B, T and dendritic cells [17]. Human thymocytes are present in the thymus of these mice where they are presumed to be educated against mouse MHC and then mature into T cells which exit the thymus and populate the host [17, 18]. Multiple research groups have demonstrated the ex vivo susceptibility of human T cells generated within these mice to HIV-1 infection [19–21]. Additionally, the susceptibility of these mice to systemic HIV-1 infection has been extensively described [19, 21–27].

The route of exposure used to study HIV-1 infection in humanized Rag2$^{-/-}$IL2Rγc$^{-/-}$ mice has been primarily intraperitoneal [19, 21–23, 25], with two reports using intravenous inoculation [26, 27] and one report utilizing both rectal and vaginal inoculation [24]. Immunofluorescence was used to demonstrate moderate levels of human leukocytes in the vagina, rectum and large intestine of humanized Rag2$^{-/-}$IL2Rγc$^{-/-}$ mice [24].

Following infection, CD4^{+} T cell depletion and human HIV-specific immune response were examined in humanized Rag2$^{-/-}$IL2Rγc$^{-/-}$ mice. CD4^{+} T cell depletion by HIV-1 in these mice has been shown in peripheral blood, primary lymphoid organs and secondary lymphoid organs [19, 22–25, 27], but HIV pathogenesis in the GALT or the female reproductive tract has not yet been examined in this model. Efforts to identify HIV-specific human immune responses in humanized Rag2$^{-/-}$IL2Rγc$^{-/-}$ mice have focused primarily on whether immunoglobulins (Ig) against HIV are produced in vivo. Human Ig specific for HIV were identified in the plasma of only 1 of 37 examined HIV-1 infected humanized Rag2$^{-/-}$IL2Rγc$^{-/-}$ mice [22, 23, 25], a disappointing result given that relatively robust human Ig production in response to immunization that had been previously reported [17, 25]. Additionally, the limited attempts to identify HIV-specific human T cell responses in these mice so far have been unsuccessful [22, 23]. Jiang, et al. recently expanded on the characterization of the CD4^{+} T cell depletion occurring in these mice by showing that human CD4^{+}FoxP3^{+} regulatory T cells are depleted from lymphoid tissues during HIV-1 infection, possibly through apoptosis [26]. Because of their putative regulatory function and

the fact that loss of these cells paralleled a decrease in plasma viral load, these authors postulated an important role for $CD4^+FoxP3^+$ regulatory T cells in HIV-1 infection in this model [26].

Humanized $Rag2^{-/-}IL2R\gamma c^{-/-}$ mice have been recently used for the pre-clinical evaluation of potential therapeutic approaches for the treatment of HIV disease. There is promising new ex vivo data using an antiviral siRNA gene therapy approach, although the in vivo efficacy of the siRNA the gene therapy utilized is not yet known [20]. In addition, peptide inhibitors of HIV transcription evaluated in humanized $Rag2^{-/-}IL2R\gamma c^{-/-}$ mice demonstrated a notable reduction in viral RNA [21].

Humanized NOD/SCID-IL2Rγc$^{-/-}$ mice

Thus far, two different approaches to humanize NOD/SCID-$IL2R\gamma c^{-/-}$ mice have been used. Hiramatsu, et al. humanized NOD/SCID-$IL2R\gamma c^{-/-}$ mice by transplanting 8–12 week old mice intravenously with human $CD34^+$ HSC [28]. Ishikawa, et al. humanized NOD/SCID-$IL2R\gamma c^{-/-}$ mice by transplanting neonates intrahepatically with human $CD34^+$ HSC [29]. In both cases human T and B lymphocytes as well as myeloid cells developed in the mice. Human thymocytes are present in the mouse thymus of humanized NOD/SCID-$IL2R\gamma c^{-/-}$ mice, where (like in humanized $Rag2^{-/-}IL2R\gamma c^{-/-}$ mice) they are presumably educated against mouse MHC [18, 28, 29]. More recently, Watanabe, et al. showed that gamma radiation preconditioning of NOD/SCID-$IL2R\gamma c^{-/-}$ mice prior to humanization is not required for the reconstitution of adult NOD/SCID-$IL2R\gamma c^{-/-}$ mice with $CD34^+$ HSC [30].

NOD/SCID-$IL2R\gamma c^{-/-}$ mice humanized as adults have been inoculated intravenously with HIV resulting in systemic dissemination, $CD4^+$ T cell depletion and an HIV-specific humoral immune response [30, 31]. $CD4^+$ T cell depletion by HIV was documented in the peripheral blood, primary lymphoid organs and secondary lymphoid organs of these mice [30, 31]. Human Ig specific for HIV were identified in the plasma of 3 of 14 examined HIV infected NOD/SCID-$IL2R\gamma c^{-/-}$ mice humanized as adults [31]. There is no published data regarding HIV-specific T cell responses in NOD/SCID-$IL2R\gamma c^{-/-}$ mice humanized as adults.

Intraperitoneal injection of NOD/SCID-$IL2R\gamma c^{-/-}$ mice humanized as neonates with HIV results in peripheral blood $CD4^+$ T cell depletion [21, 32]. However, there is no published data regarding HIV-specific Ig production or T cell responses in these mice. Kumar, et al. used this model to show that continued dosing of the antiviral siRNA against Vif/Tat targeted to mature human $CD4^+$ T cells suppressed viral replication, but it did not prevent intraperitoneal HIV-1 infection [32].

There is systemic dissemination of HIV-1 in NOD/SCID-$IL2R\gamma c^{-/-}$ mice humanized as adults and as neonates. Currently, there is no information available regarding humanization of the GALT of these mice or of viral dissemination to the gut of NOD/SCID-$IL2R\gamma c^{-/-}$ mice regardless of the humanization protocol. To date, there are no reports of mucosal HIV-1 transmission in humanized NOD/SCID-$IL2R\gamma c^{-/-}$ mice.

Humanized NOD/SCID BLT mice

In order to generate human T cells in the context of a human thymus, humanized Bone marrow Liver Thymus (or BLT) mice were developed. Currently, BLT mice are the most advanced humanized mouse model available for HIV research. BLT mice are generated by implanting human fetal liver and thymus tissue under the kidney capsule of a NOD/SCID mouse (as with SCID-hu thy/liv mice [10]) followed by transplantation of autologous human fetal liver $CD34^+$ HSC. This humanization protocol results in robust long-term systemic

reconstitution with a full complement of functional human lymphoid and myeloid cells [33, 34]. In BLT mice the human thymus is where T cell education occurs in the context of human MHC, as evidenced by human MHC-restricted T cell responses capable of controlling Epstein-Barr virus infection in vivo [33]. In BLT mice human hematopoietic cells are capable of robust human Ig production in response to immunization [35], xenograft rejection [36, 37] and of responding to toxic shock syndrome toxin-1 (TSST-1) in vivo by producing a cascade of human inflammatory cytokines, as well as upregulating key activation and maturation antigens on human dendritic cells [33]. In addition, these mice fully recapitulate the systemic expansion of human T cells expressing the vβ2 T cell receptor (TCR) in response to TSST-1 observed in humans undergoing toxic shock [33, 38]. BLT mice rectally infected with HIV have been shown to produce human anti-HIV IgG by Western blot (3 out of 4 tested) [39]. Currently, HIV-specific T cell responses have not been evaluated in BLT mice.

Immunohistochemical analysis of BLT mice intestines showed that they are populated with human B cells, T cells, monocytes/macrophages, natural killer and dendritic cells [33, 39]. This initial analysis was extended using flow cytometry to characterize the different human hematopoietic cells present in the gut of BLT mice. As in human GALT, human $CD4^+$ and $CD8^+$ T cells in gut of BLT mice express a memory phenotype [39, 40]. Also like in human gut, the dendritic cells in the intestines of BLT mice were found to be primarily lineage negative, HLA-DR^{bright} $CD11c^+$ [39, 41]. There is a population of $CD8^+$ T cells known to reside exclusively in the intraepithelial and lamina propria layers of human small intestines [42–44]. Specifically, human small intestine $CD4^{neg}CD8^+$ T cells primarily express a heterodimer with both an α and a β subunit of the CD8 molecule, but $CD4^+CD8^+$ T cells in the human small intestine primarily express a homodimer CD8 molecule of only the α subunit. Thus, $CD4^+CD8\alpha\alpha^+$ T cells are a well described gut-specific human T cell subset. Examination of the small intestine intraepithelial and lamina propria layers in BLT mice demonstrated the presence of both human $CD4^{neg}CD8\alpha\beta^+$ and $CD4^+CD8\alpha\alpha^+$ T cells [39]. These results confirm that the GALT of BLT mice is extensively humanized in a manner that faithfully recreates major aspects of human GALT, including the presence of a known gut-specific human T cell subset.

Further analysis of mucosal sites in BLT mice revealed extensive humanization in both the lung and the female reproductive tract. The regions of the female reproductive tract examined were the vagina, ectocervix, endocervix and the uterus. Human T cells (both $CD4^+$ and $CD8^+$), monocyte/macrophages and $CD11c^+$ dendritic cells were observed in each of these distinct compartments [45]. The lungs of BLT mice are also highly reconstituted with human: B cells, $CD4^+$ and $CD8^+$ T cells; monocyte/macrophages; and $CD123^+$ and $CD11c^+$ dendritic cells [33].

The extensive reconstitution of mucosal tissues in BLT mice has made this model the obvious choice to investigate key aspects of rectal and vaginal HIV-1 transmission [39, 45]. Both intravaginal and intrarectal exposure of BLT mice to HIV results in systemic dissemination of HIV-1. Regardless of the route of inoculation, mucosal HIV-1 transmission in BLT mice results in $CD4^+$ T cell depletion from peripheral blood, primary and secondary lymphoid tissues [39, 45]. Extensive $CD4^+$ T cell depletion also occurs in the lungs and liver of BLT mice [39, 45]. Following vaginal infection with a CCR5-tropic isolate, human $CD4^+CCR5^+$ T cells essentially disappear from the BLT mouse lungs [45]. Like previously described in human GALT, $CD4^+$ T cell depletion in BLT GALT included $CD4^+CCR5^+$ T cells and $CD4^+$ effector memory T cells [40, 45].

Because of their extensive mucosal reconstitution and susceptibility to mucosal HIV transmission, humanized BLT mice have been used to evaluate novel approaches to prevent

mucosal HIV transmission. Specifically, daily pre-exposure prophylaxis with a combination of emtricitabine and tenofovir disoproxil fumarate resulted in complete protection from a single vaginal inoculation with a high dose of virus. Protection of BLT mice from infection was extensively verified using stringent criteria that included absence of plasma viral antigenemia, plasma viral RNA, tissue viral DNA and the absence of replication competent virus in tissues [45]. These exciting results represent an example of the great utility that humanized mice will have in multiple areas of HIV research.

Conclusions

The new generation of humanized mice described herein is rapidly opening new opportunities for pre-clinical and basic HIV research. The accessibility of these models to many investigators will certainly accelerate translational HIV/AIDS research. Humanized mice have the potential to serve as surrogate models to investigate, in vivo, the role of HIV auxiliary proteins in viral pathogenesis. Despite extensive knowledge of the in vitro activities of these proteins, it is still unclear how each of their multiple in vitro activities relates to their contribution to in vivo pathogenesis and disease progression. One example is Nef, a lentiviral protein with at least four distinct in vitro activities, none of which has been demonstrated to be central to Nef's in vivo phenotype [46]. In vivo models of HIV pathogenesis like those outlined here will serve to test fundamental hypotheses, yielding critical information regarding the in vivo relevance of the different molecular determinants of novel antiviral targets. In addition, they will also serve to test novel antivirals as they are developed including those targeting HIV regulatory and auxiliary genes. The fact that humanized BLT mice demonstrate extensive human-like GALT reconstitution and recapitulate key aspects of HIV pathogenesis seen in the GALT of HIV infected patients will make it possible to evaluate novel therapeutic approaches aimed at GALT reconstitution. The demonstrated susceptibility of humanized Rag2$^{-/-}$IL2Rγc$^{-/-}$ and BLT mice to mucosal HIV transmission will facilitate the development and testing of topically applied or systemically administered prophylactic approaches to prevent HIV transmission. This promise has already been exploited to demonstrate the efficient protection afforded by systemic antiretrovirals to prevent HIV transmission. The recent examples noted above regarding the in vivo evaluation of novel therapeutic interventions is a clear indication of how useful these models will be in the future. Finally, one area of great interest that is likely to see further growth and development is the use of humanized mouse models for the evaluation of novel vaccine approaches to prevent HIV infection. Developing a vaccine for HIV has been extraordinarily difficult. The system most often used for pre-clinical evaluation of vaccines has been SIV infection of macaques. There is a key limitation to the SIV/macaque system. Namely, epitopes in the vaccines must be matched to the challenge virus. In other words, the immunogenicity of SIV, not HIV, epitopes is being tested [47, 48]. If determining protective immunodominant epitopes is a goal of the vaccine effort [49], then humanized mice can aid the effort as they can be infected with HIV. Their relative accessibility and low cost will facilitate parallel analysis of immune responses and actual protection from physiologically relevant challenge. Specifically, humanized mice will facilitate the analysis of immune responses in the mucosal tissues where HIV is actually transmitted and at the same time allow for mucosal challenge experiments that will serve to determine to what extent any new vaccine approach might have a protective effect against the specific viruses that are driving the epidemic. However, if humanized mice are used in vaccine research, viral epitope processing and presentation should occur in the context of human MHC, not mouse MHC. Specifically, immunodominant epitopes displayed on mouse MHC to human TCR may not have direct relation to immunodominant epitopes displayed on human MHC to the same human TCR. Thus, for vaccine research applications it will be particularly important to fully elucidate how T cells are educated in the absence of human stroma in humanized Rag2$^{-/-}$IL2Rγc$^{-/-}$ and NOD/SCID-IL2Rγc$^{-/-}$ mice. Human thymic

stroma present in the humanized BLT model allows for the education of human thymocytes in the full context of human MHC making this system highly relevant to evaluate human-specific immune responses to potential HIV vaccines.

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•• Of major importance

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Table 1

Benefits of new generation humanized mice for HIV research.

- In vivo research using human virus in the context of human cells (isolate, dose and route of human virus inoculation are easily manipulated)
- Wide availability
- Affordable cost
- Facilitates control of intra-genetic variability as multiple mice can be made from a single human donor
- Facilitates control of inter-genetic variability as separate mouse cohorts can be made from different human donors
- Constant regeneration of the human immune system from hematopoietic stem cells results in long-lived human reconstitution

Table 2

Comparative synopsis of new generation humanized mice.

	Humanized Rag2$^{-/-}$ IL2Rγc$^{-/-}$ mice	**Humanized NOD/ SCID- IL2Rγc$^{-/-}$ mice**	**Humanized NOD/ SCID BLT mice**
HIV induced CD4^{+} T cell depletion in PB, 1° and 2° lymphoid tissues	Yes	Yes	Yes
HIV induced CD4^{+} T cell depletion in liver or lung	Not evaluated	Not evaluated	Yes
HIV-specific Ig	1 in 37	3 in 14	3 in 4
HIV-specific T cell response	Not found	Not evaluated	Not evaluated
Female reproductive tract humanization	Limited	Limited	Extensive
Vaginal Transmission	Yes	Not evaluated	Yes
GALT human reconstitution	Limited	Not evaluated	Extensive
Rectal Transmission	Yes	Not evaluated	Yes
HIV induced CD4^{+} T cell depletion in GALT	Not evaluated	Not evaluated	Yes
Therapeutic/prevention modalities evaluated	Gene therapy; peptide transcription inhibitors	siRNA therapy	Anti-retroviral pre-exposure prophylaxis
Therapeutic/prevention modalities in vivo efficacy	Peptide transcription inhibitors – viral load reduced	siRNA suppressed viral load with continued dosing	Anti-retrovirals result in complete protection from vaginal HIV transmission
References	[19–27]	[21, 30–32]	[39, 45]

Fetal Tissue Fallout

R. Alta Charo, J.D.

We have a duty to use fetal tissue for research and therapy.

This statement might seem extreme in light of recent events that have reopened a seemingly long-settled debate over whether such research ought even be permitted, let alone funded by the government. Morality and conscience have been cited to justify defunding, and even criminalizing, the research, just as morality and conscience have been cited to justify not only health care professionals' refusal to provide certain legal medical services to their patients but even their obstruction of others' fulfillment of that duty.

But this duty of care should, I believe, be at the heart of the current storm of debate surrounding fetal tissue research, an outgrowth of the ongoing effort to defund Planned Parenthood. And that duty includes taking advantage of avenues of hope for current and future patients, particularly if those avenues are being threatened by a purely political fight — one that, in this case, will in no way actually affect the number of fetuses that are aborted or brought to term, the alleged goal of the activists involved.

The current uproar was ignited when an antiabortion activist, posing as a biomedical research company representative, captured on video — which he then edited in the most misleading way possible — discussions by Planned Parenthood physicians of the procedures they use (when recovering specific fetal organ tissues) and the cost ($30 to $100 to reimburse for costs). The effect was to portray the organization as callous and possibly criminal in its actions. This orchestrated effort led, predictably, to state and federal calls to end funding for all Planned Parenthood services — more than 95% of which involve such things as contraception and screening for sexually transmitted diseases, rather than abortion.

Along the way, the target broadened, and the use of fetal tissue in research was also attacked. Portrayed as ghoulish vivisection and body-part snatching, it was decried as barbaric by members of Congress. Within weeks, inquiries were announced in Arizona, Indiana, Florida, Kansas, Georgia, Louisiana, Ohio, South Carolina, Tennessee, and Texas; Arizona began looking into making it more difficult to provide tissue; and bills were drafted in Wisconsin and California to make it virtually impossible to use fetal tissue or fetal cells. The inquiries revealed no law broken by Planned Parenthood, but only time will tell how many bills will become law.

A closer look at the ethics of fetal tissue research, however, reveals a duty to use this precious resource in the hope of finding new preventive and therapeutic interventions for devastating diseases. Virtually every person in this country has benefited from research using fetal tissue. Every child who's been spared the risks and misery of chickenpox, rubella, or polio can thank the Nobel Prize recipients and other scientists who used such tissue in research yielding the vaccines that protect us (and give even the unvaccinated the benefit of herd immunity). This work has been going on for nearly a century, and the vaccines it produced have been in use nearly as long. Any discussion of the ethics of fetal tissue research must begin with its unimpeachable claim to have saved the lives and health of millions of people.

Critics point to the underlying abortions, assert that they are evil, and argue that society ought not implicitly endorse them or even indirectly benefit from them, lest it encourage more abortion or make society complicit with what they view as an immoral act. Yet they have overwhelmingly partaken of the vaccines and treatments derived from fetal tissue research and give no indication that they will foreswear further benefits. Fairness and reciprocity alone would suggest they have a duty to support the work, or at least not to thwart it.

The 1988 Fetal Tissue Transplantation Panel, which was appointed by President Ronald Reagan and included a chair and several members who opposed abortion rights, was not persuaded by arguments about complicity. Looking back over decades of research, the panel pointed out that despite fears to the contrary, there was no evidence that the possibility of deriving some good from fetal remains had ever persuaded women to have abortions they otherwise would not have chosen. But to assuage concerns, and to avoid even the theoretical possibility that the benefits of research might encourage an ambivalent woman to choose abortion, the panel recommended that the question of donation not be addressed until after a woman

had decided she was going to end a pregnancy. It also endorsed the law that prohibited tissue sale for profit (reimbursement of costs was permissible) and recommended that women not be allowed to direct tissue for transplantation to particular people.

Having separated the abortion decision from the choice to donate tissue, the panel concluded that public support is ethical: the source of the tissue poses no moral problem for some people, and in any case, the morality of the two acts can be distinguished.[1] Indeed, as to the claim of complicity, although the Committee on Pro-Life Activities of the National Conference of Catholic Bishops was concerned that the abortion could not in practice be separated from the research, it had written that "it may not be wrong in principle for someone unconnected with an abortion to make use of a fetal organ from an unborn child who died as the result of an abortion."[2] The same arguments led to similar recommendations that have been adopted by European countries.

As it reasoned its way to these recommendations, the panel noted that it is commonplace to use organs and tissues from deceased people, whether their death was caused by accident or homicide. Homicide must surely be viewed as morally evil by anyone who decries the loss of fetal life, and yet no concern is raised about personal or societal complicity with the underlying act. Organ and tissue transplant recipients often talk about the complex emotions that arise from knowing one's own life was saved because another life was taken, but they do not then feel responsible for the other person's death.

