ISSUES IN LAW & MEDICINE

Human Fetal Tissue from Elective Abortions in Research and Medicine: Science, Ethics, and the Law

Tara Sander Lee, Ph.D., et al.

VERBATIM

In the Supreme Court of the United States Brief of Amicus Curiae, In Support of Louisiana Department of Heath and Hospitals

American Association of Pro-Life Obstetricians & Gynecologists

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Verbatim

Human Fetal Tissue from Elective Abortions in Research and Medicine: Science, Ethics, and the Law

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ABSTRACT: Since the U.S. Supreme Court issued its landmark decision in 1973 to legalize abortion, over 60 million preborn have been killed by elective abortion. While alive in the womb, these preborn are abandoned and not protected under current law. But once aborted, their body parts are a highly esteemed and prized commodity amongst certain members of the scientific community. Moral discourse is disregarded for the sake of science. The public have been lulled and lured into believing that this practice must continue in order to understand and develop cures for some of the most debilitating diseases of our day. But they are mistaken. This practice is not necessary, especially in light of numerous noncontroversial alternatives. Here, we expose and consider the false and misleading claims regarding human fetal tissue (HFT) in research from scientific, legal, and ethical points of view. We endeavor deeply to understand the depth of the injustice in this practice and what forces promote and maintain it; and by revealing and understanding these forces, we set forth how these inhumane practices can be ended. An accurate portrayal of the history of HFT use in research is provided, along with a close examination of the current state of this practice under existing laws. The serious societal implications are also discussed, which will worsen beyond

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comprehension if these practices are allowed to continue. The timeliness of this information cannot be overstated, and a thorough understanding is paramount for anyone who desires to know the facts about HFT in research and medicine and its detrimental impact for humanity.

Introduction

We are at a scientific, ethical, and legal crossroads regarding the use of abortion-derived human fetal tissue (HFT) for research and medical treatment. The central argument used by scientists in favor of this research is that fetal tissue contains a higher number of immature cells that are highly proliferative, less immunogenic, and more adaptable compared to postnatal tissue cells. Therefore, fetal tissue and its derived cells (*i.e.*, fetal stem cells, tissue-specific cells) are considered an ideal source that could offer a better platform for research and therapeutic development compared to alternatives. The enticement is to harness the capacities of a developing human fetus, by collecting fresh (or primary) tissue immediately after induced death, with the hope of finding potential cures for some of the most debilitating diseases and developmental disorders, such as Alzheimer's, Parkinson's, HIV/AIDS, and autism. As Temple and Goldstein argue, "If we are to achieve medical advances for currently incurable diseases, the path forward must include fetal tissue research, for which continued public support is most critical at this time."[1] This same argument dates back to 100 years ago, when primary fetal tissues were collected from elective abortions within minutes after the procedure and used for experiments. Some of these experiments yielded positive and promising results, but many failed, faced significant technical problems, and resulted in serious complications in the case of clinical trials. The complete set of observations and results is seldom disclosed by scientists who advocate for human fetal research.

Nonetheless, regardless of whether scientific studies failed or succeeded with aborted fetal tissue, the ends do not justify the means when the research relies on electively induced human deaths, even if presently legal. HFT has been collected and used in a number of cases from fetuses at developmental ages where fetal surgery is now used to correct medical problems and save fetal lives[2] and at stages where science now demonstrates that the unborn fetus can feel pain.[3] Results or therapies derived from past, present, and future research using fetal tissue from unborn fetuses terminated by elective abortion will be forever morally and ethically compromised. So the following moral dilemma stands. Is it ethical to perform research on human fetuses whose in-

[1] S. Temple, L. S. B. Goldstein, Why we need fetal tissue research. *Science* 363 (6424), 207 (2019).

[2] C. Malloy, M. C. Wubbenhorst, T. Sander Lee, The Perinatal Revolution. *Issues in Law and Medicine* 34 (1), 15-41 (2019).

[3] S. W. G. Derbyshire, J. C. Bockmann. Reconsidering fetal pain. *J Med Ethics* 46, 3–6 (2020).

tentional killing was a mandatory prerequisite for acquiring their tissue—especially in light of so many other alternatives, including fetuses and neonates that die of natural causes (*i.e.*, miscarriage, stillbirth) or discarded tissues made available from increasingly common pre- and post-natal surgeries? This practice is also problematic for patients and doctors, who must choose between violating their consciences or accepting treatments that are conflicted by abortion-derived materials.