The panel also considered the pointlessness of refusing support for this research, which uses fetal tissue that will otherwise be discarded. There are, of course, many avenues of research using other kinds of tissue, but fetal cells can rapidly divide, grow, and adapt to new environments in ways that make them the gold standard for some disease research. And in other research areas, we don't yet know if there is anything that could substitute. Fetal tissue research has already led to investigational therapy for end-stage breast cancer and advances against cardiac causes, and transplantation research is actively being pursued for diabetes (using fetal pancreatic islet cells), amyotrophic lateral sclerosis (using neural fetal stem cells injected into the spine), and in a major European initiative, Parkinson's disease (using fetal dopamine cells).[3]

Given the panel's conclusion that research use of fetal remains is ethical, it seems clear that the needs of current and future patients outweigh what can only be symbolic or political gestures of concern. Indeed, the Vatican's Pontifical Academy for Life, while arguing for a right to refuse to use pediatric vaccines derived from fetal tissue and calling for development of vaccines through other means, nonetheless concluded in 2005 that parents' duty to protect their children from illness justifies their use of current vaccines.

Insofar as this latest threat to basic biomedical research grew out of abortion opponents' longstanding efforts to defund the vast majority of Planned Parenthood's services, such as contraceptive counseling and prescribing,[4] the irony is that reducing access to contraception is the surest way to increase the number of abortions — the inconsistent or incorrect use of contraception accounts for nearly half of the unintended pregnancies each year, and half of those end in abortion.[5]

By using the public's unfamiliarity with the history and realities of fetal tissue research as a back door for attacking Planned Parenthood, abortion opponents have added millions of people to the collateral damage of the abortion wars. This attack represents a betrayal of the people whose lives could be saved by the research and a violation of that most fundamental duty of medicine and health policy, the duty of care.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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Report of the Advisory Committee
to the Director, National Institutes of Health

Human Fetal Tissue Transplantation Research

December 14, 1988
Bethesda, Maryland

REPORT OF THE ADVISORY COMMITTEE TO THE DIRECTOR, NATIONAL INSTITUTES OF HEALTH

Human Fetal Tissue Transplantation Research

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CONTENTS

SUMMARY OF THE 58TH MEETING OF THE ADVISORY COMMITTEE TO THE DIRECTOR, NIH

DECEMBER 14, 1988

HUMAN FETAL TISSUE TRANSPLANTATION RESEARCH

EXECUTIVE SUMMARY

The Advisory Committee to the Director, National Institutes of Health (NIH), joined by representatives of the National Advisory Councils of the NIH Institutes, met on December 14 to review the Report of the Human Fetal Tissue Transplantation Research Panel. The Panel was constituted as an *ad hoc* consultants group to the Advisory Committee to the Director, NIH, and charged with reviewing the ethical, legal, and scientific issues surrounding the use of human fetal tissue derived from induced abortions in transplantation research. During its review, the Committee heard presentations by nine members of the Panel, including its Chairman, with an additional statement entered into the record without the Panel member being present. The Panel presentations summarized many of the considerations leading to the report and elaborated on some of the reasons for individual Panel member concurrence or dissent. After the Panel presentations, the Committee members and Council representatives discussed the report, inviting comments and further clarification from the Panel members present. Three unanimous recommendations emerged from the deliberations of the Advisory Committee and the Council representatives: (1) to accept the report and recommendations of the Human Fetal Tissue Transplantation Research Panel; (2) to recommend that the Assistant Secretary for Health lift the moratorium on Federal funding of human fetal tissue transplantation research utilizing tissue from induced abortions; and (3) to accept current laws and regulations governing human fetal tissue research with the development of additional policy guidance as appropriate, to be prepared by NIH staff, to implement the recommendations of the Human Fetal Tissue Transplantation Research Panel.

INTRODUCTION

In October 1987, the NIH submitted a request to the Assistant Secretary for Health for the approval of an experimental implant of human fetal cells derived from induced abortion tissue aspirates into the brain of a Parkinson's patient. The protocol was proposed by intramural investigators in the National Institute of Neurological and Communicative Disorders and Stroke. Although this research procedure did not require the approval of the Department of Health and Human Services, the Director, NIH, elected to advise the Assistant Secretary for Health of this proposed research project because of the broad scientific and ethical implications surrounding this area of research.

On March 22, 1988, the Assistant Secretary for Health responded by requesting that the NIH "convene one or more special outside advisory committees that would examine comprehensively the use of human fetal tissue from induced abortions for transplantation and advise us on whether this kind

of research should be performed, and, if so, under what circumstances." At the same time, he outlined a series of 10 questions related to this research issue to guide the panel of consultants in their deliberations. Concurrently, the Assistant Secretary for Health withheld his approval of the proposed experiment and future experiments, pending the outcome of the meeting of a panel of consultants called for the specific purpose of reviewing the legal, scientific, and ethical issues surrounding the human fetal tissue transplantation research issue.

The Human Fetal Tissue Transplantation Research Panel, which was convened as an *ad hoc* group of consultants to the Advisory Committee to the Director, NIH, met three times: September 14-16, October 20-21, and December 5, 1988. The first two days, the Panel heard public testimony from over 50 experts in the fields of science, law, and ethics, including representatives from diverse organizations. After the public testimony, the Panel met for the remainder of the time deliberating among themselves on the questions posed by the Assistant Secretary for Health, drafting responses to the questions, and developing supporting considerations to explain the Panel's rationale in arriving at the responses to the questions posed. All of the meetings of the Panel were open to the public and were well attended by interested individuals and the media.

The Advisory Committee to the Director, NIH, met on December 14 to consider the report of the Human Fetal Tissue Transplantation Research Panel and to provide the Director, NIH, with the Committee's recommendations relative to the content and recommendations contained in the report.

SUMMARY OF PRESENTATIONS BY INDIVIDUAL HUMAN FETAL TISSUE TRANSPLANTATION RESEARCH PANEL MEMBERS

Individual members of the Human Fetal Tissue Transplantation Research Panel had been invited by the Director, NIH, to address the Advisory Committee at its meeting on December 14 to provide the Committee further insight into the deliberations of the Panel. Nine of the ten members of the Panel present at the meeting, including the Chairman, made brief statements that further clarified their work on the Panel or explained their vote on the 10 questions the Panel was asked to address in developing its report. An additional statement by a Panel member was entered into the record without the member being present.

The individual Panel presentations confirmed the wide diversity of convictions, interpretations, and points of view that were reflected in the Panel report. On the question of using human fetal tissue derived from elective abortions for transplantation, the individual Panel presentations described three general positions. One position held that abortion is legal; consequently, the use of the tissue derived from such abortions for research is an acceptable, and even desirable research activity, and is consistent with sound ethical and moral principles. The second position maintained that induced abortion is immoral and that Federal funding of research using tissue from such abortions would institutionalize an immoral activity. As a middle point between these two views was the position that regardless of how serious, or even morally tragic, a decision for an abortion and the action following that decision might be, abortion is presently legal, and the issues

surrounding the abortion are entirely separable from the issues surrounding the use of the tissue in research, provided that appropriate protections are established to guide the research. Each of these three positions was given further support in the invited arguments and presentations by the individual Panel members.

One Panel member noted that the scientific community has long been concerned about the use of fetal tissue in transplantation research, and previous commissions, such as the 1975 National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, have dealt with this issue. However, the underlying "tension" in dealing with this issue revolves not around the science of this type of research, but the manner in which human fetal tissue is obtained--that is, by induced abortions. It is the tremendous polarization of attitudes on abortion that makes public debate on this issue very difficult. It was emphasized that the work of the Human Fetal Tissue Transplantation Research Panel was an excellent illustration of the benefits of such panels and commissions because a forum is created in which rational debate on complex issues is encouraged and fostered.

Another Panel member elected to concentrate on two issues--the morality of using human fetal tissue derived from an abortion and the importance of gaining maternal consent in the donation process. This Panel member's conclusion was that society should not reject using human fetal tissue for transplantation research because the tissue is derived from an induced abortion, since the use of such tissue does not imply complicity in the decision or the act of abortion. On the issue of maternal donation of fetal tissue, the Panel member underscored that it was imperative to protect the right of the pregnant woman to donate her fetal tissue since the abortion request did not negate her rights as a donor of her own tissue.

Two Panel members expressed unequivocal opposition to abortion and characterized the use of human fetal tissue for research as complicity in the act of abortion. They stressed that sanctioning the use of human fetal tissue in transplantation research would serve as a further inducement to pregnant women to abort, because a possible societal good could now be inferred from the use of aborted tissue. Additionally, if therapy using fetal tissue transplantation techniques proves beneficial in treating certain diseases, there may conceivably be an increased demand for fetal tissue that does not keep pace with the supply. This then would represent a further inducement to abort and would result in an increased number of abortions nationally.

Another Panel member pointed out that public policy needs to be based on a moral framework that recognizes the plurality of our society, that is, differences in values, beliefs, and lifestyles, and not on individual moral interpretations. Furthermore, for many moral problems there may exist more than one correct solution, and in developing public policy, open debate of the issues and building consensus is the best approach to take.

Yet another Panel member concluded that the NIH needs to take the lead in this area of research to assure that safeguards and protections are put in place to guide the research efforts of scientists. It was further pointed out

that, despite the moratorium, at least two institutions have recently engaged in privately funded transplantation research using human fetal tissue.

One of the Panel members advanced the argument that it could be considered immoral and unethical for the fetal tissue from induced abortions to be discarded if there is the potential for its positive therapeutic use. Furthermore, using human fetal tissue does not signify approval of abortion, and the Panel member drew the analogy to organ transplantation from homicide and accident victims. Use of organs donated from such sources does not mean that society approves of homicide or encourages accidents.

Finally, one of the Panel members pointed out that while the Panel did not break new ground, it did update the ethical, legal, and scientific discussions on this issue. The report of the Panel was also consistent with the international consensus on human fetal tissue transplantation research developed in eight countries, including the National Health and Medical Research Council of Australia, the British Medical Association, the French National Ethics Consultative Committee for Life and Health, and the Parliamentary Assembly of the Council of Europe. In concluding his statement, this Panel member suggested that the deliberations of the Panel underscored the need for a standing Ethics Board at the Department of Health and Human Services to allow for a recurrent review of fast-changing ethical and scientific issues.

A copy of the full text of each Panel member presentation is located in the Appendix to this report.

DELIBERATIONS OF THE MEMBERS OF THE ADVISORY COMMITTEE AND THE COUNCIL REPRESENTATIVES

In the course of its deliberations, the Advisory Committee recognized that abortion is a moral issue for many in our society, but noted that the Panel was directed to provide advice on what is the appropriate public policy in a single area--the use of post-mortem fetal tissue derived from elective abortions in transplantation research. The Advisory Committee members and the Council representatives quickly concluded that the Panel's report was clearly an impressive and skillfully crafted document, and that given the divisiveness underlying our society on the issues related to the topic under consideration, the report represented a remarkable consensus and praised the Panel for its extensive and thoughtful work. The Committee further concluded that the consensus of the Panel reflected the consensus of the country itself, where widely divergent views are held about the morality of elective abortions and about the use of fetal materials derived from such abortions for the purposes of research.

The Committee then discussed three possible actions it could take relative to the report: (1) accept or reject the report; (2) modify the report; or, (3) write its own report on this issue. After some discussion involving recommending minor word changes in the Panel report, the Committee agreed that it would not reach a different or better consensus in writing another, independent report on this issue. The Advisory Committee then voted

unanimously (19 yea) to accept the report and recommendations of the Human Fetal Tissue Transplantation Research Panel as written.

After its vote to accept the Panel report, the Committee turned its attention to the temporary moratorium on federally funded transplantation research using human fetal tissue from induced abortions issued on March 22, 1988, by the Assistant Secretary for Health. Several Committee members and Council representatives voiced the opinion that they had not read anything in the Panel report or heard any arguments earlier in the day to justify continuing the temporary moratorium. However, several other members requested a clarification on the protections and guidelines currently in place relative to this area of research and also asked what amendments or changes to existing Federal regulations would be necessary to accommodate some of the concerns expressed by the Panel in its report.

In clarifying this issue, NIH staff pointed out that the operative Federal guidelines relative to the transplantation research issue are found in 45 CFR 46. It was further emphasized that these regulations already contain most of the recommendations made by the Panel relative to issues of timing, method, and procedures used to terminate the pregnancy, right of donation, and protection from inducements. These provisions were designed to legally separate the researcher and the individuals who perform the abortion from any relationship to or decisions about termination of pregnancy. It was also suggested by NIH staff, and confirmed by the Director, NIH, that if it was the intention of the Advisory Committee, appropriate NIH staff would make a point-by-point comparison of 45 CFR 46 with the recommendations of the Panel and draft additional policy guidelines if needed. The Advisory Committee urged the NIH not to draft new regulations incorporating the Panel recommendations because the state of the science is changing rapidly and because of the lengthy departmental procedures involved in promulgating regulations that might delay the research process by several years. Furthermore, developing precise policy guidelines would be an effective approach, as they would have the force of regulations and could be developed and implemented within the research community within 2 to 4 months. This latter point was underscored by several Advisory Committee members and Council representatives, with the proviso that any policy guidelines developed presently need to be reviewed and updated as appropriate to keep pace with changes in the science.

It also was pointed out that once the policy guidelines were developed and implemented by institutions and investigators receiving Federal funds for research, compliance with the policy guidelines would be a condition for the receipt of such funds. Several Committee members observed that the existence of strong Federal guidelines usually influences the private sector to follow established Federal procedures in conducting its own research. However, in the absence of Federal direction in this area of research, researchers could continue to obtain human fetal material from induced abortions for their research efforts, but it would be procured without Federal funding or the oversight recommended by the Panel. In addition, the material and the donor would not necessarily have the protections provided in the Federal regulations and policy guidelines.

In these discussions, the Committee briefly reviewed the scientific justification for proceeding with research in this area, including the scientific evidence that intrafamilial transplantation should be prohibited on the basis of current knowledge. It was pointed out that in some disease areas, such as Parkinson's disease and juvenile diabetes, the results of animal studies provide justification for conducting human studies. The Committee was informed that in these disease conditions, first trimester fetal tissue is optimal for transplantation. One Council representative noted that recently the American Association of Neurological Surgeons had formally adopted the position that evidence now exists from animal research that justifies clinical studies on patients with Parkinson's disease. In other disease states such as Alzheimer's disease, Huntington's disease, spinal cord injury, and neuroendocrine deficiencies, experts recommend further animal studies.

The Advisory Committee concluded this portion of its deliberations by voting unanimously (19 yea) to recommend that the Assistant Secretary for Health lift the moratorium on Federal funding of human fetal tissue transplantation research utilizing tissue derived from induced abortions.

There followed a brief discussion among the Committee members and the Council representatives on a variety of issues, including concerns about screening tissue to be used in research to assure that it is disease free; providing selective demographic data to researchers and tissue recipients about tissue donors; insulating a woman's consent to abort from her consent to donate tissue; preventing monetary or other gains for the donation; requiring that procurement agencies not profit from such transactions; reaffirming that the paramount concern in obtaining fetal tissue should continue to be the health of the pregnant woman; and emphasizing that the properties of fetal tissue, such as the optimum gestational age for use in research, should not be a factor in deciding the timing or the procedure of an abortion.

The Committee also raised questions about the details of the Uniform Anatomical Gift Act (UAGA), the Hyde Amendment, and the National Organ Transplant Act as they pertain to this area of research and engaged the Panel members in further discussion. In their responses, Panel members to a great extent reemphasized their earlier views and comments. The Committee was satisfied that if any problems exist, they could be specifically identified and resolved during the drafting of additional policy guidelines.

Finally, the Advisory Committee members and Council representatives voted unanimously for a third time (19 yea) to accept current laws and regulations governing human fetal tissue research with the development of additional policy guidance as appropriate, to be prepared by NIH staff, to implement the recommendations of the Human Fetal Tissue Transplantation Research Panel.

SUMMARY AND RECOMMENDATIONS

The Advisory Committee to the Director, NIH, together with representatives of the National Advisory Councils of the NIH Institutes, met on December 14 to review the Report of the Human Fetal Tissue Transplantation Research Panel. The Advisory Committee heard individual presentations from 9 of the 10 members of the Panel present at the meeting, with an additional

statement entered into the record by a Panel member not present. The Advisory Committee members and Council representatives recognized that abortion is a moral issue for many in our society, but noted that the Panel was directed to provide advice on what is the appropriate public policy in a single area--the use of post-mortem fetal tissue derived from induced abortions in transplantation research. The Advisory Committee members and the Council representatives concluded that the Panel's report represented a remarkable consensus on the issues and praised the Panel for its thoughtful report.

After an extensive review and discussion of the Panel report, the Committee unanimously voted three recommendations:

- to accept the report and recommendations of the Human Fetal Tissue Transplantation Research Panel as written;
- to recommend that the Assistant Secretary for Health lift the moratorium on Federal funding of human fetal tissue transplantation research utilizing tissue from induced abortions; and
- to accept current laws and regulations governing human fetal tissue research with the development of additional policy guidance as appropriate, to be prepared by NIH staff, to implement the recommendations of the Human Fetal Tissue Transplantation Research Panel.

Agenda

Appendix A

AGENDA

58th Meeting of the Advisory Committee
to the Director, NIH

December 14-15, 1988

Building 31, Conference Room 10
National Institutes of Health
Bethesda, Maryland

HUMAN FETAL TISSUE TRANSPLANTATION RESEARCH

December 14, 1988

MORNING SESSION

9:00	Introduction	Dr. Wyngaarden
9:15	Status Report on Activities Resulting from June 27-28, 1988 Advisory Committee to the Director Meeting on "The Health of Biomedical Research Institutions: Report of the Regional Meetings"	Dr. Raub
9:30	Human Fetal Tissue Transplantation Research: Overview and Background	Dr. Wyngaarden
9:45	Summary of September 14-16, October 20-21, and December 5 Meetings of the Human Fetal Tissue Transplantation Research Panel	
	Overview	Judge Adams
10:00	Individual Statements by the Human Fetal Tissue Transplantation Research Panel Members	
	10:00	Dr. Ryan
	10:05	Dr. Walters
	10:10	Dr. Childress
	10:15	Dr. Delgado
	10:20	Mr. Bopp
	10:25	Dr. Clouser

A1

MORNING SESSION (continued)

10:30 Coffee Break

10:45 Continuing Statements by the Human Fetal Tissue Transplantation Research Panel Members

10:45 . . . . . Ms. King

10:50 . . . . . Prof. Burtchaell

10:55 . . . . . Prof. Robertson

11:00 Summary of Considerations and Recommendations of Human Fetal Tissue Transplantation Research Panel--Scientific Issues

Chairman . . . . . Dr. Ryan

- **Assistant Secretary for Health (ASH) Question 5A: Should there be and could there be a prohibition on the donation of fetal tissue between family members or friends and acquaintances?**
- **ASH Question 5B: Would a prohibition on donation between family members jeopardize the likelihood of clinical success?**
- **ASH Question 9: For those diseases for which transplantation using fetal tissue has been proposed, have enough animal studies been performed to justify proceeding to human transplants? Because induced abortions during the first trimester are less risky to the woman, have there been enough animal studies for each of these diseases to justify the reliance on the equivalent of the second trimester human fetus?**
- **ASH Question 10: What is the likelihood that transplantation using fetal cell cultures will be successful? Will this obviate the need for fresh fetal tissue? In what time frame might this occur?**

General Discussion . . . . . Members, Advisory Committee to the Director and the Human Fetal Tissue Transplantation Research Panel

12:15 Lunch

A2

AFTERNOON SESSION

1:15 Summary of Considerations and Recommendations of Human Fetal Tissue Transplantation Research Panel--Legal and Ethical Issues

Chairman . . . . . Dr. Walters

- ASH Question 1: Is an induced abortion of moral relevance to the decision to use human fetal tissue for research? Would the answer to this question provide any insight on whether and how this research should proceed?

- ASH Question 2: Does the use of the fetal tissue in research encourage women to have an abortion that they might otherwise not undertake? If so, are there ways to minimize such encouragement?

- ASH Question 3: As a legal matter, does the very process of obtaining informed consent from the pregnant woman constitute a prohibited "inducement" to terminate the pregnancy for the purposes of the research--thus precluding research of this sort, under HHS regulations?

- ASH Question 4: Is maternal consent a sufficient condition for the use of the tissue, or should additional consent be obtained? If so, what should be the substance and who should be the source(s) of the consent, and what procedures should be implemented to obtain it?

- ASH Question 6: If transplantation using fetal tissue from induced abortions becomes more common, what impact is likely to occur on activities and procedures employed by abortion clinics? In particular, is the optimal or safest way to perform an abortion likely to be in conflict with preservation of the fetal tissue? Is there any way to ensure that induced abortions are not intentionally delayed in order to have a second trimester fetus for research and transplantation?

- ASH Question 7: What actual steps are involved in procuring the tissue from the source to the researcher? Are there any payments involved? What types of payments in this situation, if any, would fall inside or outside the scope of the Hyde Amendment?

- ASH Question 8: According to HHS regulations, research on dead fetuses must be conducted in compliance with State and local laws. A few States' enacted version of the Uniform Anatomical Gift Act contains restrictions on the research applications of dead fetal tissue after an induced abortion. In those States, do these restrictions apply to therapeutic transplantation of dead fetal tissue after an induced abortion? If so, what are the consequences for NIH-funded researchers in those States?

AFTERNOON SESSION (continued)

	General Discussion	Members, Advisory Committee to the Director and the Human Fetal Tissue Transplantation Research Panel
3:00	Coffee Break	
3:15	Continuation of Discussion of Legal and Ethical Issues	
5:00	Adjourn	

December 15, 1988*

MORNING SESSION

9:00	Consideration of Report and Recommendations of the Human Fetal Tissue Transplantation Research Panel's Report	
	Chairman	Dr. Healy
	Speakers	Dr. Cooper Dr. Palade
	General Discussion and Recommendations	Members, Advisory Committee to the Director and the Human Fetal Tissue Transplantation Research Panel
10:30	Coffee Break	
10:45	Continuation of Advisory Committee Members' Discussion	
12:00	Adjourn	

*The Advisory Committee to the Director concluded its review of the Panel Report on December 14. Consequently, the Advisory Committee Meeting scheduled for December 15 was not held.

Meeting Participants

Appendix B

ADVISORY COMMITTEE TO THE DIRECTOR, NIH

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*These Committee members did not attend the December 14, 1988, meeting of the Advisory Committee to the Director, NIH.

B1

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B4

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B5

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B6

Presentations by Individual Members of the Human Fetal Tissue Transplantation Research Panel, December 14, 1988

Appendix C

STATEMENT TO THE ADVISORY COMMITTEE TO THE DIRECTOR, NIH

December 14, 1988

Judge Arlin M. Adams

It is a pleasure to be here, and it has been a great pleasure to serve as chairman of the Panel. I concur with Dr. Wyngaarden that the Panel is broad-based, encompassing many of our disciplines. It was a very fine, courteous, and intelligent Panel. We had many disagreements, but we were never disagreeable.

The voting, as you probably have seen in the material that has been distributed, would favor going ahead with this type of research, but--and it is a strong "but," as far as I am concerned--NIH should do so only with carefully crafted guidelines and an additional provision for periodic reviews, because we are entering into a field where we do not know all of the answers.

As we proceeded with answering the questions that had been posed to us by Dr. Windom--and those questions are in front of you--we thought it insufficient merely to answer the questions, as difficult and as important as that task appeared to us, but to supply the members of the Advisory Committee with explanations or, as we put it, "considerations," which prompted the votes that were taken.

Those considerations appear immediately after the so-called "answers" to the questions. For example, Question 1 is posed and then the response of the Panel and, at the bottom, considerations for Question 1.

Finally, some of the members of the Panel--most of them--believed that we should permit individual members of the Panel to express their views in concurring or dissenting statements. They are immediately behind the answers to the questions and the considerations. I commend them to your attention.

The staff that you made available to us, Dr. Wyngaarden, was most courteous and extremely helpful. I personally am indebted to them and most particularly to Dr. Moskowitz, who was continuously available to us.

We are prepared to continue to assist you and this advisory group, as well as other members of the government as may be necessary to resolve these difficult matters.

C1

STATEMENT TO THE ADVISORY COMMITTEE TO THE DIRECTOR, NIH

December 14, 1988

Kenneth J. Ryan, M.D.

What I am presenting now is a personal viewpoint, which I believe is what each of the Panel participants will be doing until we get to the general discussion of the report itself.

The scientific community has itself been concerned with the ethical issues surrounding the use of cadaveric fetal tissue in transplantation research.

Evidence of this is that I was asked to deliver a lecture on the subject of the ethics of the use of such tissue at an international meeting of neuroscientists at MIT in March of this year. And, ironically, as I was driving home from the lecture, I turned on the car radio, and I heard about Assistant Secretary Windom's moratorium about the use of such tissue.

We are in a sense revisiting the atmosphere of 1974 and 1975, when the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, which I chaired, was formed under the cloud of a congressional moratorium to publicly debate the then even broader issue of fetal research in general. The underlying tension then and now is that fetal tissue can be obtained from therapeutic interruptions of pregnancy or induced "abortions."

Our present Panel, which was formed 14 years later in 1988, like the original commission, was composed of individuals with diverse views and backgrounds. We have had to express these views and debate them in public. It is unlikely that much has been overlooked or omitted in the way of arguments pro or con on the use of cadaveric fetal tissue from abortion.

I personally applaud the tradition of using commissions or panels to work in public under the Sunshine Law and place the debate in a civilized and rational forum so we can deal fairly and democratically with the issues. Unfortunately, when the issue is abortion, we are more polarized than in most public policy debates. And as I have often said, it even stalks the halls of Congress.

There are, however, two legitimate principled positions on abortion itself, which can be defended and should be respected in a democratic society, and these issues are that abortion is moral; that is, a woman should not be forced to remain pregnant against her will; and that, conversely, abortion is immoral and the fertilized egg and fetus have a claim to life, which is absolute.

In any case, for the discussion, our Panel focused on the morality of separating the abortion itself from the use of fetal remains. I believe the only strident and dissonant note to our debate was some panelists who characterized scientists who use fetal remains as being as evil as the doctors who used tissue from the Nazi death camps.

C3

While this has been amply rebutted in the material that has been distributed to you, I do wish to add that the reason the abortion debate is so difficult is that there are no close human analogies to the plight of the pregnant woman who has a conflict with the pregnancy in her body.

I would add that the trend in the last 15 years has been, from a medical point of view, to make abortion safer, quicker, and less expensive for women. There is no evidence that the procedure has been influenced in any way by the uses to which fetal remains are occasionally put, either for teaching or research.

Finally, the decision of the Panel was clear, that transplantation research could and should proceed if the research was kept separate from the decision-making, the techniques, and the economics of abortion, and if it was made non-commercial; that is, set up in a system similar to the transplantation of organs. This is what other countries, like Sweden, have already adopted.

I believe you have a fair report, amply argued, from the Panel, which I wholeheartedly commend to you as a response to Assistant Secretary Windom.

C4

STATEMENT TO THE ADVISORY COMMITTEE TO THE DIRECTOR, NIH

December 14, 1988

LeRoy Walters, Ph.D.

The guidelines on fetal tissue research that are included in our Panel's report constitute at least the ninth set of guidelines formulated on this topic since 1971. Committees or deliberative bodies involved in formulating earlier sets of guidelines represented numerous parts of the industrialized world, including the United Kingdom, the U.S., Australia, the Netherlands, France, Sweden, the Council of Europe, and Canada. There are remarkable similarities in the guidelines formulated in these diverse jurisdictions. In fact, there is an impressive international consensus on the ethical standards that should govern the use of fetal tissue for research. The positions adopted in the Panel's report are located squarely in the middle of this international consensus. We broke no new ground in approving this research in principle or in trying to isolate the research issue from the abortion decision. If we have contributed anything original in our report, it has been to update the scientific, ethical, and legal discussions and to provide a rationale for or explanation of the Panel's recommendations.

There is, of course, no guarantee that the eight committees and the one parliamentary assembly have reached a conclusion that is ethically correct. However, we are less likely to make a serious moral mistake when numerous groups of conscientious men and women from around the world have sought to study an issue with great care and have reached virtually identical conclusions about appropriate public policy.

My second and final comment has to do with the process through which the Panel's report and recommendations have been formulated. We have, I think, been fortunate to be able to arrive at such a substantial consensus in such a short time. We have had a fair-minded and vigorous chairman and a most attentive and diligent staff. The Panel members came from a diversity of backgrounds and represented numerous ethical viewpoints, yet we attempted to treat one another with respect. In some ways, the Panel deviated from the role originally envisioned for it. We held no deliberations in executive session because Dr. Wyngaarden courageously opened all of our meetings to the press and the public. Also, we were asked to finish our work in September, after a single 3-day meeting. In fact, we found it necessary to meet three times, especially if we were to provide an <u>explanation</u> for our recommendations.

Future *ad hoc* panels may not be so fortunate. In my view, the experience of our Panel points up the need for an ongoing ethics advisory committee or board within the Department of Health and Human Services. Ideally, such a body would be able to <u>anticipate</u> important ethical questions that are likely to confront NIH or the Department and to provide counsel that is at once timely, thoughtful, and balanced. Another possible role for such a standing body would be to provide recurrent review for fast-changing issues like the one before us today.

C5

STATEMENT TO THE ADVISORY COMMITTEE TO THE DIRECTOR, NIH

December 14, 1988

James F. Childress, Ph.D.

I am grateful for the opportunity I have had to serve on the Human Fetal Tissue Transplantation Research Panel and to appear here today. The first and fourth questions were two of the most important and divisive questions faced by the Panel. The first question invites us to consider whether the act of elective abortion disqualifies society from using the tissue of the aborted fetus, and the fourth question invites us to consider whether a woman's decision to abort disqualifies her from donating fetal tissue for use in transplantation research.

Regarding the first question, I would stress that different Panel members have very different views about why the act of elective abortion is morally relevant to the use of fetal tissue. Some view abortion as raising no moral problems; others view it as raising moral problems but not as absolutely wrong; and others view it as absolutely wrong. We were not asked to--and we could not--settle this issue of abortion. But whatever one thinks about abortion itself, the moral dispute about abortion in our society makes the source of fetal tissue morally relevant. Society faces a moral question about how to respect divergent views on this important matter. The majority of the Panel held--rightly in my judgment--that the fact that fetal tissue becomes available through an elective abortion should not lead society to reject its use in transplantation research. It is possible to use fetal tissue following elective abortions without complicity in abortions and without directly encouraging abortions.

The fourth question focuses on the sufficiency of maternal consent. The majority of the Panel held that maternal consent is both necessary and sufficient to transfer fetal tissue after an elective abortion (except where the father's objection is known). The Panel chose among several different ways to transfer human tissues: donation (express or presumed); abandonment; sales; and expropriation. The Panel clearly gave priority to transfer or acquisition of fetal tissue through express donation.

But who is the appropriate donor? And, specifically, does the pregnant woman's decision to abort disqualify her from being the donor? The Panel affirmed, and I strongly believe, that a woman who has a legal abortion remains the proper decisionmaker about the disposition and transfer of fetal remains. Societal disputes about the morality of her legal decision to abort should not disqualify her as a decisionmaker about donation. I quote from the Panel's rationale: "She still has a special connection with her fetus, and she has a legitimate interest in its disposition and use. Furthermore, the dead fetus has no interests that the pregnant woman's donation would violate."

Winston Churchill once remarked that democracy is the worst form of government except for all others. His comment is relevant here, too--the alternatives to express maternal donation of fetal tissue have even worse moral features. Of the possible ways to transfer fetal tissue, maternal donation is

the most congruent with our society's traditions, laws, policies, and practices, including the UAGA.

If we accept maternal donation as the best mode of transfer of fetal tissue, all things considered, and if we accept the moral relevance of abortion to the use of fetal tissue, for whatever reason, then it is important to develop procedures to separate as much as possible the abortion decision from the donation decision. And that is what the Panel's various recommendations attempt to do, for example, through the prohibition of remuneration for transfer, and the prohibition of the designation of transplant recipients.

WRITTEN STATEMENT PROVIDED TO THE ADVISORY COMMITTEE TO THE DIRECTOR, NIH

December 14, 1988

Jane L. Delgado, Ph.D.

As the President and Chief Executive Officer of the National Coalition of Hispanic Health and Human Services Organizations, I feel it is important to bring to your attention the reasons why the deliberations of this Panel are of particular relevance to the Hispanic community:

- Almost one-third of U.S. Catholics are Hispanics.
- The majority of Hispanics (85 percent) are Catholic.
- According to a recent study (Henshaw and Silverman, 1988):
  - Hispanics represented 8.4 percent of women aged 15-44 and 12.8 percent of abortion patients in that age category.
  - Hispanic women were 60 percent more likely than non-Hispanics to have an unintended pregnancy terminated by abortion.
- Hispanics suffer disproportionately from diabetes and AIDS--diseases where an effective treatment might be developed from current fetal tissue transplantation research.
- Women's issues, Hispanic issues, and Hispanic women's issues are usually at best ignored and at worst maligned.

These facts were important considerations as we developed answers to the questions raised by Dr. Windom. Our deliberations, although generally collegial, unfortunately, were sometimes filled with not-so-polite accusations by articulate persons who used language to veil their own "feelings" while attacking others who were more candid in identifying "feelings" as the essential underpinning for values and beliefs. Besides these displays, I am also concerned about the inappropriate drawing of historical and situational parallels--most notably those to the Holocaust. Dr. Moscona's statement to this effect should be read carefully.

In summary, over the past several months I have had the opportunity to serve on this committee, review the testimony of experts in a variety of fields, and hear the range of concerns raised by members of this Panel. The answers have been developed by taking diverse ideologies and weaving them into a pattern which will benefit and enhance all of humanity. I concur with the responses developed by the Panel because they represent clearly understood, responsible positions.

C9

STATEMENT TO THE ADVISORY COMMITTEE TO THE DIRECTOR, NIH

December 14, 1988

James Bopp, Jr., Esq.

It is my pleasure to address the Director's Advisory Committee, and it has been, indeed, my distinct pleasure to serve on the Panel, which considered an issue about which there is a significant public interest.

You should note that there is, in fact, no consensus concerning the Panel's report. You will find in the documents prepared by the Panel a majority report of the Panel, and then you will find 11 members of the Panel filing concurrences and 4 members of the Panel filing dissents.

So at least 15 members of the 21-member Panel felt it necessary to explain and elaborate their views, put shadings on the recommendations that have been made by the Panel, some of which I think are important for this Advisory Committee to consider as they consider the majorities' recommendations.

Now, the question posed by the Assistant Secretary, in my view, can be summed up as whether transplantation research using human fetal tissue derived from induced abortion is an acceptable act for sponsorship by an agency of the Federal Government.

I think that the Panel's responsibility here was primarily ethical in nature. Since tissue for transplant was obtained from induced abortion, the essential ethical question before the Panel was whether or not the beneficial prospect of transplantation research is subverted by its association with induced abortion.

Some of the other members of the Panel, including myself, were guided by this ethical principle, that one may not take the life of a human being for the benefit of another human being.

Some of us proceeded on the assumption that abortion is, in fact, the taking of a human life and, thus, is morally objectionable except for the gravest of reasons.

Thus, in this inquiry, one of the ethical questions presented to me and to others of us is: Will fetal transplant lead some women to abort who would not have otherwise done so?

Some of us have concluded that it would, in fact, do so; and, thus, fetal tissue transplantation research, which could lead to this result, should not be funded by the Federal Government.

Now, it is reasonable to expect that abortion would increase, if fetal tissue transplantation became common, as a result of two distinct effects of this successful therapy: first, that it would provide a reason for some women to abort who would not have otherwise done so; and, secondly, that the market forces that can be expected to come into play would ensure that abortion clinics encouraged abortion.

As a preface to this, you have to understand that successful fetal tissue therapy involves an institutional relationship between abortion clinics and those who participate in this therapy.

It involves a contract with abortion clinics, people on site to gain the fresh tissue, consent from the woman, and reimbursement of expenses to the abortion clinic. In other words, the relationship necessitates a constant supply of fetal tissue from future abortions from abortion clinics and assurance that that supply will continue.

This, thus, is not a casual relationship, or an accidental one, but an intentional one requiring the most intimate cooperation between those involved in fetal tissue transplant or their agents who would use the tissue and the abortion clinic.

Now to the two effects. First, if fetal tissue transplant becomes common, this will influence some women to have an abortion. It is well-documented in the literature that ambivalence toward abortion is a common reaction of a woman facing a problem pregnancy.

There is a period of intense anxiety and ambivalence that is often experienced during the 24 hours preceding an abortion. This ambivalence is reflected in the fact that one-fourth to approximately one-half of women aborting find the decision difficult to make.

In addition, in studies of pregnant women who choose to abort and others who choose to deliver their children, approximately one-third to 40 percent of the women, whatever their ultimate decision, were reported to have changed their decision at least once, with women who aborted being significantly more likely to report their decision as a relatively difficult one, to rethink their initial choice, and to regret having to have made that decision.

Some women who make an initial decision to abort will change their minds at the last minute, with approximately 5 percent changing their minds after making an appointment to have an abortion and approximately 1 percent changing their minds at the abortion clinic itself.

Significantly, studies reveal that some 24 percent to 37 percent of women who abort do not make up their minds until just before the procedure. In addition, studies reflect that women, when they decide whether or not to abort, often consider multiple reasons, on the average four reasons, in deciding whether or not to have an abortion.

For those women who are ambivalent about abortion, that is, the 40 percent of pregnant women who have changed their minds at least once or who have found the abortion decision difficult, the pros and cons of the decision were somewhat evenly balanced, regardless of what decision is made. Most women who decide to abort are uncertain and uncommitted in their abortion decision. For them, abortion is a marginal good at best.

We also find that women, regarding their reasons to abort, consider the benefits or concerns of others. Thus, I would submit two facts: one, that if fetal tissue transplantation therapies became common, it would become common knowledge among women who were considering whether or not to abort that fetal

tissue transplant is a possible result of their abortion; and when you add a beneficent reason to the number of reasons that women consider when deciding whether or not to have an abortion, some would abort who would not have otherwise done so.

The Panel does acknowledge this result. The Panel admits that, "Transplantation and research with fetal tissue will become general knowledge" if it becomes successful.

They also acknowledge "that knowledge of the possibility for using fetal tissue in research and transplantation might constitute motivation, reason, or incentive for a pregnant woman to have an abortion."

Thus, I would submit that if fetal tissue transplant therapy became common and successful, that this would necessarily influence women, some women, to decide to have an abortion that would not otherwise occur.

Secondly, we cannot ignore the market forces that would be at work. Based on the testimony that we have heard before the Panel, if this therapy became successful, for instance, for Parkinson's disease or diabetes, the demand would greatly outstrip the supply.

Current levels of abortion can provide only enough tissue yearly for fetal transplant for those two conditions for less than 5 percent of those who would benefit from the therapy if successful. This necessarily would create financial incentives for abortion clinics to encourage abortion, even if they are only receiving reimbursement for their expenses.

Indeed, I would submit that these market forces will ensure what we have already come to know, that no one who is not otherwise obligated to follow NIH guidelines would follow them.

Indeed, as we sit here, fetal tissue transplants for Parkinson's disease is underway and has been conducted at the University of Colorado and at Yale during the period of time of the NIH moratorium, during which we were to develop voluntary guidelines to ensure that this research and ultimate therapy are conducted ethically.

Thus, in my view, abortion can reasonably be expected to increase as a result of NIH-funded research, if the research leads to successful therapies.

Now, let me turn briefly to the Panel report. The Panel does acknowledge that "it is of moral relevance that human fetal tissue for research has been obtained from induced abortion."

They then proceed to recommend guidelines which the Panel says is to prevent encouragement of abortion. But the Panel does not say why. The Panel does not explain why it is that guidelines should be adopted to prevent encouragement of abortion. They do hint, though, at some of the views of members of the Panel.

In one of the Considerations to one of the Answers, the Panel says that a majority of the Panel found "that it was acceptable public policy to support transplantation research from fetal tissue either because the source of the

tissue posed no moral problem"; thus, some members of the Panel did not view abortion as morally objectionable, "or because the immorality of its source could be ethically isolated from the morality of its use in research."

I would submit that those who would support guidelines to prevent the encouragement of abortion, but who do not view abortion as morally objectionable, have adopted an incoherent position. If abortion is not morally objectionable and if there are great benefits to be derived from fetal tissue, why is it that you would not encourage abortions?

Indeed, there is no moral or ethical objection to organ transplant from dead adults, provided proper consent is given, and, thus, we spent a lot of time and money encouraging organ transplant.