Here, we provide an in depth treatment of the scientific, legal, and ethical issues surrounding the use of HFT from elective abortions in research. The goal is to accurately portray the landscape of the field—including the myths, errors, and injudicious pursuits. A major result of our analysis is the basis for a sound rebuttal of many false and misleading claims made by scientists, who have an interest in continuing to have access to abortion-derived fetal tissue for their research despite many widely available, well-established, effective alternatives.

To better understand the practice of HFT in research, we examine some of the earliest historical accounts of using human cadavers, including fetuses, for scientific experimentation. The science and practice of using HFT in research is then outlined in great detail, so that one can fully appreciate the various legal, ethical, and societal issues and implications discussed in the final sections.

Human Dissection and Exploitation of the Marginalized in Society

The initial practice of human dissection dates back to the third century B.C. in ancient Greece, where scientists Herophilus of Chalcedon and Erasistratus of Ceos moved beyond dissecting animals and performed the first systematic dissections on human beings. In a quest for discovery, they conducted dissections on human cadavers, as well as human vivisections on condemned criminals who were kept alive for the sole purpose of experimentation and scientific research. As Heinrich Von Staden of Yale University reports, people of their time justified human dissection of the living and the dead by "claiming that both 'hidden' and 'evident' causes of disease must be known, as must the 'natural activities' of the internal parts, if one is to treat patients effectively."[4] Von Staden also points to the intellectual and cultural atmosphere of the time, when many scholars placed emphasis on innovation and "engaged in relatively unshackled speculation or experimentation."

Dissection on human cadavers was nearly abandoned after the death of Herophilus and Erasistratus, but then revived centuries later with the establishment of several academic universities.[5] With increased pressure from anatomists in the rapidly growing medical schools worldwide, acts of legislation were passed in England and the United States to legally allow access to cadavers for dissection. Often, the cadavers of the

[4] H. von Staden. The Discovery of the Body: Human Dissection and Its Cultural Contexts in Ancient Greece. *The Yale Journal of Biology and Medicine* 65, 223-241 (1992).

[5] S. K. Ghosh, Human cadaveric dissection: a historical account from ancient Greece to the modern era. *Anat Cell Biol* 48, 153-169 (2015).

most marginalized groups within society that were least advantaged and most vulnerable (*e.g.*, prisoners, poor, disabled, Blacks, mentally ill) were allowed to be used in research.[6]

The church played an important role during this time, since they sponsored many of the universities conducting cadaveric dissections. In a Papal Bull (*De Sepulturis*), while Pope Boniface VIII (1294-1303) did not condemn dissection of cadavers for medical research, he rather wrote against the abuse of corpses that was occurring during that time (*e.g.*, cutting up bodies of the dead, cooking them so the bones would be separated from the flesh and carrying the bones back for burial in their homelands).[7] Such written works are equivalent to current laws that call for respect of human remains in research.

The bodies of fetuses and infants became an especially prized commodity amongst anatomists and academics in the late 1700s and 1800s, as discussed in Dittmar and Mitchell's review.[8] Illegitimate and unwanted infants killed by infanticide were collected from unwed mothers. Pregnant women and fetuses were examined postmortem, often acquired in secret and without consent, for medical museum collections. The unclaimed bodies of abandoned infants who died of disease in charitable hospitals were also readily available for dissection.

Fast forward to the 20th and 21st centuries, where quests for innovation, scientific discovery, and finding cures to human disease *still* remain as justification for the practice of using human fetal bodies from abortions. The only difference is that the aborted fetus is the present-day marginalized faction in our society—easily obtainable and exorbitantly available, with millions of abortions occurring worldwide and nearly 900,000 annually in the U.S. alone.[9]

Human Fetal Tissue in Research

As described earlier, cadaveric human fetuses were collected and used by anatomists centuries prior. But the first attempt to use HFT for treating a patient with transplantation took place in 1921 in the United Kingdom. The experiment failed in trying to treat Addison's disease, using a "graft removed from a foetus just after death."[10] Other early studies collected HFT to study the polio virus. In 1936, Albert Sabin described the collection of brain, lungs, kidneys, liver, and spleen from second-trimester

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[6] Ibid.

[7] Boniface VIII. *Papal Bull De Sepulturis*, 1299, described on p 459 of The Catholic Encyclopedia: An International Work of Reference on the Constitution, Doctrine, Discipline, and History of the Catholic Church. Edited by Charles G. Herbermann, Edward A. Pace, Conde B. Pallen, Thomas J. Shahan, John J. Wynne. The Universal Knowledge Foundation, Copyright 1907, 1913 by The Encyclopedia Press. New York.

[8] J. M. Dittmar, P. D. Mitchell, From cradle to grave via the dissection room: the role of foetal and infant bodies in anatomical education from the late 1700s to early 1900s. *J Anat* 229, 713-722 (2016).

[9] R. K. Jones, E. Witwer, J. Jerman, Abortion Incidence and Service Availability in the United States, *Guttmacher Institute*. Available at *https://www.guttmacher.org/sites/default/files/report_pdf/abortion-incidence-service-availability-us-2017.pdf*. [Accessed February 19, 2020].

[10] A. F. Hurst, W. E. Tanner, A. A. Osman, Addison's disease with severe anemia treated by suprarenal grafting, *Proc R Soc Med* 15, 19 (1922).

fetuses "obtained aseptically by Cesarean section."[11] In 1952, Drs. Weller, Enders *et al*. reported the dissection of fetuses "obtained under sterile precautions at the time of abdominal hysterotomy for therapeutic indications" in order to collect skin, connective tissue, muscle, intestine, and brains to study the propagation of polio virus in suspended cell cultures.[12] At this same time, Drs. Thicke, Duncan, and Rhodes studied the polio virus in cell lines established from human fetuses in which "no macerated specimens were used" and in many, "the heart was still beating at the time of receipt in the virus laboratory."[13] Early published studies using HFT were often nondescript and lacked transparency regarding the details of where and how they obtained the fetuses, and even calls into question whether the fetuses used were miscarried or aborted.

The Law and Access to Human Fetal Tissue

The inroads and continued use of HFT in research in the U.S. was, and still is, closely tied to accessibility of federal funds. In 1988, the Reagan administration rejected a request from the National Institutes of Health (NIH) for permission to transplant fetal tissue into the brain of a patient with severe Parkinson's disease, and shortly thereafter, issued a moratorium on all research using tissue from aborted fetuses.[14] A 21-person NIH special advisory panel then convened to hear scientific, legal, and ethical views from invited speakers as well as testimony from representatives of public interest groups.[15] A panel report was written, containing the responses and considerations, along with the panel vote, for each of the assistant secretary's 10 questions assigned to the committee. The report also included two dissenting statements (by David Bleich and by James Bopp and James Burtchaell); and a final dissenting letter (Daniel Robinson).[16] The final panel report was submitted to the Director's Advisory Committee of NIH and after review, concluded that fetal tissue research was "acceptable."

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[11] A. B. Sabin, P. K. Olitsky, Cultivation of Poliomyelitis Virus in vitro in human embryonic tissue. *Proc Soc Exp Biol Med* 34, 357-359 (1936).

[12] T. H. Weller, J. F. Enders, F. C. Robbins, M. B. Stoddard, Studies on the Cultivation of Poliomyelitis Viruses in Tissue Culture : I. The Propagation of Poliomyelitis Viruses in Suspended Cell Cultures of Various Human Tissue. *Journal of Immunology* 69, 645-671 (1952).

[13] J. C. Thicke, D. Duncan, W. Wood, A. E. Franklin, A. J. Rhodes, Cultivation of Poliomyelitis Virus in Tissue Culture; Growth of the Lansing Strain in Human Embryonic Tissue. *Canadian Journal of Medical Science* 30, 231-245 (1952).

[14] 42 U.S.C. 289g-1 and g-2; and D. Colburn, The Fetus. *The Washington Post*. Available at *https://www.washingtonpost.com/archive/lifestyle/wellness/1988/10/18/the-fetus/7a519117-637e-4ca1-9dd5-e433e9ec-14ba/*. Deposited 18 October 1988. [Accessed February 19, 2020].