It is only if abortion is morally objectionable is it coherence to suggest, as the Panel attempts to, that abortion should not be encouraged to derive tissue therefrom.

Thus, in order to understand the report, it is important to know the view of those supporting its recommendations. And we find that view. In the Robertson concurrence, a majority of the Panel members who supported this report, nine so far, do not view abortion as morally objectionable, on the one hand; and, secondly, are perfectly prepared to disregard certain of these guidelines, if more fetal tissue is necessary for transplantation.

In the Robertson concurrence, a majority of the panelists supporting the report say that "if there were a substantial increase in the number of abortions, it still would not follow that fetal tissue transplantation research and therapy should not occur."

"Given the rudimentary development of early fetuses," up to 6 months old, I would add, "the potentially great benefits to recipients, and the legality of abortion, such transplants might still be ethically and legally acceptable."

A positive effect upon abortion increase is, thus, considered no obstacle to medical progress. The majority of panelists supporting the report are in favor of the guideline to prohibit research on fetuses conceived in order to be aborted for their use as fetal tissue because there appears to be no present need for it in research.

Quoting now from the majority of the Panel supporting the report, "In light of these supply considerations," the restriction is accepted. But, "if the situation changes so that the supply of fetal tissue from family planning abortions proves inadequate, the ban "should be reexamined."

Thus, I would suggest that a majority of the panelists supporting this report do not find abortion morally objectionable.

What conclusions can you derive from this fact concerning the report itself? Well, first, since the report provides no basis for its view that encouragement of abortion should not occur, we do not know the ethical basis upon which that report is based.

Secondly, for those on the Panel who believe that abortion is not morally objectionable, we can only conclude that they are recommending these guidelines as a temporary expedient to gain NIH funding, to gain Federal sponsorship, and to gain government approval for fetal transplantation research and therapy.

In any event, however, the guidelines will not prevent encouragement of abortion, as I have already explained. Thus, the guidelines do not separate the abortion decision from the use of tissue thereafter. That is, in fact, as the Panel acknowledges, inseparable if the research becomes successful.

Thus, it is my view, and some others, that fetal tissue transplant from induced abortion leads to ethically unacceptable results, the taking of a life of one human being for the benefit of another.

And research that can be expected to lead to that result should not be funded by NIH.

STATEMENT TO THE ADVISORY COMMITTEE TO THE DIRECTOR, NIH

December 14, 1988

K. Danner Clouser, Ph.D.

Rather than focus on any of the details of our report, I would rather devote my 5 minutes to a more overarching matter which was never discussed as such by our Panel. I want to comment on the moral framework within which such discussions as the one we are engaged take place. There is no time here to defend the moral point of view I am about to describe, but rigorous arguments are available for doing so.[1]

I would urge the Advisory Committee to view the relevant moral issues before us from a moral framework more universal in scope, more cognizant of our society's plurality of values, beliefs, and lifestyles, and more basic than the special moralities from whom we have now and again heard on our Panel. The moral framework I am urging I believe to be the appropriate stance for decisions in the public arena. It is based on rationality, is applicable to all rational persons, and serves the mutual self-interest of all by deriving its moral rules from rationality. These rules proscribe us from causing specified harms to each other, and thus comprise a moral code which would have universal agreement, since all rational persons would avoid harm unless they had a reason not to.

This basic morality is itself a public policy. It is a policy that applies impartially to all rational persons who meet certain specifiable basic requirements such as being able to understand its moral rules and to act in accord with them. These persons comprise the moral community. It is only within and among this community that morality's demands make sense by having a basis in universal agreement and the means of being carried out. Rational persons do not much agree on what is good, but they do agree on what is harmful, that is, what a rational person would avoid unless he had an adequate reason not to. Consequently, rational persons would espouse moral rules prohibiting harm. It is to the interest of all to do so.

We should note that this basic morality is not to be confused with many other look-alikes. It is not a philosophy of life dedicated to the achieving of chosen goods; it is not an elite club delighting in its own secret rules and rituals; and it is not a religious morality based on metaphysical beliefs which not all persons by virtue of rationality alone would have to accept. Rather it is a basic morality, universal and public, that all rational persons by virtue of their rationality alone would espouse.

Now, from this general account of morality certain observations follow that are relevant to the proceedings and the report of our Panel.

1. This basic morality I have described is what is relevant in a pluralistic society because it deals with that on which rational persons might agree on the basis of rationality alone. It is devoid of

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[1]For example, Bernard Gert, Morality: A New Justification of the Moral Rules. Oxford University Press, 1988.

subjective goals, lifestyles, and metaphysical beliefs on which we could get little agreement.

2. Equally rational and moral persons can disagree on the weighting or ranking of evils (i.e., harms), and, consequently, disagree on their moral judgments about certain matters. This means that for many moral problems there is not necessarily one correct solution. And it is appropriate in those instances to settle a moral issue by consensus.

3. The moral community does not include those beings which do not understand the mutuality of morality nor how or why they should be moral. These beings could be trees, animals, or fetuses. This does not necessarily mean that we may treat those beings outside the scope of morality in any way we please, but it does mean that we have a profoundly different basis for our moral relationship with other rational persons than we do with those outside the scope of the moral community.

4. We in the moral community can of course grant rights to those beings outside. But why would we do that? Perhaps, for example, those beings would suffer, and many of us feel a kinship with those beings and want to avoid their suffering. But whatever our individual or personal reasons for wanting to grant certain rights to those outside, there are no universally compelling reasons as there are for our moral rules which pertain impartially to all rational persons within the moral community. So on these matters of our relationships to those beings outside the moral community we must struggle for consensus and compromise. If we ourselves feel a natural empathy for certain others outside the scope of morality, we might try to convince others to empathize--or we might compromise by agreeing to protect something for which they feel a natural empathy or regard. In short, there is nothing here to compel universal agreement, and equally moral, rational persons can and do disagree. And so it was that our Panel members disagreed, but we compromised, namely, by our efforts to insulate the abortion decision from the research and therapy possibilities--either as a protection for that which we felt some empathy or out of concession to those who did have strong empathetic concerns. This must not be written off as a weasel compromise unbecoming the grand enterprise of ethics. Rather it is an entirely appropriate procedure in areas not amenable to determination grounded strictly on rationality.

5. That there are disagreements on the treatment of those beings outside the scope of basic morality implies absolutely nothing about how we might therefore treat other fellow human beings. We are not on any sort of moral slippery slope whatsoever. Within the community of rational persons it is clearly immoral to cause each other harm--such as depriving them of life or liberty, or causing them pain, or deceiving them. And that is why analogies between what has happened to persons in the past and what is happening to fetuses now will not work.

In summary, in the public arena we must deal with basic morality which is founded on rationality. Certain basic rules follow from that rationality and are applicable to all rational beings within the moral community. And from this moral point of view the majority recommendations of the Panel are moral. However much special interests may see them as immoral, there is a strong and universal basis for regarding the recommendations as morally acceptable while recognizing that equally moral and rational persons can disagree on our relationship to those beings outside the moral community.

Those of us who do have strong empathies and concerns for those outside the moral community can of course continue to build a consensus for those particular interests. But the charge to our Panel is not the appropriate occasion.

STATEMENT TO THE ADVISORY COMMITTEE TO THE DIRECTOR, NIH

December 14, 1988

Patricia A. King, J.D.

I appreciate the opportunity to speak with you today. As I feared when I saw my place in the line-up, many of the points that I wished to make have been more ably made by some who have preceded me, and so I will take this opportunity to depart from what I have prepared to just make a few points.

I would urge the members of the Director's Advisory Panel to adopt the recommendation of the Fetal Tissue Transplantation Panel because I believe that those recommendations represent not only a consensus of the Panel, but perhaps a consensus of broader opinion.

I say "consensus" because the vast majority of the Panel, despite our diverse backgrounds, views, and perspectives, were able to reach an agreement on the wording of recommendations and the wording of the considerations that we gave you.

That is not to say that we would not all have wished to have written our precise views and considerations, and some of us, indeed, tried to do that, in concurring opinions and dissents. But I emphasize that the document that you have before you does indeed represent, in my view, well-thought-out recommendations that the vast majority of us could indeed agree with.

There are a few additional points that I would like to make. I chose to speak today because I believe that the document insufficiently addressed some issues. For me, the document insufficiently pointed out the analogy between research with fetal tissues and organ transplantation, which is an accepted therapeutic procedure in our society.

It is no surprise that we ignored or gave insufficient attention to the organ transplantation analogy, since we were asked to respond specifically to ten questions.

Every good lawyer knows that the person who asks the question helps to shape the framework for the answer. That is something that I respect, and I like to think of myself as a good lawyer. But because the questions were worded in a particular fashion, it is no surprise that our answer, in trying to be responsive to our mandate, reflected the particular framework of the questions.

But in being responsive, I would stress that we ignored, in my view, the analogy to existing practices that we, as a society, have found acceptable. I believe that the issue of research with fetal tissue is analogous to organ transplantation. We are talking about using cadaveric tissue.

We are also talking about a very significant and promising area of research. We would not be here if we had not had some indication of the significant benefit that such research might bring. And, indeed, the Panel

heard nothing that would dissuade us of that view. To the contrary, our views have been re-enforced--this is an important and promising area of research.

In my view, because we did not focus on analogies to organ transplantation, we spent far too much time on the question of the association of fetal tissue research with the issue of abortion.

And, as a result, I believe that our efforts to develop principles by which this research might be ethically conducted is too related to the question of whether or not abortion will be encouraged.

I point out to you that the principles that we adopted, the principles of separation, and the ways in which we specify them, are principles that are present in the practice of therapeutic organ transplantation.

It is an area--therapeutic organ transplantation--that we have asked not be commercialized, for example, and our Federal law reflects that fact. Moreover, in therapeutic organ transplantation, we have separated the issues of obtaining organs, and the means by which we obtain those organs, from the question of who will receive the organs and, indeed, under what circumstances those recipients might be designated.

And so I repeat that I think that the guidelines that we have given you would support doing fetal tissue research, in my view, the guidelines are justified, and I would have found applicable if I had not been asked any questions concerning abortion.

Just a few final points. It seems to me that we should keep in mind that we are talking about NIH sponsorship and oversight of fetal tissue research. I emphasize this point because much of our discussion was premised on the fact that this research might prove so promising that other consequences would follow.

But I repeat that we are talking just about research. We do not know what we will find if this research is funded; and finally, it is very important for NIH to take the lead in funding this research, so that NIH can take the lead in setting up the guidelines by which this research will be conducted.

I note that there have been two attempts to do fetal tissue transplantation in the United States already, but I would still emphasize that it is important that NIH be clear about what its role is and about the justification for appropriate guidelines. And I have confidence that the scientific community will voluntarily adhere to those guidelines.

STATEMENT TO THE ADVISORY COMMITTEE TO THE DIRECTOR, NIH

December 14, 1988

Professor James T. Burtchaell

I begin by noting three frustrations. The first is that the documentation resulting from our fall and winter work is substantial, and I am quite sure that the statement and concurring and dissenting documents that were sent to you were crafted with great stress and care, each word having been weighed.

I regret that those documents have been made available to the members of the Advisory Committee for so brief a time before this meeting. For busy people, I am sure it must have been very difficult to find appropriate time to read them and, thus, to appreciate much of what we are going to say today.

My second frustration is that while the questions put by the Assistant Secretary were primarily ethical in nature, a very large part of the response to them was based, not upon ethical, but upon legal, considerations.

And a great deal of that was done simply by setting aside the prospective victims of this research--that is, the aborted children--by simply excluding them, as has been said, from the moral community.

We always exclude from the moral community whomever we wish to exploit. The Fourteenth Amendment had to reverse one instance of that activity. The Nuremberg Code was a more recent rectification of that.

My third frustration regards something that we never spoke of. There would not be the human fetal tissue in such abundance available were it not for the 1973 Supreme Court decisions. Those decisions struck down existing legislation in 50 States and Federal legislation as well, and they have been severely criticized by very serious jurists.

Public opinion polling for the last 30 years demonstrates that there has not yet been a majority of public opinion in support of abortion on demand. And for the National Institutes of Health to presume that this is a dependable source of tissue for the indefinite future strikes me as improvident.

Four of the panelists strongly disagree with the primary recommendation of the Panel. I speak as one of them. I speak on behalf of three of our objections very briefly.

There is, first of all, no person who can fulfill the Nuremberg requirements for authentic voluntary consent. Consent to donate remains can be made by a human being in prospect of death or by someone who has custody of that human being: a parent of a minor child, a court-appointed guardian, a person given power of attorney. That power is only awarded for one purpose: protective care. It is quite clear that the act of abandonment implied in the abortion decision terminates such a trust, and it <u>is</u> a trust.

Therefore, in prospect of the unborn offspring's death, the mother has forfeited, or abrogated, her power to make such a decision on behalf of the still living child.

After death, the next of kin has a right, morally and usually legally, to dispose of their remains, no longer merely for the care of the now deceased unborn, yet, in conformity with the respect due to that deceased human.

The proposal of the Panel is almost unprecedented, to give that uniquely ante-mortem decision over another's remains to another human being, not as a caretaker, but as a person pursuing her own interests, and that is the explicit explanation given by a majority of those supporting this decision.

We have almost no antecedent for that except chattel slavery, and chattel slavery, even in the United States, never gave that large a selfish power over the one who was in control.

Our second objection is that, despite the attempts of the Panel to segregate the moral implications of abortion from the potential therapeutic usage, it does not work.

It is the same argument used by a banker who is laundering funds from drug transactions already completed. The function of the banker in no way affects those transactions, because they already took place. They would have taken place without the banker there ready to launder the funds. Nevertheless, the banker is an accessory: he is complicit by this institutionalized arrangement of interaction and association with those in the drug industry.

The more potent analogy, which is indeed distasteful to a number of our colleagues, comes from the very root of all contemporary literature on the protection of human subjects of research. One of the outrages brought to light in the medical trials at Nuremberg was the research use of cadaveric remains with the same disregard for victims we discern in the programs proposed to the Panel--because they were considered outside the moral community.

The explicit rationalizations given by the scientists engaged in that usage were, if not word-for-word, at least meaning-for-meaning, replicated in the justifications given for present fetal tissue research: "We had nothing to do with the source. Therefore, it is not a concern of ours." On the contrary, we argue that there is indeed complicity after the fact.

The third of our arguments has already been dealt with by Mr. Bopp: that for women facing the excruciatingly difficult and very ambivalent decision to abort, the prospect of bringing good out of tragedy, as they would see it, is going to be not insignificant.

And the financial incentives for those for whom abortion has now become an industry--practitioners who, in largest part, have already moved aside from the mainstream of the obstetrical profession--will prove to be, in its own right, a strong incentive.

We worked a great deal of time on our dissent. I hope that the discussion time provided throughout the rest of this meeting will allow us the opportunity to respond to the questions that it should naturally provoke.

STATEMENT TO THE ADVISORY COMMITTEE TO THE DIRECTOR, NIH

December 14, 1988

John A. Robertson, J.D.

At the risk of sounding redundant, I would like to make a point that I do not believe has been made. The point is about burden of proof. Given the likely benefits of fetal tissue transplant research, the burden of showing that such research should not occur falls--and should fall--on its opponents. In the view of the Panel, the opponents have not met that burden.

The Panel's position recommending NIH support of fetal tissue research is based on the fact that more than 1.5 million elective abortions occur annually in the United States. Because this tissue will be available regardless of research needs and will otherwise simply be discarded, tissue from these abortions can be used for transplant research without involving researchers or recipients in the abortion itself. Indeed, one could reasonably argue that it would be unethical to discard this tissue rather than use it in research that could save many lives.

In making use of fetal tissue from induced abortions, the Panel has recommended a number of safeguards to assure that research needs do not influence the abortion decision. These include postponing requests to use the tissue until after the decision to abort has been made, prohibiting donations to family members, and prohibiting money payments for fetal tissue donation.

The Panel's view is that with these safeguards NIH support for fetal tissue transplant research would not signify approval of or encourage abortion or involve the Federal Government in supporting abortion. It simply recognizes the reality that abortions occur in large numbers, and that once having occurred, there may be better uses of fetal remains than incineration. The most relevant parallel is solid organ transplantation, which makes use of cadaveric organs from accident and homicide victims, without encouraging or approving the actions that make the organs available.

Given these considerations, persons who oppose NIH support of fetal tissue research should have the burden of showing that such great harm or such clearly unethical practices would result that the benefits of fetal tissue transplant research should be foregone. To that end, opponents claim that federal support of any fetal tissue transplant research will necessarily lead to more abortions, and that any increase in abortions, no matter how small or marginal, makes the program causing that increase unacceptable.

After careful consideration the Panel has found unpersuasive the notion that women, who otherwise would have decided not to abort, will choose to abort because tissue may be anonymously donated for research or therapy. The Panel heard no convincing evidence that a pregnant woman's decision against abortion would be changed by the prospect of anonymous tissue donation. The recommended safeguards further lessen the possibility of such influence.

To argue otherwise, as opponents do, requires a different perception of the motivations of women contemplating abortion and of the efficacy of the

recommended safeguards. But it also requires a further assumption--the assumption that federal research support will make fetal tissue transplants so successful and widely known that the prospect of anonymous tissue donation will inevitably alter the decision of pregnant women contemplating abortion.

But the assumption of widespread success, on which the opponent's claim of influence on abortion decisions rests, is itself highly questionable at this very early stage of clinical research. As you well know, there is no certainty or guarantee that fetal tissue transplants will work for any disease, much less that they will be successful for all diseases for which they offer hope. If they are successful, it may be that they will be successful only for certain patient subgroups, or that fetal tissue transplants will be a temporary way station to development of cell lines or biochemical substitutes that in 7-10 years replace fetal tissue transplants totally.

Nevertheless, opponents would ban all federally supported fetal tissue research at this early stage, and thus cut off further investigation that could lead to important findings in many areas, out of the hypothetical fear, which the Panel has rejected, that abortions will increase if the "best case" scenario of widespread success occurs. They would thus prevent federally sponsored research which may have little or no effect on abortion decisions, yet significantly help subgroups of patients. Indeed, they would even prevent the research that might lead to cell lines and other substitutes for fetal tissue, because of the speculative fear that "some" increase in abortions might occur if fetal tissue transplants were a stunning success.

But even if fetal tissue transplants turn out to be a stunning success, the opponents have presented no persuasive reasons to think that that success would have a substantial, as opposed to a minor or marginal, impact on the incidence of abortion. It is not enough to show that there will be some increase in the number of abortions that would not otherwise have occurred from widespread use of fetal tissue. Opponents have the burden of showing that the increase would be substantial, indeed, so substantial that the great benefits that may be possible from fetal tissue research should be foregone to avert this increase. None of the dissenting statements address the size of impact which they speculate would occur, arguing only that some increase or an increment in the number of abortions would result. Apparently their premise is that any increase in abortion, no matter how small, would render fetal transplants unacceptable.

Thus they are in the position of saying that any public policy that has the risk of increasing even slightly the number of abortions at some future time is unacceptable, regardless of the benefits to chronically ill patients. Needless to say, such a position applied to other public policies would ground or stop most progress, since many policies, from building roads, bridges, and airports to approving drugs, may cause the loss of human lives that would not otherwise have occurred--and not just fetal lives. In the case of policies that permit knives and guns to be sold, some of the increased deaths will be intentionally caused.

It is for these reasons that the Panel finds that persons opposed to fetal tissue transplant research have not met the burden of showing that such great harm or such clearly unethical practices would occur that such research should not go forward. Given the great good that is possible from fetal tissue research and the large number of abortions that will be occurring regardless of

tissue transplants, the Panel has found that it is acceptable public policy for the NIH to support such research, and recommends that this Advisory Committee so find as well.

Comments Prepared by Dr. George E. Palade on the Report of the Human Fetal Tissue Transplantation Research Panel

(for the record)

Appendix D

COMMENTS ON THE REPORT OF THE HUMAN FETAL TISSUE TRANSPLANTATION RESEARCH PANEL

George E. Palade, M.D., Yale Medical School

In trying to provide answers to the questions raised by Dr. Windom, the Assistant Secretary for Health, the Panel on Human Fetal Tissue Transplantation Research had to deal with a difficult set of problems. So difficult that it was not possible to concentrate mostly, if not exclusively, on the central pertinent issue: to wit: Should the NIH support research on human fetal transplantation for experimental purposes, primarily for potential therapeutic applications?

The scope of the discussions was enlarged to include the much wider and currently divisive issue of the morality of abortion. This move by part of the members of the Panel generated minority opinions written with eloquence, zeal, and determination, but not always based on unquestionable arguments.