[15] J. F. Childress, "Deliberations of the Human Fetal Tissue Transplantation Research Panel." Biomedical Politics. Institute of Medicine (US) Committee to Study Decision Making; Hanna KE, editor. Washington (DC): National Academies Press (US) (1991). Available at: *https://www.ncbi.nlm.nih.gov/books/NBK234204/* [Accessed February 21, 2020].

[16] Ibid; opinion of James Bopp can also be found at: J. Bopp Jr., Fetal Tissue Transplantation and Moral Complicity with Induced Abortion, Chapter 4 in "The Fetal Tissue Issue: Medical and Ethical Aspects," ed. by Peter Cataldo and Albert Moraczewski, 1994.

In 1993, President Clinton signed a memorandum lifting the Reagan moratorium, thus allowing the NIH to fund HFT research with federal tax dollars. As part of the NIH Revitalization Act of 1993 (42 USC 289g-1), general provisions were established (based on recommendations from the original ethics committee under President Reagan) regarding research conducted or supported by the NIH involving research on the transplantation of HFT for therapeutic purposes.[17] This law involves any HFT "obtained pursuant to a spontaneous abortion or induced abortion or pursuant to a stillbirth."

Under this law, specific conditions must be met in order for the HFT to be used in research.[18] First and foremost, the donor (woman having the abortion) must give informed consent to donate the fetal tissue for use in research. In addition, the physician must declare that the consent of the woman for the abortion preceded consent for donation of the fetal tissue for use in research. The physician must also declare that no alteration of the timing, method, or procedures used to terminate the pregnancy were made solely for purposes of obtaining the tissue. The researcher and tissue recipient must also declare that he or she had no part in any decisions as to the timing, method, or procedures used to terminate the pregnancy for the purposes of research. It is also unlawful for any person who solicits or knowingly acquires, receives, or accepts the donation to have provided "valuable consideration" for the costs associated with the abortion. While the term "valuable consideration" is not specifically defined, the law does allow "reasonable payments" associated with transportation, processing, preservation, quality control, and storage of HFT.

Exposure of a Fetal Tissue Market by Undercover Investigation

Chris Wallace of ABC's news magazine, "20/20," conducted a hidden-camera investigation into alleged profiteering from the sale of fetal tissue and organs that aired on March 8, 2000.[19] The main target was Dr. Miles Jones, a Missouri pathologist, and his Illinois-based company, Opening Lines, which served as a middleman, obtaining fetal tissue from abortion clinics and then providing it to medical research labs. The company sold several different types of fetal tissue under their fee-for-service schedule, and even offered discounts if tissue was not intact. The greater value attached to intact fetal bodies provides an economic motivation for the physician to conduct the abortion procedure in a way that recovers as much intact tissue as possible. The next day on March 9, 2000, the Committee on Commerce of the House of Representatives held a subcommittee hearing on the question of "Fetal Tissue: Is It Being Sold In Violation of Federal Law?," where a bill was introduced called the "Human Fetal Tissue Reporting

[17] National Institutes of Health Revitalization Act of 1993. Public Law 103-43, 10 June 1993. Available at *https://history.nih.gov/research/downloads/pl103-43.pdf*. [Accessed February 19, 2020].

[18] Ibid.

[19] ABC 20/20 report-Parts for Sale. March 8, 2000. "People Make Thousands of Dollars Off the Sale of Fetal Body Parts." Video available at *https://www.youtube.com/watch?v=mltRMb5GDKE* and https://www.newsbusters.org/blogs/nb/matthew-balan/2015/08/06/flashback-2000-chris-wallace-aired-undercover-report-abc-about.

and Disclosure Act" (HR3980).[20] The bill was referred to the House Committee on Commerce and Subcommittee on Health and Environment, but never reached the floor for a vote. Thereafter, this uncovered HFT market garnered no significant media attention for another 15 years.