The key issue is the status of the human fetus. Is it a human person entitled to personal protection against everybody (including the prospective mother)? Is it a person whose rights are guaranteed by the Constitution of this country? In fact, a human fetus is not yet a person; it is a person in the making, and the time when it becomes a human person is still a matter of debate and argument.

This uncertainty explains, I believe, the decision of the Supreme Court in the widely known and so often discussed Roe v. Wade decision. Be it as it may, that decision is now the law of the country. Questioning it as immoral implies that we have an amoral or immoral Supreme Court. People may criticize the Court or disagree with some of its decisions, but I wonder how many are ready to label it immoral.

Equating abortion with feticide and feticide with homicide may generate impressive prose but leads to obvious inconsistencies. If feticide is homicide, why are the doctors performing the abortions not put on trial? And why are the women who become accessory to those crimes not treated accordingly?

If more than one and one-half million voluntary abortions are performed every year in this country, we should conclude that something is amiss in our society. The families, the churches, the synagogues, the schools, the media, and our system of health information and assistance are failing in their mission by that large figure. Addressing the causes that create and maintain this unhappy situation is an area in which zeal and crusading spirit would be most welcome.

Another issue of equal importance is the fate of those one and one-half million infants born, but unwanted by their mothers, if abortions become effectively forbidden. Is our society ready and willing to take care of them? We seem to have problems with the health maintenance, proper nutrition, and adequate education of those who are not unwanted.

By comparison with these major issues, the argument about the morality of the use of fetal tissue in transplantation experiments loses strength. The causes and the consequences of the current unhappy situation must be addressed.

Prevention of immorality or questionable morality, like prevention of disease, should be better than cure.

Notwithstanding its limited reproductive capacity, the human species has succeeded in performing the equivalent of a biological miracle: It started by being an endangered species and remained so through millennia, but the situation changed drastically over the last century. At present, Homo sapiens endanger all other species, itself, and the environment. It is clear that mankind does not need more numbers. It needs improvements in the quality of life, be it at the simple nutritional level in underdeveloped countries or at the level of broad education, ethics included, in economically advanced communities.

Perhaps some of the dogmas with which we have to cope in our time reflect our past condition as endangered species. Conceived by men or inspired by God, they responded to the needs of that condition: They were designed to make sure that the species loses as few individuals as possible.

Conditions change and so do dogmas, but they do not change in phase. Dogmas are slow in changing. In 1633, Galileo Galilei was condemned by the Catholic Church for heresy, obliged to deny his discoveries, and stop teaching. He also had to promise that he would denounce all who supported his ideas. Last year, the Church rehabilitated Galileo and recognized that back in 1633 he was right and the Church was wrong.

To redress the damage done by the dogma, it took 250 years, more than compelling evidence, and a courageous Pope. But the rehabilitation came much too late to do Galileo any good as a person. In a less formal way, the same applies for the victims of inquisition in Western Europe from the 15th to the 17th centuries and for the victims of the witch trials in the New England of the 17th and 18th centuries. Perhaps in a century--or less than a century--mankind will look at our current problems with a different understanding.

It does not mean, however, that dogmas must be altogether discarded. They are, in fact, an important element in the continuity of our civilization. They have done, in the past, more good than harm for us. Moreover, we should understand that dogmas have a hard time in periods of rapid change. We should help bring them closer to the realities of the human condition in our time.

Notwithstanding dissentions, abstentions, lively discussions, and passionate prose, the Panel provided useful answers to Dr. Windom's questions. The answers, supported by a large majority of the Panel's members, recommended that the NIH support experimental work with human fetal cell or tissue transplants; it identified the disease in which transplantation is expected to be beneficial (parkinsonism and juvenile diabetes, primarily), and defined in significant detail the conditions under which cadaveric fetal tissue should be collected and independent consent be obtained for its use in research from the pregnant woman. The conditions are designed to preclude commercialization of fetal tissue transplantation and to insure, within possible limits, that therapeutic use will not encourage more women to undergo abortion.

Of course, the entire development is built on a premise--the voluntary abortion--which remains questionable, even regrettable or repugnant for part of the public. Yet, as the majority of the Panel concluded, the use of cadaveric fetal tissue for biomedical research is "acceptable public policy" under our

current laws. This general position is essentially pragmatic: It tries to make the best out of an unhappy situation for which both the pregnant woman and a careless society are responsible. In any case, it provides the recommendations needed for setting in place regulatory and control mechanisms for a type of research that will remain highly vulnerable to public dissent, at least until truly beneficial results will be obtained.

The scientific basis for experimental therapy and other forms of biomedical research of direct health interest has been, in the meantime, considerably strengthened and enlarged.

Two Swedish Groups (A. Borklund and L. Olsen) have proceeded methodically to show that fetal transplants are viable and functional in rodents. And a group at Yale was able to demonstrate that collected brain tissue can be frozen for months without losing viability. This situation provides the researchers with the time needed to check the biochemical specificity of the tissue--which should include potential dopamine-secreting neurons--as well as the state of health of the intended graft, which should be free of either viral or bacterial pathogens. In addition, this reasonably long interval makes possible a satisfactory separation in time, space, and personnel between abortion and transplantation.

The Yale group has developed a detailed, carefully worked out protocol. Both groups--Swedish and American--have demonstrated feasibility in animal models, and the Yale group has obtained apparent cure of experimental parkinsonism in adult monkeys by transplantation of fetal monkey tissue containing potentially dopaminergic neurons. The Yale group has also succeeded in transplanting human fetal tissue in the striatum of normal monkeys and in demonstrating its survival and characteristic enzymic activity (tyrosine hydroxylase). In other words, the work has proceeded systematically, one step at a time, towards the final goal, which is transplantation of a human fetal explant taken from the appropriate region of the midbrain of a dead fetus to the part of the brain that needs dopamine-secreting neurons for its normal function in an adult human patient afflicted by parkinsonism. The final step was, in fact, performed on Thursday, December 8. Other transplantations will probably follow.

Notwithstanding the promise implied by the results of these preliminary (or preparatory) experiments, further experimentation will still be needed to define optimal conditions for each major step (tissue collection, storage, testing, and implantation) as well as for assessing the extent and the stability of clinical improvements. And the entire process will take time because of a relatively long period of latency (months) before the activity of the transplanted neurons can begin to favorably affect the disease.

The work on fetal pancreatic islets transplanted into juvenile diabetics is expected to follow similar lines; work on other diseases that may require neuron replacement is just beginning.

The Panel heard testimony of the desirability of using established cultured neuronal cell lines instead of tissue transplants, and experimentation is proceeding in this direction. Fetal cadaveric explants will still be needed to establish the cultures. And additional controls will have to be introduced to ascertain that the cells retain their specific activities in culture, in

spite of possible genotypic and phenotypic drift, and to prove that their growth can be adequately regulated in the brain. They may generate tumors.

The Panel has concentrated its attention on experimental therapeutic transplantation and has not considered other possible, biomedically important applications of fetal tissue transplants. But very recently, perhaps too recently for attracting the attention of the Panel, an important application of human fetal tissue transplantation was reported by Irving Weissman's laboratory at Stanford Medical School. The primary move came from a young M.D., Ph.D., J.D. MacClure, who--as a result of residency at the San Francisco General Hospital where he took care of AIDS patients--conceived the idea of transplanting human fetal lymphopoietic organs (thymus, lymph nodes, and liver) into mice homozygote for a severe combined immunodeficiency syndrome (SCID). These mice lack B cells and T cells; they do not reject the transplanted human cells, which establish themselves in their foreign host and produce a "hybrid" mouse (SCID/hu) provided with a human immune system.

The immediate potential use of these mice is as a convenient animal model for the study of the human acquired immunodeficiency syndrome (AIDS), but many other applications seem possible. The SCID/hu mice can allow the study of the human immune system response to other retroviruses. It can also provide an appropriate model for the study of the development of the human immune system and for exploring conditions that can prevent autoimmune disease or improve immunosurveillance against neoplastic cells. The SCID/hu mice open, in fact, much broader vistas for beneficial application than those considered in parkinsonisms or diabetes.

Dr. Windom's questions were formulated in conjunction with the current moratorium on Federal (NIH) funding of fetal research. The moratorium does not apply to research supported by private, non-Federal funds. Research done at Yale has been and continues to be supported by such funds. Therefore, legalistically, the work does not infringe on the moratorium. Why did the work of the Yale team move ahead of a decision on the moratorium instead of waiting for it? There are, I am sure, specific reasons. But we should realize that a democratic society like ours is organized in such a way as to use all possible drives and forces, altruistic or selfish, the desire to do good as well as the desire for self-promotion, greed as well as generosity, and harness them all to the slow, lumbering wagon of society's progress. Systems based entirely on idealistic considerations do not work in the long run. Sooner or later they are obliged to rediscover the virtues (or merits) of messy democracy by democratization.

Of course we should take advantage of this diversity of motivations and put them to work. But at the same time a reasonable regulatory system is definitely advisable to prevent abuse, to set standards, and to maintain quality. The NIH should enter the field for two reasons: The field is clearly promising--more promising than we believed a few months ago. And a regulatory system is needed given the sensitivity of part of the public in such matters. The NIH already has functioning mechanisms for quality control--scientific, ethic, and otherwise--of the research it supports. The NIH can set standards that will be followed by other agencies. It can also have power of enforcement as it has in the case of affirmative action. And it has the experience of reasonable and adaptable regulatory activity acquired in relation to recombinant DNA experimentation.

D4

Rush D. Holt
Chief Executive Officer and
Executive Publisher, *Science*

April 25, 2016

To: Chairwoman Marsha Blackburn
Select Investigative Panel, House Energy and Commerce Committee

Dear Chairwoman Blackburn:

On behalf of the American Association for the Advancement of Science (AAAS), the world's largest general scientific society, I write in response to the March 30 letter from Chairwoman Blackburn of the Select Panel on Infant Lives. I appreciate the opportunity to present scientific information on the efficacy of fetal tissue research and to assist the committee in understanding its important role in addressing questions about medical research to promote human health.

As we indicated in our March 15 letter,[1] the decision to terminate a pregnancy does not bear on the decision to donate tissue. Scientific studies, such as one conducted by the University of California, San Francisco (UCSF),[2] reveal that reasons for this decision may relate to socioeconomic status, age, health, and marital status. Furthermore, the guidelines set forth in the National Institutes of Health Revitalization Act, PL 103-43, clearly stipulate that the option to donate tissue cannot be discussed with the woman until after she has made a decision to terminate a pregnancy.

Scientists who work with fetal tissue—many of whom are hesitant to be cited due to safety concerns—state that fetal tissue is unique and useful because it can offer information that other types of research, such as research using animal or adult tissue, do not always provide. Studies on animals may be predictive of results in humans, but not always. Fetal tissue is specific to early human development and may provide a level of assurance that may not be found solely utilizing adult or animal tissue.

It is used to study areas such as infectious diseases, eye development and disease, and to better understand fetal development.[3] AAAS has long taken the position that research on cells derived from all sources, when conducted under strong ethical guidelines, should be conducted to answer questions about human health and development.[4] This is in part because science is unpredictable. We do not know where the next medical advance will emerge, but we do know that sometimes, breakthroughs come from surprising places.

Regarding your inquiries about scientific information surrounding medical advances, vaccines, or cures achieved through the use of human fetal tissue research, fetal tissue research has been conducted since the

[1] http://www.aaas.org/sites/default/files/AAAS_FTR_March%202016.pdf
[2] http://bmcwomenshealth.biomedcentral.com/articles/10.1186/1472-6874-13-29
[3] http://www.nature.com/news/the-truth-about-fetal-tissue-research-1.18960#graphic
[4] http://www.aaas.org/sites/default/files/content_files/Stem%20Cell%20Research%20and%20Applications%20Report.pdf

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1930's and was instrumental, for example, in discovering the vaccine for polio, where researchers infected fetal kidney cells in petri dishes to produce a large amount of virus that they could then harvest, purify and use to vaccinate people. This kind of discovery is made possible by allowing multiple lines of inquiry, and by utilizing a range of tools, which include fetal tissue research.

Perhaps the timeliest example to demonstrate the potential for scientific advancement from research that uses donated tissue involves the Zika virus. As you are aware, the Zika virus has been linked to fetal deaths and birth defects such as microcephaly, prompting the World Health Organization to declare it an international public health emergency. In order to understand the virus' effect on pregnant women and their fetus, scientists are using fetal tissue to test how the virus may cause these birth defects. Donated tissue gives unique insight as to the *in vivo* effects of the virus, and as stated by the Nowakowski study on Zika,[5] it provides scientists a more comprehensive understanding of how the virus operates. Donated fetal tissue allows scientists to gain the necessary information on how the virus affects the fetus *in utero*, and to test a range of potential therapies and treatments for safety and efficacy.

To cite another recent example, there is a potential new prenatal stem-cell therapy to treat *osteogenesis imperfecta,* known as brittle bone disease, which was featured in a news article in *Science*.[6] This debilitating disease is genetic, and researchers are preparing a clinical trial to test this therapy in pregnant women. The therapy involves the use of mesenchymal stem cells (MSCs) from donated fetal liver that is infused through an umbilical vein that directly treats bone development of the fetus before birth. Early tests overseas have shown sufficient promise to move to a clinical trial, and one of the promises of this therapy is that this specific type of stem cell has not demonstrated as strong of an immune reaction as blood stem cells.

Examples like these demonstrate the need to explore many different types of research, including research using donated tissue. By limiting the scope of research and restricting the scientific community's ability to follow the evidence, we thereby limit the possibility of discovering new medical advances, vaccines, or cures aimed at bettering society.

Finally, we want to reiterate our concern expressed in our March 15 letter over reports that the Select Panel plans to issue subpoenas that would risk making public the names of researchers, students, and others involved in fetal tissue research. There is, unfortunately, a history of scientists being harassed and threatened for conducting certain types of research, and AAAS has long sought to support and defend these researchers. Scientists do not choose their careers to court controversy. They do so because they want to answer important questions, and to advance science in service of society. As history has shown, answers to these questions can sometimes change the world for the better.

Sincerely,

Rush D. Holt

Rush D. Holt, PhD
Chief Executive Officer and
Executive Publisher, *Science* Family of Journals

cc: Rep. Jan Schakowsky

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[5] http://www.sciencedirect.com/science/article/pii/S1934590916001181
[6] http://science.sciencemag.org/content/352/6283/284.full

The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL REPORT

Zika Virus and Birth Defects — Reviewing the Evidence for Causality

Sonja A. Rasmussen, M.D., Denise J. Jamieson, M.D., M.P.H., Margaret A. Honein, Ph.D., M.P.H., and Lyle R. Petersen, M.D., M.P.H.

SUMMARY

The Zika virus has spread rapidly in the Americas since its first identification in Brazil in early 2015. Prenatal Zika virus infection has been linked to adverse pregnancy and birth outcomes, most notably microcephaly and other serious brain anomalies. To determine whether Zika virus infection during pregnancy causes these adverse outcomes, we evaluated available data using criteria that have been proposed for the assessment of potential teratogens. On the basis of this review, we conclude that a causal relationship exists between prenatal Zika virus infection and microcephaly and other serious brain anomalies. Evidence that was used to support this causal relationship included Zika virus infection at times during prenatal development that were consistent with the defects observed; a specific, rare phenotype involving microcephaly and associated brain anomalies in fetuses or infants with presumed or confirmed congenital Zika virus infection; and data that strongly support biologic plausibility, including the identification of Zika virus in the brain tissue of affected fetuses and infants. Given the recognition of this causal relationship, we need to intensify our efforts toward the prevention of adverse outcomes caused by congenital Zika virus infection. However, many questions that are critical to our prevention efforts remain, including the spectrum of defects caused by prenatal Zika virus infection, the degree of relative and absolute risks of adverse outcomes among fetuses whose mothers were infected at different times during pregnancy, and factors that might affect a woman's risk of adverse pregnancy or birth outcomes. Addressing these questions will improve our ability to reduce the burden of the effects of Zika virus infection during pregnancy.

POTENTIAL RELATIONSHIP BETWEEN ZIKA VIRUS INFECTION AND BIRTH DEFECTS

Since the identification of the Zika virus in Brazil in early 2015, the virus has spread rapidly throughout the Americas (www.cdc.gov/zika/geo/active-countries.html). An increase in the number of infants with microcephaly in Brazil was first noted in September 2015, after the recognition of Zika virus transmission in the country earlier in the year[1]; this was followed by the recognition of a similar increase in French Polynesia after an outbreak there in 2013 and 2014.[2] Despite accumulating evidence that supports the link between Zika virus infection and microcephaly, most experts have taken care not to state that Zika virus infection is causally related to these adverse outcomes.[3] This cautious approach toward ascribing Zika virus as a cause of birth defects is not surprising, given that the last time an infectious pathogen (rubella virus) caused an epidemic of congenital defects was more than 50 years ago, no flavivirus has ever been shown definitively to cause birth defects in humans,[4] and no reports of adverse pregnancy or birth outcomes were noted during previous outbreaks of Zika virus disease in the Pacific Islands.[5,6]

On the basis of the available evidence, the public health response to the outbreak of Zika virus disease has moved forward, with the distribution of health messages about the impor-

tance of mosquito-bite prevention, recommendations by public health authorities in some of the most severely affected countries to delay pregnancy, and advisories that pregnant women avoid travel to areas with active Zika virus transmission.[7] However, communications regarding Zika virus have been challenging: a recent survey showed low levels of knowledge and concern about Zika virus in the United States.[8] The recognition of Zika virus as a cause of microcephaly and other serious brain anomalies would allow for more direct communication, which might lead to improved understanding of and adherence to public health recommendations. Therefore, a review of the evidence linking Zika virus infection and adverse pregnancy and birth outcomes is needed.

As is typically the case in epidemiology and medicine, no "smoking gun" (a single definitive piece of evidence that confirms Zika virus as a cause of congenital defects) should have been anticipated. Instead, the determination of a causal relationship would be expected to emerge from various lines of evidence, each of which suggests, but does not on its own prove, that prenatal Zika virus infection can cause adverse outcomes. Two approaches have been used to identify potential teratogens (exposures to a mother during pregnancy that have a harmful effect on her embryo or fetus)[9]: first, the identification of a combination of a rare exposure and a rare defect (sometimes referred to as the astute clinician approach),[10] and second, the use of epidemiologic data to confirm an association. Many teratogens were first identified by means of the rare exposure–rare defect approach, including rubella virus, which was identified after an ophthalmologist noted a characteristic form of cataracts in infants whose mothers had rubella during pregnancy,[11] and heavy alcohol use, which was identified as a teratogen after the recognition of a characteristic pattern of malformations that became known as the fetal alcohol syndrome.[12] In contrast, some teratogens have been identified on the basis of epidemiologic studies (e.g., valproic acid was identified as a teratogen after a case–control study showed an odds ratio of 20 for the association of spina bifida with use of this drug during the first trimester of pregnancy).[13]

SHEPARD'S CRITERIA

In 1994, Thomas Shepard, a pioneer in the field of teratology, proposed a set of seven criteria for "proof" of human teratogenicity (Table 1) that incorporated both approaches.[9] These criteria were an amalgamation of criteria developed by other teratologists and guided by methods that were used to identify previous teratogens. These criteria have been used to guide discussions about causation in teratology-related litigation[30] and to assess other potential teratogens.[10] We used Shepard's criteria[9] as a framework to evaluate whether the currently available evidence supports the hypothesis that prenatal Zika virus infection is a cause of microcephaly and other brain anomalies (Table 1).

According to these criteria, causality is established when either criteria 1, 3, and 4 (rare exposure–rare defect approach) or criteria 1, 2, and 3 (epidemiologic approach) are fulfilled. The first criterion states that a proven exposure to an agent must occur at a critical time during prenatal development. The severe microcephaly and other brain anomalies that have been observed in many infants are consistent with an infection occurring in the first or early second trimester of pregnancy. Several case reports and studies have shown that women who had fetuses or infants with congenital brain anomalies that were believed, on the basis of the mother's symptoms or laboratory confirmation, to be due to Zika virus infection were infected in the first or early second trimester of pregnancy, as determined either according to the timing of the symptoms or according to the timing of travel to an area where Zika virus is endemic.[14-20] An analysis of the timing of laboratory-confirmed Zika virus transmission in certain states in Brazil and of the increase in the cases of microcephaly identified the first trimester as the critical time period for infection.[1] Zika virus infections that occur later in pregnancy have been associated with poor intrauterine growth, fetal death, or in some pregnancies, defects on prenatal imaging that have not yet been confirmed postnatally because the pregnancies are ongoing.[14] We conclude that Shepard's first criterion has been met.

Shepard's second criterion requires that two epidemiologic studies of high quality support

Table 1. Shepard's Criteria for Proof of Teratogenicity in Humans as Applied to the Relationship between Zika Virus Infection and Microcephaly and Other Brain Anomalies.*

Criterion No.	Criterion	Evidence	Criterion Met?
1	Proven exposure to the agent at one or more critical times during prenatal development	On the basis of case reports, case series, and epidemiologic studies of microcephaly that are associated with laboratory-confirmed or presumed Zika virus infection, the timing of Zika virus infection associated with severe microcephaly and intracranial calcifications appears to be in the late first or early second trimester.[14-20]	Yes
2	Consistent findings by ≥2 high-quality epidemiologic studies, with control of confounding factors, sufficient numbers, exclusion of positive and negative bias factors, prospective studies if possible, and relative risk ≥6	On the basis of data from Brazil, the temporal and geographic association between Zika virus illness and cases of microcephaly is strong.[1] Two epidemiologic studies have been published. In a study in Brazil[14] that used a prospective cohort design, 29% of women with Zika virus infection at any time during pregnancy had abnormalities on prenatal ultrasonography, some of which have not been confirmed postnatally, In a study in French Polynesia,[2] retrospective identification of eight cases of microcephaly and the use of serologic and statistical data and mathematical modeling suggested that 1% of fetuses and infants born to women with Zika virus infection during the first trimester had microcephaly; the risk ratio in this analysis was approximately 50, as compared with the baseline prevalence of microcephaly. No other epidemiologic studies have examined this association to date.	Partially
3	Careful delineation of clinical cases; a specific defect or syndrome, if present, is very helpful	The phenotype has been well characterized in fetuses and infants with presumed congenital Zika virus infection, including microcephaly and other serious brain anomalies, redundant scalp skin, eye findings, arthrogryposis, and clubfoot.[15,20-23] The phenotype in some infants appears to be consistent with the fetal brain disruption sequence,[20,22] which has been observed after infection with other viral teratogens.[24]	Yes
4	Rare environmental exposure that is associated with rare defect	Reports of fetuses and infants with microcephaly who are born to women with brief periods of travel to countries with active Zika virus transmission are consistent with Zika virus being a rare exposure.[16,18,19] The defect, congenital microcephaly, is rare, with a birth prevalence of approximately 6 cases per 10,000 liveborn infants, according to data from birth-defects surveillance systems in the United States.[25]	Yes
5	Teratogenicity in experimental animals important but not essential	No results of an animal model with Zika virus infection during pregnancy and fetal effects have yet been published.	No
6	Association should make biologic sense	Findings are similar to those seen after prenatal infection with some other viral teratogens (e.g., cytomegalovirus, rubella virus).[26] Animal models have shown that Zika virus is neurotropic,[27,28] which supports biologic plausibility. Evidence that Zika virus infects neural progenitor cells and produces cell death and abnormal growth,[29] along with evidence of Zika virus in brains of fetuses and infants with microcephaly, on the basis of immunohistochemical staining and identification of Zika virus RNA and live virus,[16,17,19] provides strong biologic plausibility.	Yes
7	Proof in an experimental system that the agent acts in an unaltered state	This criterion applies to a medication or chemical exposure, not to infectious agents.	NA

* The criteria listed here were proposed by Shepard.[9] Criteria 1, 2, and 3 or criteria 1, 3, and 4 are considered to be essential, whereas criteria 5, 6, and 7 are helpful but not essential. Partial evidence is insufficient to meet a criterion. NA denotes not applicable.

the association. Although ecologic data do not necessarily qualify as an epidemiologic study, data from Brazil regarding the temporal and geographic association between Zika virus infection and the later appearance of infants with congenital microcephaly are compelling.[1,31,32] Two epidemiologic studies also provide support.[2,14] In a study conducted during the outbreak in Brazil, 88 pregnant women who had had an onset of rash in the previous 5 days were

tested for Zika virus RNA. Among the 72 women who had positive tests, 42 underwent prenatal ultrasonography, and fetal abnormalities were observed in 12 (29%); none of the 16 women with negative tests had fetal abnormalities. The abnormalities that were observed on ultrasonography varied widely, and some findings lacked postnatal confirmation because the pregnancies were ongoing.[14]

A retrospective analysis after the 2013–2014 outbreak of Zika virus disease in French Polynesia identified eight cases of microcephaly; the authors used serologic and statistical data and mathematical modeling to estimate that 1% of the fetuses and neonates who were born to mothers who had been infected with Zika virus in the first trimester had microcephaly[2] — a prevalence that was approximately 50 times as high as the estimated baseline prevalence. However, this estimate was based on small numbers, confidence intervals were wide, and the risk of other adverse outcomes (e.g., other brain anomalies) was not assessed.[2] Although these studies provide important evidence in support of a causal relationship between Zika virus and microcephaly and other brain anomalies, both have limitations as noted by their authors, such as a lack of control for confounding factors and relatively small numbers of cases, and therefore they do not meet the stringent criteria set by Shepard. Thus, we conclude that Shepard's second criterion has not yet been satisfied.

The third criterion, careful delineation of clinical cases with the finding of a specific defect or syndrome, appears to be met. Previous teratogens have caused specific birth defects or syndromes rather than a broad range of birth defects.[33] Many fetuses and infants with presumed congenital Zika virus infection have had a typical pattern, including severe microcephaly, intracranial calcifications, and other brain anomalies, sometimes accompanied by eye findings, redundant scalp skin, arthrogryposis, and clubfoot[15,20-23]; such findings have led authors to use the term "congenital Zika syndrome."[22,34,35] On the basis of clinical details from a limited number of cases, some infants with presumed congenital Zika virus infection have had features that were consistent with fetal brain disruption sequence,[24] a phenotype involving the brain that is characterized by severe microcephaly, overlapping cranial sutures, prominent occipital bone, redundant scalp skin, and considerable neurologic impairment.[20,22] For example, 11 of 35 infants (31%) with microcephaly whose cases were reported to a Brazil Ministry of Health registry had excessive and redundant scalp skin,[20] a finding that is not typically seen in other forms of microcephaly.[36] These findings suggest an interruption of cerebral growth, but not in that of the scalp skin, after an injury (e.g., viral infection, hyperthermia, or vascular disruption) that occurred after the initial formation of brain structures, followed by partial collapse of the skull. The fetal brain disruption sequence is rare; only 20 cases were identified in a literature review in 2001.[24]

Shepard's fourth criterion refers to the association between a rare exposure and a rare defect; we conclude that this criterion also has been met. The concept behind this criterion is that a rare defect occurring after a rare exposure during pregnancy implies causation because of the unlikelihood of the two rare events occurring together.[10] Microcephaly is a rare defect that is estimated to occur in 6 infants per 10,000 liveborn infants in the United States.[25] Zika virus would not be a rare exposure among women living in Brazil during the Zika virus outbreak. However, reports of adverse birth outcomes among travelers who spent only a limited time period in an area where there is active Zika virus transmission are consistent with Zika virus being a rare exposure.[16,18,19]

A recent report is illustrative: a pregnant woman traveled for 7 days to Mexico, Guatemala, and Belize during her 11th week of gestation and had a positive test for Zika virus immunoglobulin M (IgM) antibodies 4 weeks later. On fetal ultrasonography and magnetic resonance imaging performed at 19 to 20 weeks of gestation, severe brain anomalies were diagnosed in the fetus, and the pregnancy was terminated at 21 weeks of gestation. Microcephaly was not present at the time of pregnancy termination, but the head circumference had decreased from the 47th percentile at 16 weeks of gestation to the 24th percentile at 20 weeks of gestation (a finding that is consistent with the timing of diminishing head sizes in previous cases),[14] which suggests that microcephaly would have developed in the fetus had the pregnancy continued.[16] In this woman, Zika virus would be considered a rare exposure, and her fetus had a rare outcome.

The last three criteria are helpful if they are present, but they are not considered to be es-

sential. The fifth criterion, the need for an animal model that shows teratogenicity, has not been met. Although animal models have shown that Zika virus is neurotropic,[27,28] no studies that tested for teratogenicity in an animal model have been published, although studies are under way. The sixth criterion, that the association should make biologic sense, is clearly met here. Other viral infections have had similar effects (microcephaly and eye problems).[24,26] In addition, pathologic evidence supports this association: Zika virus RNA has been seen in damaged mononuclear cells (presumably glial cells and neurons) in the brains of newborns with microcephaly,[17] and the virus appears to be neurotropic.[17,19] Live Zika virus has been cultured from the brain of a fetus with severe brain anomalies after maternal infection at 11 weeks of gestation.[16] Furthermore, Zika virus efficiently infects neural progenitor cells and produces cell death and abnormal growth, thus providing a possible mechanism for microcephaly.[29] The seventh criterion, proof in an experimental system that the agent acts in an unaltered state, is aimed at medications or chemical exposures and does not apply to infectious agents. Thus, given Shepard's criteria as a framework, criteria 1, 3, and 4 have been satisfied — evidence that is considered sufficient to identify an agent as a teratogen.

OTHER CRITERIA

Other criteria can also be used to assess this relationship. Koch's postulates, developed in the late 19th century, are often cited as necessary to show causation in infectious disease; however, many authors have noted the need for Koch's postulates to be updated to accommodate modern technologies.[37-39] The Bradford Hill criteria[40] provide another framework to assess causation; Frank et al. recently used these criteria to assess the relationship between prenatal Zika virus infection and microcephaly and concluded that additional information was needed to assume that the relationship was causal.[41] However, several key pieces of evidence have become available since they performed their analysis, including two epidemiologic studies,[2,14] a study of the effects of Zika virus on neural progenitor cells,[29] and a case report of a fetus with brain anomalies and decreasing head size from whose brain live Zika virus was isolated.[16] On the basis of our update of their analysis, which incorporates newly available evidence (Table 2), nearly all the relevant criteria have been met, with the exception of the presence of experimental evidence. However, Hill emphasizes that meeting all nine criteria is not necessary[40]; instead, the criteria should serve as a framework to assess when the most likely interpretation of a relationship is causation.

ASSESSMENT OF CRITERIA

Thus, on the basis of a review of the available evidence, using both criteria that are specific for the evaluation of potential teratogens[9] and the Bradford Hill criteria[40] as frameworks, we suggest that sufficient evidence has accumulated to infer a causal relationship between prenatal Zika virus infection and microcephaly and other severe brain anomalies. Also supportive of a causal relationship is the absence of an alternative explanation; despite the extensive consideration of possible causes, researchers have been unable to identify alternative hypotheses that could explain the increase in cases of microcephaly that were observed first in Brazil and then retrospectively in French Polynesia, and now in preliminary reports that are being investigated in Colombia.[1,2,42]

Moving from a hypothesis that Zika virus is linked to certain adverse outcomes to a statement that Zika virus is a cause of certain adverse outcomes allows for direct communications regarding risk, both in clinical care settings and in public health guidance, and an intensified focus on prevention efforts, such as the implementation of vector control, the identification of improved diagnostic methods, and the development of a Zika virus vaccine.[44] In addition, after recognizing a causal relationship between Zika virus infection and adverse pregnancy and birth outcomes, we can focus research efforts on other critical issues: First, understanding the full spectrum of defects caused by congenital Zika virus infection; if Zika virus is similar to other teratogens, an expansion of the phenotype would be expected (e.g., with the congenital rubella syndrome, the phenotype was expanded from cataracts to include other findings such as hearing loss, congenital heart defects, and microcephaly).[11] Second, quantifying the relative and absolute risks among infants who are born to women who were infected at different times during pregnancy. Third, identifying factors that

Table 2. Bradford Hill Criteria for Evidence of Causation as Applied to the Relationship between Zika Virus Infection and Microcephaly and Other Brain Anomalies*

Criterion	Evidence	Criterion Met?
Strength of association	A recent epidemiologic study from French Polynesia suggests a strong association between prenatal Zika virus infection and microcephaly (estimated risk ratio, approximately 50).[2] The substantial increase in the number of cases of microcephaly and other brain anomalies that have been associated with the Zika virus outbreak in Brazil suggests a strong association.[1,2]	Yes
Consistency	Two epidemiologic studies, one from Brazil and one from French Polynesia,[2,14] support the association between prenatal Zika virus infection and microcephaly and other serious brain anomalies. The observed increase in the number of cases of microcephaly after outbreaks of Zika virus infection in Brazil and French Polynesia, as well as preliminary reports of cases in Colombia, support consistency.[1,2,42] Case reports of Zika virus infection in fetuses or infants with microcephaly or other brain anomalies who were born to mothers who traveled to areas of active Zika virus transmission support consistency.[16,18,19]	Yes
Specificity	Other causes of microcephaly exist; however, on the basis of clinical descriptions that are available for a small number of infants with presumed congenital Zika virus infection,[20] the clinical phenotype linked to the Zika virus appears to be an unusual form of microcephaly that is consistent with the fetal brain disruption sequence.	Yes
Temporality	Zika virus infection in mothers during pregnancy precedes the finding of microcephaly or other brain anomalies in fetuses or infants.[14-20] Zika virus outbreaks in Brazil and French Polynesia preceded the increase in the number of cases of microcephaly.[1,2]	Yes
Biologic gradient	Infection is a phenomenon that is either present or absent; there is no dose–response relationship. No data are available regarding whether women with an increased viral load have a higher risk of adverse pregnancy or birth outcomes.	NA
Plausibility	Findings are similar to those seen after prenatal infection with some other viral teratogens (e.g., cytomegalovirus and rubella virus).[26] Evidence that Zika virus infects neural progenitor cells and produces cell death and abnormal growth,[29] along with evidence of Zika virus in brains of fetuses and infants with microcephaly, on the basis of on immunohistochemical staining and identification of Zika virus RNA and live virus,[16,17,19] provides strong biologic plausibility.	Yes
Coherence	No results in an animal model of effects of Zika virus on pregnancy have yet been published, but animal models have shown that Zika virus is neurotropic,[27,28] a finding that is consistent with prenatal Zika virus infection causing microcephaly and other brain anomalies. Zika virus infects neural progenitor cells and produces cell death and abnormal growth,[29] a finding that is consistent with a causal relationship between Zika virus infection and microcephaly.	Yes
Experiment	No experimental animal model of Zika virus teratogenicity is available.	No
Analogy	No other flavivirus has been shown to definitively cause birth defects in humans,[4] but flaviviruses, Wesselsbron and Japanese encephalitis viruses, have been shown to cause stillbirth and brain anomalies in animals.[43] Findings are similar to those seen after prenatal infection with other viral teratogens (e.g., cytomegalovirus, rubella virus).[26]	Yes

* The criteria listed here were proposed by Hill.[40] We have updated a recent analysis by Frank et al.[41]

modify the risk of an adverse pregnancy or birth outcome (e.g., coinfection with another virus, preexisting immune response to another flavivirus, genetic background of the mother or fetus, and severity of infection). Addressing these issues will improve our efforts to minimize the burden of the effects of Zika virus infection during pregnancy.

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PERSPECTIVE

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Rethinking schizophrenia

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How will we view schizophrenia in 2030? Schizophrenia today is a chronic, frequently disabling mental disorder that affects about one per cent of the world's population. After a century of studying schizophrenia, the cause of the disorder remains unknown. Treatments, especially pharmacological treatments, have been in wide use for nearly half a century, yet there is little evidence that these treatments have substantially improved outcomes for most people with schizophrenia. These current unsatisfactory outcomes may change as we approach schizophrenia as a neurodevelopmental disorder with psychosis as a late, potentially preventable stage of the illness. This 'rethinking' of schizophrenia as a neurodevelopmental disorder, which is profoundly different from the way we have seen this illness for the past century, yields new hope for prevention and cure over the next two decades.

The challenge of creating a vision of schizophrenia for 2030, which I attempt here, is a difficult one. There is certainly a risk in predicting scientific progress—the most important discoveries will probably be ones we cannot imagine today. But it is equally true that we can use past experience and the present state of knowledge to predict some aspects of the future. For schizophrenia, our knowledge base in 2010 is mostly based on clinical observation.

Schizophrenia is a syndrome: a collection of signs and symptoms of unknown aetiology, predominantly defined by observed signs of psychosis. In its most common form, schizophrenia presents with paranoid delusions and auditory hallucinations late in adolescence or in early adulthood. These manifestations of the disorder have changed little over the past century.

A century ago we had large public institutions for serious mental illness, tuberculosis and leprosy. Of these three, today only mental illness, especially schizophrenia, remains unchanged in prevalence and disability[1].

Sustained recovery occurs in less than 14% within the first five years following a psychotic episode[2]. Longer-term outcomes may be marginally better: a large international 25-year follow-up study reported an additional 16% with late-phase recovery[3]. Throughout Europe, less than 20% of people with schizophrenia are employed[4]. A large US study found nearly 20% homeless in a one-year follow up[5]. And a recent report from a patient advocacy group reported that in the US those with serious mental illness were three times more likely to be found in the criminal justice system than in hospitals. (http://www.treatmentadvocacycenter.org)

Although many have attributed this lack of progress to failed systems of care (http://www.mentalhealthcommission.gov/), we still do not have a basic understanding of the pathophysiology of the disorder and therefore lack the tools for curative treatment or prevention needed for most people with schizophrenia. If we are to transform outcomes by 2030, we can start by offering individuals and families challenged by serious mental illness a candid account of the current state of knowledge and a thoughtful consideration of future prospects.

One-hundred years of schizophrenia

The history of schizophrenia says more in many ways about the perspectives of the observer than the observed. In the late nineteenth century, Kraepelin defined "dementia praecox" or premature dementia as distinct from the insanity of tertiary syphilis or the cyclic, non-deteriorating psychosis of manic depressive illness[6]. Bleuler, who coined the term schizophrenia in the early twentieth century, was less convinced of its deteriorating course but emphasized the notion of a fundamental disorder of thought and feeling, which every psychiatrist for decades learned as the four 'a's—disturbances of associations, affect, ambivalence and autistic isolation[7]. These early formulations emerging before the split between neurology and psychiatry were consistent with the notion of a mental disorder rooted in brain pathology. Yet for much of the twentieth century, with the predominance of psychoanalytic theory, the study of the mind ignored the brain. Schizophrenia was a psychotic reaction, a fragmented ego due to a rejecting or ambivalent mother and treatments included re-mothering to build a stable ego[8].

In the second half of the twentieth century, with the emergence of neuroleptic drugs, the pendulum swung in the other direction—a focus on brain chemistry deemphasized the mind. Schizophrenia was considered a 'dopamine disorder' based on the psychosis-inducing effects of dopamine-releasing drugs, such as amphetamine, and the anti-psychotic efficacy of a score of drugs that blocked the dopamine D2 receptor[9]. This neurochemical view of schizophrenia yielded medications that transformed the treatment of psychosis, allowing patients to be treated outside of hospitals and, in some cases, resulting in remission of the major symptoms of the illness. Early neuroleptic medications, examples of which are chlorpromazine and haloperidol, have been increasingly replaced by 'atypical' antipsychotics that have fewer extrapyramidal side effects (such as tremor and rigidity) but usually do not seem to be significantly more efficacious than the original dopamine D2 receptor antagonists[10]. Although both conventional and atypical antipsychotics reliably reduce delusions and hallucinations, they have not enhanced functional recovery (for example, employment) for people with schizophrenia. One explanation is that the disability of schizophrenia is largely due to cognitive deficits, such as problems with attention and working memory, which these drugs fail to improve.

A focus on cognitive symptoms has led to a more recent hypothesis of schizophrenia as a 'glutamate disorder' (reviewed in ref. 11) Healthy volunteers given low doses of NMDA receptor antagonists, such as ketamine, manifest select aspects of schizophrenia, including some of the attentional and memory problems. Conversely, agents that modulate the glycine modulatory site on the NMDA receptor have been reported to reduce some of the cognitive symptoms of schizophrenia. The theory is that schizophrenia, particularly the cognitive symptoms of the disorder, may result from low activity of the NMDA receptor on GABA inhibitory interneurons in the prefrontal cortex.

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Although there can be little argument that medications have transformed the treatment of psychosis, research focusing on the drugs instead of the illness has thus far yielded too little progress on the pathophysiology of schizophrenia. It is not clear, for instance, that either dopamine D2 receptors or interneuron NMDA receptors are related to the cause of this disorder. Although post-mortem studies have consistently reported a loss of GABA and reductions in key enzymes for glutamate biosynthesis, potentially consistent with the glutamate hypothesis, these changes may represent the effects of chronic illness or treatment of the disorder rather than the cause of schizophrenia[11].