During this time, research continued using HFT collected from elective abortions. The most common method of abortion used when collecting fetal tissue parts was the dilation and evacuation (D&E) surgical procedure. The majority of D&E cases involve significant fragmentation of the fetus, including collapse of the skull bones and fragmentation of the soft brain tissue; many of the thoracic and abdominal viscera are also loosened such that they are no longer positioned in their respective body cavities.[21] Nevertheless, parts of fetal brain, liver, kidney, lung, skin, and thymus tissue could still be identified and collected by researchers for their studies. Some researchers reported trying to mitigate problems with timing of tissue collection and fragmentation by "prior scheduling of elective abortions" and informing the physician performing the abortion procedure to "try to maintain brain integrity."[22] Others avoided fragmented fetal body parts altogether and would collect fetuses delivered intact by induced abortion, which were then immediately dissected or taken back to the researcher's lab for dissection.[23]

Verbatim descriptions of methods used to collect the tissues are highlighted below:

> *Mid-gestation (11–22 wk, n = 57) human fetal ductus arteriosus and ascending aorta were obtained at elective terminations of pregnancy in healthy women. Prostaglandins were not used during the terminations. Cervical ripening was performed using laminaria (compressed seaweed). Ductus and aorta samples were isolated and snap frozen in liquid nitrogen within 30 minutes of termination. Gestational age was determined by fetal foot length.*[24]

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[20] "Fetal Tissue: Is It Being Sold in Violation of Federal Law?" Hearing before the Subcommittee on Health and Environment of the House Committee on Commerce, 106th Congress, 9 March 2000. Available at *https://www.govinfo.gov/content/pkg/CHRG-106hhrg63102/html/CHRG-106hhrg63102.htm*. [Accessed February 19, 2020.

[21] L. M. Ernst, Lori Gawron, M. K. Fritsch, Pathologic examination of fetal and placental tissue obtained by dilation and evacuation. *Arch Pathol Lab Med* 137, 326-337 (2013).

[22] J. Lu, L. C. Delli-Bovi, J. Hecht, R. Folkerth, V. L. Sheen, Generation of Neural Stem Cells from Discarded Human Fetal Cortical Tissue. *Journal of Visualized Experiments (JoVE)*. 51 (2011). A video of the procedure using human fetal brains is available at *http://www.jove.com/details.php?id=2681*. [Accessed February 19, 2020].

[23] B. Gridelli et al., Efficient Human Fetal Liver Cell Isolation Protocol Based on Vascular Perfusion for Liver Cell–Based Therapy and Case Report on Cell Transplantation. *Liver Transplantation* 18, 226-237 (2012); N. Waleh et al., Patterns of gene expression in the ductus arteriosus are related to environmental and genetic risk factors for persistent ductus patency, *Pediatr Res* 68(4), 292–297 (2010); C. Pekor, J. C. Gerlach, I. Nettleship, E. Schmelzer, Induction of Hepatic and Endothelial Differentiation by Perfusion in a Three-Dimensional Cell Culture. Model of Human Fetal Liver. *Tissue Engineering: Part C* 21 (7),705-715 (2015); G. Pietros, C. Chinnaci, Report on Liver Cell Transplantation Using Human Fetal Liver Cells, Peggy Stock and Bruno Christ (eds.), *Hepatocyte Transplantation: Methods and Protocols, Methods in Molecular Biology*, vol. 1506, Chapter 20, Springer Science+Business Media New York (2017).

[24] N. Waleh et al., Patterns of gene expression in the ductus arteriosus are related to environmental and genetic risk factors for persistent ductus patency, *Pediatr Res* 68(4), 292–297 (2010).

. . .

…the fetuses went to the pathologists for routine analysis after liver removal. The specimens were placed into sterile bags containing University of Wisconsin liver storage solution, and each specimen was transported on ice immediately after the abortion to minimize the transfer time until cell isolation. Because we obtained the tissue from intact abdomens and removed the livers surgically under cGMP conditions, the tissue could be obtained in a sterile manner. The logistics of the transfer of the fetus to the cell isolation facility required no more than 1 hour…[25]

In the summer of 2015, The Center for Medical Progress (CMP) released new undercover videos exposing undisclosed features of the supplying of HFT in research. Citizen journalists David Daleiden and Sandra Merritt, both of CMP, went undercover as potential buyers for aborted fetal tissues and recorded their conversations with abortion providers and third-party vendors,[26] covering such topics as abortion procedures, tissue collection practices, and pricing.