One approach that could separate cause from effect is genetics. Just as neuropharmacology dominated schizophrenia research in the late twentieth century, genetics has been a leading focus in the first decade of this century. Although in the 'genomic era' such a shift was inevitable, it was also presaged by a generation of twin and family studies demonstrating high heritability[12,13]. Reported concordance in monozygotic twins was roughly 50%, never the 100% figure one might expect for a Mendelian disorder, but considerably higher than dizygotic twins or siblings[14].

High heritability has not, however, translated into a satisfying search for genetic lesions. Although early genome-wide or candidate-gene studies searching for common variants associated with schizophrenia were mostly disappointing, either because early findings failed to replicate or large-scale studies failed to detect genome-wide significance, recent international consortia combining single nucleotide polymorphism (SNP) data from several independent studies have found replicable associations with genes of the major histocompatability complex (MHC) region on chromosome 6p21.3-22.1, *ZNF804A* on chromosomes 2q32.1, neuregulin 1 (*NRG1*) on chromosome 8, as well as transcription factor 4 (*TCF4*) on 18q21.2 (refs 15–17). Other studies have reported SNPs in candidate genes associated either with schizophrenia or a broad phenotype of psychosis, notably for genes within the neuregulin–ERBB4 signalling pathway[18], synaptic protein genes (for example, *NRX1* (also known as *PNO1*))[19], a potassium channel (*KCNH2*)[20] and many other brain-expressed proteins (for example, dysbindin)[21]. Currently, at least 43 candidate genes have been identified, but individual effect sizes are consistently modest (http://www.schizophreniaforum.org/res/sczgene/TopResults.asp), especially relative to the evidence for high heritability[22,23]. Epistatic or additive effects of these variants may explain more of the risk, but results thus far on individual variants from case–control studies have not been useful for understanding an individual's risk for schizophrenia.

In addition to the many reports of common single nucleotide variations, many rare structural genomic variants, such as copy number variants and translocations, have been described in schizophrenia (reviewed in ref. 24). These rare variants seem to have larger causative effects than previously reported SNPs, but most are not specific to schizophrenia and some occur only in a single family. The diversity and private nature of these mutations preclude a simple genetic explanation for schizophrenia, but these findings may yield important clues to pathophysiology. For instance, although the *DISC1* translocation that confers very high risk for psychiatric disorder has been detected in only a single Scottish family, this private mutation has revealed important mechanisms of disease and identified a site where common variation may also confer risk (reviewed in ref. 25). Even more encouraging, the consistent reports that so many of these structural variants affect genes implicated in brain development may predict the future of schizophrenia research.

Mapping the pathophysiology of schizophrenia

A starting point for mapping the pathophysiology of schizophrenia can begin with the increasing recognition that this is a neurodevelopmental disorder, or perhaps more accurately a collection of neurodevelopmental disorders that involve alterations in brain circuits. Although Feinberg[26], Weinberger[27] and Murray[28] proposed this approach more than two decades ago, the field is only now providing the evidence and recognizing the implications of shifting to a neurodevelopmental approach[29,30].

Psychosis nearly always emerges in late adolescence or early adulthood, with a peak between ages 18 and 25, when the prefrontal cortex is still developing. We still do not understand all of the changes in normal or abnormal cortical development during this period. Attempts to map functional connectivity defined by imaging the default network demonstrate little integration until after age nine[31]. Longitudinal neuroimaging studies demonstrate changes in grey matter density until the mid-twenties with the prefrontal cortex being the last to mature[32]. The cellular basis for the observed reduction in grey-matter density with magnetic resonance imaging (MRI) is not clear although classical anatomical post-mortem studies indicate that both synaptic elimination and increased myelination continue into early adulthood[33,34]. Whereas the literature from human post-mortem neuroanatomy of adolescence is scant, studies in non-human primate brain demonstrate that the refinement of circuits during early adulthood includes pruning of asymmetric (excitatory) synapses, proliferation of inhibitory circuits and the continued elaboration of pyramidal dendrites as targets of inhibitory input[35–37]. Together these observations indicate that this late stage of brain maturation involves a careful calibration of excitatory–inhibitory balance in the cortex with the prefrontal cortex the last region to mature (Fig. 1). As one potentially relevant modulator of this balance, dopamine innervation of the prefrontal cortex increases markedly during adolescence[38,39].

Although schizophrenic psychosis usually emerges between ages 18–25, several longitudinal population-based studies indicate that problems are evident much earlier. For instance, a recent report from a 45-year follow up of a Copenhagen birth cohort demonstrated that adults with schizophrenia have a history of delayed maturation including delayed developmental milestones in the first year[40]. Data from the Dunedin birth cohort, consistent with many previous studies[41], indicated that IQ is reduced early and persistently in children destined to develop schizophrenia[42]. These precursors of schizophrenia are subtle and non-specific, but the consistency of the finding supports the hypothesis that psychosis does not emerge from a completely healthy brain.

The emerging picture from genetic studies also indicates that early brain development is affected. As noted earlier, many of the structural variants associated with schizophrenia implicate neurodevelopmental genes involved with neuronal proliferation, migration, or synapse formation[43]. Even genes that are not exclusively developmental seem to influence schizophrenia by their early disruption[44]. In a particularly intriguing example, Niwa *et al.*[45] reported that a transient knockdown of *DISC1* in the frontal cortex in the pre- and perinatal mouse brain led to neurochemical and behavioural disruptions emerging in early adulthood. Moreover, some of the vulnerability alleles of candidate genes, such as *NRG1* and *DISC1*, seem to selectively influence splice variants expressed predominantly in developing cortex, implicating isoforms that show large developmental changes in expression in the prefrontal cortex[46–48]. As a final link to development, the genetics of schizophrenia overlaps with the genetics of autism and other neurodevelopmental disorders[19,49]. It is unclear why the same genetic variation associated with many different neurodevelopmental syndromes is manifested in some by age 3 years (autism) and in others after age 18 years (schizophrenia). Presumably there are genomic modifiers or possibly environmental influences that determine the specific syndrome. The study of discordant twins may yield important information for understanding the mismatches between genotype and phenotype.

Environmental factors identified so far have also implicated prenatal or perinatal events. Maternal malnutrition during famine[50,51], infections in the second trimester[52], perinatal injury[53] and cytokine exposure[54] have all been associated with subsequent increased risk for schizophrenia. Most of these effects are modest (less that twofold increase in risk) and none seem specific for schizophrenia, but in aggregate they demonstrate that early adverse experiences, including mid-gestational insults, are a risk factor for psychosis occurring two decades later. Gene-by-environment studies may demonstrate more robust effects[55], but an even more promising approach may be epigenetic maps indicating the 'scars' of early experience or the stochastic changes emerging across development[56]. As an example, a gene disrupted by a rare copy number variant in autism was found to be repressed by hypermethylation in a

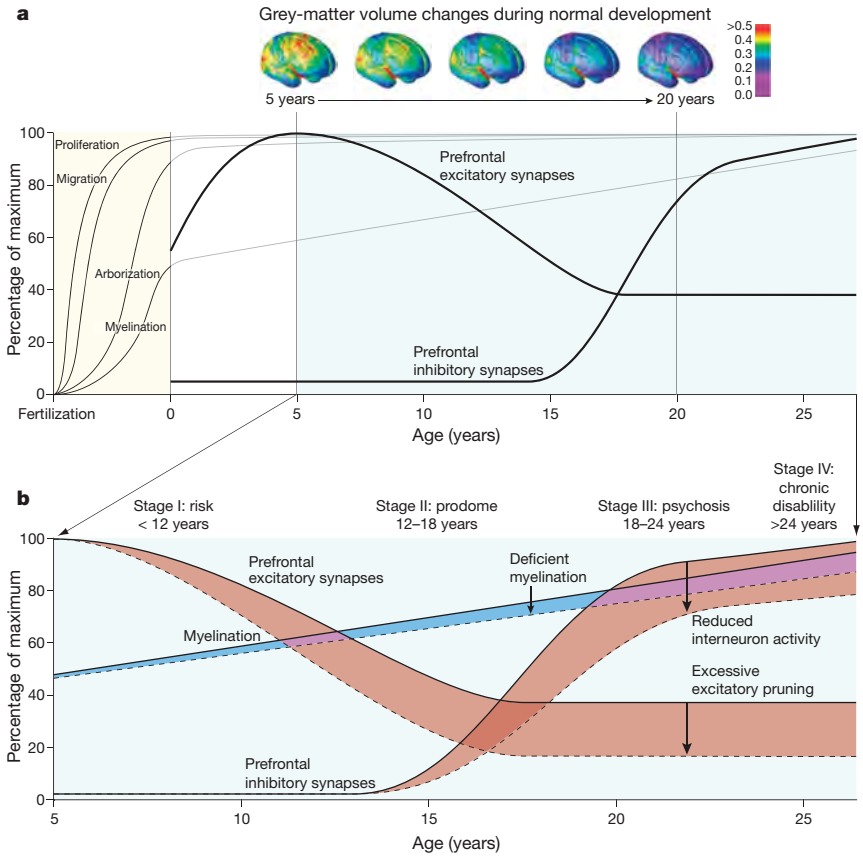

Figure 1 | Neurodevelopmental model of schizophrenia. **a**, Normal cortical development involves proliferation, migration, arborization (circuit formation) and myelination, with the first two processes occurring mostly during prenatal life and the latter two continuing through the first two post-natal decades. The combined effects of pruning of the neuronal arbor and myelin deposition are thought to account for the progressive reduction of grey-matter volume observed with longitudinal neuroimaging. Beneath this observed overall reduction, local changes are far more complex. Data from human and non-human primate brain indicate increases in inhibitory and decreases in excitatory synaptic strength occurring in prefrontal cortex throughout adolescence and early adulthood, during the period of prodrome and emergence of psychosis. **b**, The trajectory in children developing schizophrenia could include reduced elaboration of inhibitory pathways and excessive pruning of excitatory pathways leading to altered excitatory–inhibitory balance in the prefrontal cortex. Reduced myelination would alter connectivity. Although some data support each of these possible neurodevelopmental mechanisms for schizophrenia, none has been proven to cause the syndrome. Detection of prodromal neurodevelopmental changes could permit early intervention with potential prevention or preemption of psychosis.

large number of children with autism who had a perfectly normal genomic sequence[57].

The model that emerges from this neurodevelopmental perspective is that of an early insult, a latent period through much of neural development, and the emergence of psychosis in late adolescence or early adulthood. One possibility is a lesion early in development that does not manifest until a much later developmental stage when compensatory changes can no longer suffice. Thompson and Levitt[58] have called this developmental allostasis. A second, not mutually exclusive possibility is that the developmental lesion influences a pathway or a regulatory process, such as the fine tuning of excitatory and inhibitory synapses in the prefrontal cortex, which may have only subtle effects until a precise balance is required in late adolescence. Current data cannot distinguish between these two options, but either way a neurodevelopmental perspective implies the importance of timing and the opportunity for earlier intervention and prevention.

How will we map the trajectory of schizophrenia as a neurodevelopmental disease? Recent longitudinal studies of children with a rare, early-onset form of schizophrenia have used neuroimaging to identify differences in the trajectory of brain development. In these studies, children with schizophrenia seem to undergo excessive losses of grey matter and cortical thinning, essentially overshooting the normal pattern described earlier for adolescents[59,60]. These findings, although intriguing, are limited in that they do not reveal the changes before psychosis.

An opportunity for mapping earlier phases of the trajectory can be found in velocardiofacial syndrome, a syndrome associated with a microdeletion of chromosome 22q11 (reviewed in ref. 61). Approximately 30% of children with a microdeletion of 22q11 will develop a form of schizophrenia that clinically and neurocognitively cannot be distinguished from the idiopathic disorder[62,63]. Most of these children are detected as toddlers because of their cardiac disease. Important insights into the trajectory from risk to disorder may be gained from ongoing longitudinal studies of these children comparing cognitive, affective and neural development in those who do and do not develop psychosis among this cohort with a similar genomic deletion.

Will animal studies reveal the neurodevelopmental trajectory of schizophrenia? Unlike the many disorders in medicine that can be modelled in mice or flies, an animal model of schizophrenia seems unlikely. Indeed, aspects of the prefrontal neuroanatomy and the executive function deficits of schizophrenia seem to be distinctively human. This is not to say that studies in animals, especially non-human primates, will be unimportant for schizophrenia. We lack fundamental information on the normal development of the forebrain, from the timing and geography of gene expression to the patterns of circuit formation under various environmental conditions. With current technology, these critical developmental maps will only be derived from studies in animals. Animal studies can also aid the study of abnormal development. Whereas animal models of schizophrenia are not likely, 'model animals' such as mice and flies

engineered with schizophrenia candidate genes will be highly informative for linking genetic variation to changes in cell and circuit function. For instance, mice with homologous deletions to the 22q11 lesion of velocardiofacial syndrome manifest differences in circuit formation and synaptic plasticity[64,65]. Such model animals will not only yield studies of disease mechanisms but opportunities for new treatment development.

Increasingly, however, it seems that humans may prove the best animal for modelling schizophrenia. Just as genes can create relevant models in non-human animals, genes can serve as a portal to mapping the pathophysiology of schizophrenia in cells from patients with the disorder. With induced pluripotent stem cells derived from fibroblasts of patients with schizophrenia, we should soon be able to study many different neural cell types, including their development, functional connections and response to perturbations. These cells do not need to recreate the disorder in a dish; they need only yield disordered molecular networks to reveal targets for developing new therapies. Through identifying new targets and high-throughput screening of existing small molecule libraries, we can expect the next generation of treatments for schizophrenia to be based on molecular pathophysiology rather than serendipity.

The stages of schizophrenia

Perhaps the most fundamental change from re-conceptualizing schizophrenia as a neurodevelopmental disorder is the notion of trajectory of illness. If the disorder begins in prenatal or perinatal life, then the psychosis of late adolescence must be seen not as the onset but as a late stage of the disorder. Indeed, we can begin to hypothesize four stages of schizophrenia, from risk to prodrome to psychosis to chronic disability[66] (Table 1). At present, the diagnosis is based on the symptoms and signs of psychosis. With the advent of biomarkers and new cognitive tools as well as the identification of subtle clinical features, we are beginning to detect earlier stages of risk and prodrome.[67]

The earliest stage is risk, before detectable deficits. In 2010 we do not have the risk architecture of this syndrome, but we can begin to see some of the outlines, based on genomics. Beyond the rare, highly penetrant mutations (for example, *DISC1* and the 22q11 deletion), epistatic interactions between more common, less penetrant variations may yield higher predictions of risk than our current list. Of course, the 50% concordance rate of homozygous twins reminds us that genomics will not predict all forms of risk. Identifying environmental factors, detecting critical epigenomic modifications, or mapping neural circuit differences may render more of the blueprint for risk, much as the algorithms for coronary artery disease use family history, plasma lipids and dietary history. The extent to which the risk factors for schizophrenia will be modifiable in the sense that we can reduce the risk for coronary artery disease or lung cancer remains to be seen. And although this earliest stage may not involve distress or help-seeking, longitudinal studies have begun to identify subtle but reproducible evidence for behavioural and cognitive problems in early childhood[68–70]. To define this earliest stage we will need to define the full architecture of individual risk: genetic and epigenetic biomarkers, cognitive indicators and physiological predictors of vulnerability to the disorder.

Over the past two decades, the pioneering work of McGorry and his colleagues[71,72] has established the prodrome of schizophrenia as a valid second stage of the illness before psychosis. Whether defined as ultra-high risk or pre-psychosis, the prodrome is now identified based on changes in thoughts (for example, bizarre ideas falling short of psychotic ideation), social isolation and impaired functioning (for example, reduced school performance). Recognizing that these features might seem endemic to adolescence, the Structured Interview for Prodromal Syndromes (SIPS) was developed to distinguish high risk for psychosis from more common adolescent angst[73]. Recently a large multi-site project in the United States of 291 adolescents followed for 2.5 years reported that the prodrome represented a 405-fold increase in risk (relative to the general population) and that a combination of three factors (for example, genetic risk with recent functional decline, unusual thought content, and either suspicion/paranoia or reduced social functioning) resulted in a positive predictive power for conversion to psychosis of 74–81% (ref. 74). The addition of biomarkers, detected with functional or structural neuroimaging (reviewed in ref. 75), or the use of neuropsychological tests of reaction time or verbal memory[76,77] may enhance detection and increase the predictive power. Given the high rate of behavioural distress in adolescence and the likelihood that many with prodromal symptoms will either mature out of them or develop other disorders, the challenge is to increase sensitivity for detecting ultra-high risk while not sacrificing specificity[78]. Specificity is a challenge: many of those who seek help for prodromal symptoms will develop other forms of psychopathology, not schizophrenia. What will we need to define this stage of schizophrenia? Although standardized clinical assessments will help and longitudinal imaging may yield biomarkers, it is likely that cognitive changes, such as reductions in working memory, may be the best predictor of the psychotic phase of schizophrenia[79]. Over the next few years, cognitive neuroscience will have a critical role in providing the tools for increasing the sensitivity and specificity of the schizophrenic prodrome[80].

It is unclear to what extent intervening during the prodrome will either prevent or forestall psychosis. Results from single-site trials of atypical antipsychotics[81], antidepressants[82], lithium[83] and cognitive behaviour therapy[84] have had, at best, modest effects in reducing symptoms or preventing conversion to psychosis. A recent randomized double-blind placebo-controlled 12-week trial of long-chain omega-3 polyunsaturated fatty acids reported a 12-month conversion to psychosis in 2 of 41 (4.9%) individuals in the treated group versus 11 of 40 (27.5%) individuals in the placebo group[85]. Although promising, the overall rate of conversion (13 of 81) is lower than that observed in most prodromal cohorts. Current efforts to use cognitive remediation may identify a low-risk approach that could be used even if specificity were low[86]. An innovative, broad effort on youth mental health in Australia is addressing the issues of false positives, low specificity and potential stigma from early diagnosis by developing community-based, resilience-based interventions[66].

Stage III of schizophrenia is psychosis manifested by hallucinations, delusions, disorganization of thought and behaviour, and psychomotor abnormalities. It is now clear that negative symptoms (loss of will, anhedonia, poverty of thought) and cognitive deficits (reduced working

Table 1 | Stages of schizophrenia

	Stage I	Stage II	Stage III	Stage IV
Features	Genetic vulnerability Environmental exposure	Cognitive, behavioural and social deficits Help-seeking	Abnormal thought and behaviour Relapsing–remitting course	Loss of function Medical complications Incarceration
Diagnosis	Genetic sequence Family history	SIPS Cognitive assessment Imaging	Clinical interview Loss of insight	Clinical interview Loss of function
Disability	None/mild cognitive deficit	Change in school and social function	Acute loss of function Acute family distress	Chronic disability Unemployment Homelessness
Intervention	Unknown	Cognitive training? Polyunsaturated fatty acids? Family support?	Medication Psychosocial interventions	Medication Psychosocial interventions Rehabilitation services

Stage I, pre-symptomatic risk; stage II, pre-psychotic prodrome; stage III, acute psychosis; stage IV, chronic illness.

memory, poor cognitive control) are core features of the disorder that account for much of the long-term morbidity and poor functional outcomes[87]. Although the avolitional component of the disorder may define a special subgroup[88], there is a new consensus that the negative symptoms and cognitive aspects of pathology are major unmet therapeutic needs[89,90]. If risk is analogous to hyperlipidemia, prodrome comparable to angina, then psychosis can be thought of as myocardial infarction with frequent residual loss of function. In spite of consistently positive acute responses to antipsychotic medications and psychosocial treatments, relapse rates approach 80% (ref. 2). Cognitive deficits and negative symptoms, whether preceding or emerging with psychosis seem, at best, only modestly responsive to current antipsychotic treatments[91,92]. The most urgent research priority in the near term will be effective treatments for the cognitive deficits, including the lack of insight that often inhibits adherence to both medication and psychosocial treatments.