CMP's undercover videos renewed widespread national awareness of the gruesome nature of the practice of buying and selling HFT. Through interviews with high-level executives and abortion providers the videos revealed a cynical culture of disregard for human fetuses by high-level executives and senior abortion practitioners. There was substantial public outcry, with nearly universal agreement—on all sides of the abortion debate—to uphold the existing laws that prohibit profiteering from HFT trafficking. Many also condemned the entire practice and called for a ban on all research that involved using HFT from elective abortions. The exposé also renewed efforts to investigate Planned Parenthood's role in this practice, as the largest single provider of abortion services in the United States.

Congressional Investigations

In response to the CMP undercover videos, the United States House of Representatives and Senate independently investigated the practice of HFT trafficking. The House Committee on Energy and Commerce Select Investigative Panel on Infant Lives, chaired by Marsha Blackburn (R-TN), led an investigation with two hearings in 2016 and published a final report.[27] The Senate Judiciary Committee also held an investigation and filed a 2016 report.[28] Both reports provide key information regarding the various agents

[25] B. Gridelli et al., Efficient Human Fetal Liver Cell Isolation Protocol Based on Vascular Perfusion for Liver Cell–Based Therapy and Case Report on Cell Transplantation. *Liver Transplantation* 18, 226-237 (2012).

[26] The Center for Medical Progress. Investigative footage available at *https://www.centerformedicalprogress.org*. [Accessed February 19, 2020].

[27] Final Report, Select Investigative Panel of the Energy & Commerce Committee. US House of Representatives. December 30, 2016. A compilation of activities available at *https://www.govinfo.gov/content/pkg/CPRT-114HPRT24553/html/CPRT-114HPRT24553.htm*. [Accessed February 19, 2020].

[28] Final Report, Committee on the Judiciary United States Senate. December 2016. Available at *https://www.judiciary.senate.gov/imo/media/doc/2016-12-13%20MAJORITY%20REPORT%20-%20Human%20Fetal%20Tissue%20Research%20-%20Context%20and%20Controversy.pdf*. [Accessed February 19, 2020].

and business models of the fetal tissue marketplace. Particular attention is given to the middleman model, which involves (1) abortion clinics that provide the aborted fetus (*e.g.*, Planned Parenthood [PP]), (2) third-party middlemen who collect the aborted fetus from the abortion clinic and process the tissue (*e.g.*, Advanced Bioscience Resources [ABR], StemExpress at that time), and (3) the researcher who pays a middleman for the HFT.

Specific transaction details are provided in the reports. Researchers routinely made payments to tissue procurement organizations (TPOs) for fetal eyes, livers, thymuses, hearts, spinal cords, skin, and brains. In one example, ABR paid $60 to an abortion clinic in 2014 for a 20-week-old fetus. The TPO then processed and resold the brain, eyes, liver, thymus, and lung to five different research clients, charging $2,275 total in "Service Fees." There were additional charges for shipping, disease screening, cleaning, and freezing, but these fees were not provided.[29] Human fetuses are being treated as nothing but purchased commodities.

The Select Investigative Panel reported that abortion providers may have modified abortion procedures, in apparent violation of the law, to increase the likelihood of obtaining an intact infant cadaver (*e.g.*, increase the number of laminaria placed in a patient's cervix to achieve greater dilation). Such modifications would also increase the likelihood that infants were born alive during late second-trimester abortions. This raised the question whether the civil rights of these born alive were violated by abortion providers.[30] The Panel's investigation also found that systematic violations of the Health Insurance Portability and Accountability Act of 1996 (HIPAA) Privacy Rule were committed when the abortion clinics disclosed patients' individually identifiable health information to companies to facilitate efforts to procure HFT for resale. These practices also constitute a serious disregard for the health and privacy of the women of aborted infants, who are also patients.

Fallout for Companies Involved in Human Fetal Trafficking

As a result of these investigations, some companies involved in selling HFT faced state and federal legal sanctions; others made their own decisions to change business practices altogether. In 2017, the *Los Angeles Times* reported that two related companies in California, DaVinci Biosciences and DV Biologics, "reached a $7.785-million settlement with the Orange County district attorney's office over allegations that they illegally sold fetal tissue to companies around the world."[31] The same companies were featured in the CMP tapes for sourcing fetal tissue from PP. "The agreement also [required] the

[29] Final Report, Select Investigative Panel of the Energy & Commerce Committee. US House of Representatives. December 30, 2016. A compilation of activities available at *https://www.govinfo.gov/content/pkg/CPRT-114HPRT24553/html/CPRT-114HPRT24553.htm*. [Accessed February 19, 2020].