Stage IV of schizophrenia involves chronic disability. In 1988, in the height of the AIDS epidemic, the editor of *Nature* noted that "schizophrenia is arguably the worst disease affecting mankind, even AIDS not excepted."[93] Not all individuals progress to this late stage of the illness, but for those who do the disability is not only psychiatric but medical. The oft-cited psychiatric deficits lead to unemployment, homelessness and incarceration, as noted earlier. A Finnish birth cohort study recently reported a 7% rate of suicide in schizophrenia, accounting for 50% of all deaths by age 39 (ref. 94). The medical complications of chronic schizophrenia are less well known. In 2010, smoking and obesity are epidemic among people with schizophrenia, with estimates of nicotine dependence ranging from 58–90% (ref. 95) and metabolic syndrome (obesity, hyperlipidemia, hyperglycemia and hypertension) present in 40% (ref. 96). Life expectancy for those with serious mental illness has been estimated at 56 years, approximately 25 years of premature mortality resulting usually from cardiopulmonary disease or other chronic medical conditions[97]. Importantly, many of the medical complications of schizophrenia can be prevented through tobacco cessation, dietary management and programs to manage cardiovascular health.

Schizophrenia in 2030

What is the prognosis of schizophrenia for 2030? I will venture a few predictions based on hope more than knowledge and recognizing that progress in understanding and treating schizophrenia may come from distant fields of science that have not yet been engaged in this area (Fig. 2).

Prevention

Judging from the success of preventive approaches to cardiac death and disability, refocusing our approach to schizophrenia on early detection and early intervention could yield substantial improvements in outcomes over the next decade or two. This will, of course, require sensitive and specific diagnostic tools as well as safe and effective interventions. The diagnostic tools for schizophrenia, like the diagnostic tools for cardiovascular risk, will probably require a combination of approaches, including measures of genetic risk, imaging the efficiency of neural circuits, and, probably most specifically, early cognitive changes. Interventions that include an aggressive focus on cognition along with family support may prove surprisingly effective for preempting or forestalling psychosis. Although a 'statin-like' medication would be an unambiguous breakthrough, we should not assume that a medication will be more effective than harnessing the developing brain's intrinsic plasticity for reversing the neural trajectory that leads from risk to prodrome. If the preemptive interventions are as effective as what we have today for coronary artery disease and if these are widely deployed, by 2030 we should expect a profound reduction in first-episode psychosis.

Reducing the cognitive deficits

The disability of schizophrenia in 2010 results more from the under-recognized and treatment-refractory cognitive deficits than from the more obvious and frequently treatable positive symptoms[98]. Over the next decade, potentially leveraging current research on cognition in Alzheimer's disease, we can expect a series of pharmacological and nonpharmacological interventions that will reverse or mitigate the cognitive deficits of the disorder. Early initiation of these interventions will be transformative, but even in patients following psychosis, cognitive remediation may enhance employment, social inclusion and function in the community[99]. With interventions that reduce cognitive deficits, by 2030 we will be combining somatic, psychosocial and cognitive treatments with a goal of curing this disease for many patients.

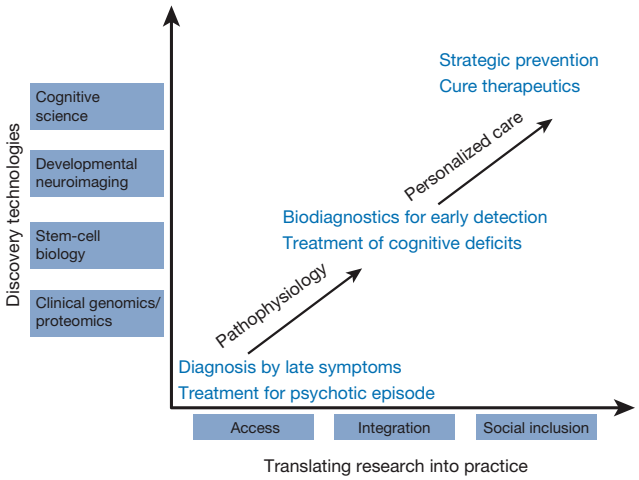

Figure 2 | A vision for schizophrenia over the next two decades. Currently diagnosis follows psychosis (stage III) and treatment focuses on reducing psychotic symptoms. The use of discovery technologies, which have already transformed the understanding and treatment of many other medical disorders, can transform our understanding of schizophrenia, yielding earlier diagnosis (stages I or II) with treatments focused on the cognitive deficits of this disorder. The ultimate goal, however, is cure and prevention based on an understanding of individual risk and the development of personalized care. In practice this means not only identifying risk and preemptive interventions but ensuring access to these interventions, integrating care and ensuring full social inclusion for people at any stage of the schizophrenia trajectory.

Integration of care

One of the most egregious aspects of schizophrenia treatment in 2010 is the fragmentation of care, with medical care separated from psychiatric care and both isolated from psychosocial interventions, such as supportive employment and family education, which have a strong evidence base for effectiveness. Arguably, doing better with current treatments is our best short-term strategy for enhancing outcomes. A large multi-site effort in the United States, the Recovery After Initial Episode of Schizophrenia (RAISE) project, is developing a best-practices approach to bundled services that should provide some data about how much this can enhance outcomes. One can hope that in the near future, well before 2030, we will see all aspects of care being integrated in a continuous way, as is done increasingly for diabetes and other chronic disorders. Note, however, that the treatment of schizophrenia involves challenges not observed in most other chronic diseases. Denial of illness, paranoia, irrational thoughts, deficits in executive function and disruptive behaviour can all be part of the syndrome of untreated schizophrenia, complicating care for those with this disorder. Better treatments, not only better systems, will be necessary for better outcomes.

Stigma

Just as warehousing in institutions is mostly a memory today, imagine if the stigma associated with schizophrenia today were gone in 2030. In contrast to many other medical disorders, schizophrenia today too often defines a person rather than describing the illness. Our fear of psychosis or disruptive behaviour may keep us from seeing the heroic struggle that

people with this disorder face just to survive amidst the internal chaos and panic that is part of this chronic illness. Our expectations of these citizens are low: they should stay out of jail, on their medications and not distress their families, friends and fellow citizens. They deserve better. As a vision for 2030, people who suffer from any stage of schizophrenia will be considered to be educable, employable and capable of living in intimate relationships with others.

Will we still use the term schizophrenia in 2030? The accumulating genomic evidence indicates that there may be scores or hundreds of lesions contributing to this final common syndrome. The clinical evidence supports the possibility that what we have labelled schizophrenia for the past century may be many different disorders with different outcomes[88]. And the stigma associated with the diagnosis, and the past history of misunderstanding and mistreatment also indicate that a change in the term may be advisable. In 2002, the Japanese terms for schizophrenia 'Seishin-Bunretsu-Byo' ('mind-split disease') was replaced officially by 'Togo-Shitcho-Sho' ('integration disorder')[100]. Some evidence indicates that this name change led to reduced stigma, in that fewer people associated the new name with criminality[100].

Although semantic changes can be helpful, the transformations needed for those with this serious illness are likely to require not only a better label but better science (Fig. 2). In the next decade the challenge will be to integrate the impact of genetics, experience and development to identify a complete blueprint of the risk architecture of this syndrome. This should lead to a new taxonomy, identifying the many disorders within the syndrome we now call 'schizophrenia' and hopefully replacing this aggregate label with a series of more precise diagnoses based on pathophysiology. We need a personalized and preemptive approach, based on understanding and detecting individual risk and facilitated by safe and effective interventions for those in stages I and II of this disorder. In the meantime, we can create policies for social inclusion, family support and continuity of care to ensure that those in later stages of the syndrome have the best chance for recovery. Importantly, if recovery defined as a life in the community is our primary goal today, for 2030 our goals must include prevention, preemption and cure.

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- Votes
- Nominations
- Calendars & Schedules
- Congressional Record
- Treaties
- Bills & Resolutions
- Appropriations Bills
- Legislative Process
- Public Disclosure
- Active Legislation

U.S. Senate Roll Call Votes 102nd Congress - 2nd Session XML

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Vote Summary

Question: On the Conference Report (H.R. 2507 Conference Report)

Vote Number:	115	**Vote Date:**	June 4, 1992, 03:39 PM
Required For Majority:	1/2	**Vote Result:**	Conference Report Agreed to

Measure Number: H.R. 2507 (National Institutes of Health Revitalization Amendments of 1991)

Measure Title: A bill to amend the Public Health Service Act to revise and extend the programs of the National Institutes of Health, and for other purposes.

Vote Counts:		
	YEAs	85
	NAYs	12
	Not Voting	3

Vote Summary By Senator Name By Vote Position By Home State

Alphabetical by Senator Name

Adams (D-WA), **Yea**
Akaka (D-HI), **Yea**
Baucus (D-MT), **Yea**
Bentsen (D-TX), **Yea**
Biden (D-DE), **Yea**
Bingaman (D-NM), **Not Voting**
Bond (R-MO), **Nay**
Boren (D-OK), **Yea**
Bradley (D-NJ), **Yea**
Breaux (D-LA), **Yea**
Brown (R-CO), **Yea**
Bryan (D-NV), **Yea**
Bumpers (D-AR), **Yea**
Burdick, Quentin S (D-ND), **Yea**
Burns (R-MT), **Nay**
Byrd (D-WV), **Yea**
Chafee (R-RI), **Yea**
Coats (R-IN), **Nay**
Cochran (R-MS), **Yea**
Cohen (R-ME), **Yea**
Conrad (D-ND), **Yea**
Craig (R-ID), **Nay**
Cranston (D-CA), **Yea**
D'Amato (R-NY), **Nay**
Danforth (R-MO), **Yea**
Daschle (D-SD), **Yea**
DeConcini (D-AZ), **Yea**
Dixon (D-IL), **Yea**
Dodd (D-CT), **Yea**
Dole (R-KS), **Yea**
Domenici (R-NM), **Yea**
Durenberger (R-MN), **Not Voting**
Exon (D-NE), **Yea**
Ford (D-KY), **Nay**
Fowler (D-GA), **Yea**
Garn (R-UT), **Yea**
Glenn (D-OH), **Yea**
Gore (D-TN), **Yea**
Gorton (R-WA), **Yea**
Graham (D-FL), **Yea**
Gramm (R-TX), **Nay**
Grassley (R-IA), **Yea**
Harkin (D-IA), **Yea**
Hatch (R-UT), **Nay**
Hatfield (R-OR), **Yea**
Heflin (D-AL), **Yea**
Helms (R-NC), **Not Voting**
Hollings (D-SC), **Yea**
Inouye (D-HI), **Yea**
Jeffords (R-VT), **Yea**
Johnston (D-LA), **Yea**
Kassebaum (R-KS), **Yea**
Kasten (R-WI), **Yea**
Kennedy (D-MA), **Yea**
Kerrey (D-NE), **Yea**
Kerry (D-MA), **Yea**
Kohl (D-WI), **Yea**
Lautenberg (D-NJ), **Yea**
Leahy (D-VT), **Yea**
Levin (D-MI), **Yea**
Lieberman (D-CT), **Yea**
Lott (R-MS), **Yea**
Lugar (R-IN), **Yea**
Mack (R-FL), **Yea**
McCain (R-AZ), **Yea**
McConnell (R-KY), **Yea**
Metzenbaum (D-OH), **Yea**
Mikulski (D-MD), **Yea**
Mitchell (D-ME), **Yea**
Moynihan (D-NY), **Yea**
Murkowski (R-AK), **Yea**
Nickles (R-OK), **Nay**
Nunn (D-GA), **Yea**
Packwood (R-OR), **Yea**
Pell (D-RI), **Yea**
Pressler (R-SD), **Nay**
Pryor (D-AR), **Yea**
Reid (D-NV), **Yea**
Riegle (D-MI), **Yea**
Robb (D-VA), **Yea**
Rockefeller (D-WV), **Yea**
Roth (R-DE), **Yea**
Rudman (R-NH), **Yea**
Sanford (D-NC), **Yea**
Sarbanes (D-MD), **Yea**
Sasser (D-TN), **Yea**
Seymour (R-CA), **Yea**
Shelby (D-AL), **Yea**
Simon (D-IL), **Yea**
Simpson (R-WY), **Yea**
Smith (R-NH), **Nay**
Specter (R-PA), **Yea**
Stevens (R-AK), **Yea**
Symms (R-ID), **Nay**
Thurmond (R-SC), **Yea**
Wallop (R-WY), **Yea**
Warner (R-VA), **Yea**
Wellstone (D-MN), **Yea**
Wirth (D-CO), **Yea**
Wofford (D-PA), **Yea**

Vote Summary By Senator Name By Vote Position By Home State

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The Votes page of the Virtual Reference Desk provides voting procedure information, research guides, and essays about historic votes.

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The Votes category on the Statistics page features facts and figures about votes made by Senators.

Grouped By Vote Position

YEAs ---85

Adams (D-WA)	Gore (D-TN)	Moynihan (D-NY)
Akaka (D-HI)	Gorton (R-WA)	Murkowski (R-AK)
Baucus (D-MT)	Graham (D-FL)	Nunn (D-GA)
Bentsen (D-TX)	Grassley (R-IA)	Packwood (R-OR)
Biden (D-DE)	Harkin (D-IA)	Pell (D-RI)
Boren (D-OK)	Hatfield (R-OR)	Pryor (D-AR)
Bradley (D-NJ)	Heflin (D-AL)	Reid (D-NV)
Breaux (D-LA)	Hollings (D-SC)	Riegle (D-MI)
Brown (R-CO)	Inouye (D-HI)	Robb (D-VA)
Bryan (D-NV)	Jeffords (R-VT)	Rockefeller (D-WV)
Bumpers (D-AR)	Johnston (D-LA)	Roth (R-DE)
Burdick, Quentin S (D-ND)	Kassebaum (R-KS)	Rudman (R-NH)
	Kasten (R-WI)	Sanford (D-NC)
Byrd (D-WV)	Kennedy (D-MA)	Sarbanes (D-MD)
Chafee (R-RI)	Kerrey (D-NE)	Sasser (D-TN)
Cochran (R-MS)	Kerry (D-MA)	Seymour (R-CA)
Cohen (R-ME)	Kohl (D-WI)	Shelby (D-AL)
Conrad (D-ND)	Lautenberg (D-NJ)	Simon (D-IL)
Cranston (D-CA)	Leahy (D-VT)	Simpson (R-WY)
Danforth (R-MO)	Levin (D-MI)	Specter (R-PA)
Daschle (D-SD)	Lieberman (D-CT)	Stevens (R-AK)
DeConcini (D-AZ)	Lott (R-MS)	Thurmond (R-SC)
Dixon (D-IL)	Lugar (R-IN)	Wallop (R-WY)
Dodd (D-CT)	Mack (R-FL)	Warner (R-VA)
Dole (R-KS)	McCain (R-AZ)	Wellstone (D-MN)
Domenici (R-NM)	McConnell (R-KY)	Wirth (D-CO)
Exon (D-NE)	Metzenbaum (D-OH)	Wofford (D-PA)
Fowler (D-GA)	Mikulski (D-MD)	
Garn (R-UT)	Mitchell (D-ME)	
Glenn (D-OH)		

NAYs ---12

Bond (R-MO)	D'Amato (R-NY)	Nickles (R-OK)
Burns (R-MT)	Ford (D-KY)	Pressler (R-SD)
Coats (R-IN)	Gramm (R-TX)	Smith (R-NH)
Craig (R-ID)	Hatch (R-UT)	Symms (R-ID)

Not Voting - 3

Bingaman (D-NM)	Durenberger (R-MN)	Helms (R-NC)

Vote Summary By Senator Name By Vote Position By Home State

Grouped by Home State

Alabama:	Heflin (D-AL), **Yea**	Shelby (D-AL), **Yea**
Alaska:	Murkowski (R-AK), **Yea**	Stevens (R-AK), **Yea**
Arizona:	DeConcini (D-AZ), **Yea**	McCain (R-AZ), **Yea**
Arkansas:	Bumpers (D-AR), **Yea**	Pryor (D-AR), **Yea**
California:	Cranston (D-CA), **Yea**	Seymour (R-CA), **Yea**
Colorado:	Brown (R-CO), **Yea**	Wirth (D-CO), **Yea**
Connecticut:	Dodd (D-CT), **Yea**	Lieberman (D-CT), **Yea**
Delaware:	Biden (D-DE), **Yea**	Roth (R-DE), **Yea**
Florida:	Graham (D-FL), **Yea**	Mack (R-FL), **Yea**
Georgia:	Fowler (D-GA), **Yea**	Nunn (D-GA), **Yea**
Hawaii:	Akaka (D-HI), **Yea**	Inouye (D-HI), **Yea**
Idaho:	Craig (R-ID), **Nay**	Symms (R-ID), **Nay**
Illinois:	Dixon (D-IL), **Yea**	Simon (D-IL), **Yea**
Indiana:	Coats (R-IN), **Nay**	Lugar (R-IN), **Yea**
Iowa:	Grassley (R-IA), **Yea**	Harkin (D-IA), **Yea**
Kansas:	Dole (R-KS), **Yea**	Kassebaum (R-KS), **Yea**
Kentucky:	Ford (D-KY), **Nay**	McConnell (R-KY), **Yea**
Louisiana:	Breaux (D-LA), **Yea**	Johnston (D-LA), **Yea**
Maine:	Cohen (R-ME), **Yea**	Mitchell (D-ME), **Yea**
Maryland:	Mikulski (D-MD), **Yea**	Sarbanes (D-MD), **Yea**
Massachusetts:	Kennedy (D-MA), **Yea**	Kerry (D-MA), **Yea**
Michigan:	Levin (D-MI), **Yea**	Riegle (D-MI), **Yea**
Minnesota:	Durenberger (R-MN), **Not Voting**	Wellstone (D-MN), **Yea**
Mississippi:	Cochran (R-MS), **Yea**	Lott (R-MS), **Yea**

Missouri:	Bond (R-MO), **Nay**	Danforth (R-MO), **Yea**
Montana:	Baucus (D-MT), **Yea**	Burns (R-MT), **Nay**
Nebraska:	Exon (D-NE), **Yea**	Kerrey (D-NE), **Yea**
Nevada:	Bryan (D-NV), **Yea**	Reid (D-NV), **Yea**
New Hampshire:	Rudman (R-NH), **Yea**	Smith (R-NH), **Nay**
New Jersey:	Bradley (D-NJ), **Yea**	Lautenberg (D-NJ), **Yea**
New Mexico:	Bingaman (D-NM), **Not Voting**	Domenici (R-NM), **Yea**
New York:	D'Amato (R-NY), **Nay**	Moynihan (D-NY), **Yea**
North Carolina:	Helms (R-NC), **Not Voting**	Sanford (D-NC), **Yea**
North Dakota:	Burdick, Quentin S (D-ND), **Yea**	Conrad (D-ND), **Yea**
Ohio:	Glenn (D-OH), **Yea**	Metzenbaum (D-OH), **Yea**
Oklahoma:	Boren (D-OK), **Yea**	Nickles (R-OK), **Nay**
Oregon:	Hatfield (R-OR), **Yea**	Packwood (R-OR), **Yea**
Pennsylvania:	Specter (R-PA), **Yea**	Wofford (D-PA), **Yea**
Rhode Island:	Chafee (R-RI), **Yea**	Pell (D-RI), **Yea**
South Carolina:	Hollings (D-SC), **Yea**	Thurmond (R-SC), **Yea**
South Dakota:	Daschle (D-SD), **Yea**	Pressler (R-SD), **Nay**
Tennessee:	Gore (D-TN), **Yea**	Sasser (D-TN), **Yea**
Texas:	Bentsen (D-TX), **Yea**	Gramm (R-TX), **Nay**
Utah:	Garn (R-UT), **Yea**	Hatch (R-UT), **Nay**
Vermont:	Jeffords (R-VT), **Yea**	Leahy (D-VT), **Yea**
Virginia:	Robb (D-VA), **Yea**	Warner (R-VA), **Yea**
Washington:	Adams (D-WA), **Yea**	Gorton (R-WA), **Yea**
West Virginia:	Byrd (D-WV), **Yea**	Rockefeller (D-WV), **Yea**
Wisconsin:	Kasten (R-WI), **Yea**	Kohl (D-WI), **Yea**
Wyoming:	Simpson (R-WY), **Yea**	Wallop (R-WY), **Yea**

Vote Summary By Senator Name By Vote Position By Home State

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I hereby certify that on June 7, 2016, I electronically filed the foregoing *Amicus Curiae* brief with the Clerk of the Court for the United States Court of Appeals for the Ninth Circuit by using the CM/ECF system. I certify that all participants in the case are registered CM/ECF users and that service will be accomplished by the CM/ECF system.

Dated: June 7, 2016 CROWELL & MORING LLP

s/ Jason C. Murray
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Attorneys for *Amici Curiae*