[30] Ibid.

[31] D. Langhorne, Firms reach $7.8-million settlement over allegations of selling fetal tissue Los Angeles Times, Deposited 9 December 2017. Available at *https://www.latimes.com/local/lanow/la-me-fetal-tissue-20171209-story.html*. [Accessed February 19, 2020].

companies to admit liability for violations of state and federal laws prohibiting the sale or purchase of fetal tissue for research purposes…"[32] StemExpress, a biomedical tissue procurement firm that sourced electively aborted fetal tissue from PP, severed its ties with PP in the wake of the CMP tapes.[33] The company no longer lists fetal tissues at its website.[34] ABR was contracted by the U.S. Food and Drug Administration (FDA) to source fetal tissue from PP for use in government biomedical research. In 2018, the U.S. Department of Health and Human Services (HHS) revoked the FDA contract with ABR, and the U.S. Department of Justice investigated ABR for criminal wrongdoing.[35]

While we do not propose to litigate any allegations here, these examples do indicate a propensity for abuse arising from the commodification of human remains, specifically those of fetuses who die by elective abortion. Whether or not violations of existing laws have occurred regarding profiteering, privacy, patient safety, *etc.*, the objectification of fetal human beings for the sake of scientific progress is unacceptable.

New Guidelines for Human Fetal Tissue Research

In December 2018, the Subcommittees on Healthcare, Benefits, and Administrative Rules and Government Operations for the House Committee on Oversight and Government Reform held a hearing on "Exploring Alternatives to Fetal Tissue Research." In addition, HHS conducted a comprehensive review of all research involving fetal tissue to ensure consistency with statutes and regulations governing such research and to ensure adequate procedures and oversight.

In June 2019, HHS announced that it would discontinue intramural (*i.e.*, internal) research projects at the NIH that involved primary HFT derived from elective abortions. Taxpayer money could no longer be used by NIH researchers to buy human fetal brain, liver, thymus, or any other desired organ obtained from an elective abortion.[36] NIH would also allow to expire an existing contract for primary HFT research with the University of California at San Francisco. In addition, new extramural (*i.e.*, outside the NIH) grant applications and contracts that proposed to use abortion-derived primary HFT would be subject to a congressionally authorized review by an appointed ethics advisory board.

Most of the intramural NIH research labs impacted by the new HHS rule, *i.e.* those with projects that have previously used abortion-derived primary HFT but can no longer do so, continued to receive millions of dollars in federal funding for non-fetal tissue research.[37] Some of these labs even received *more* funding (for non-fetal tissue

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[32] Ibid.

[33] *https://www.politico.com/story/2015/08/planned-parenthood-fetal-tissue-company-cuts-ties-videos-121371*. [Accessed February 19, 2020].

[34] *https://www.stemexpress.com*. [Accessed February 19, 2020].

[35] *https://www.hhs.gov/about/news/2018/09/24/statement-from-the-department-of-health-and-human-services.html*. [Accessed February 19, 2020].

[36] *https://www.hhs.gov/about/news/2019/06/05/statement-from-the-department-of-health-and-human-services.html*. [Accessed February 19, 2020].

[37] Example:https://projectreporter.nih.gov/project_info_details.cfm?aid=10014196&icde=48030808.

research) in 2019 after the new rule took effect.[38] This outcome demonstrates that important research does not necessarily stop when ethical guidelines are put in place. Science continues to move forward without exploiting HFT from ongoing abortions.

Despite these new government regulations, an estimated $116 million in federal taxpayer money still funds HFT research each year (FY2020) via extramural grants.[39] This money is used to purchase HFT from product suppliers. Primary HFT can be obtained from tissue repositories, including the Birth Defects Research Laboratory at the University of Washington and the Human Fetal Tissue Repository at Albert Einstein College of Medicine. Several universities and affiliated hospitals also provide aborted fetal tissue to researchers (*e.g.*, Yale University School of Medicine, San Francisco General Hospital). And commercial for-profit vendors, like ScienCell Research Laboratories, provide human primary cells isolated from aborted fetal tissue.[40] Fetal tissues from elective abortions can also be requested from biobanks outside the U.S., such as the MRC-Wellcome Trust Human Developmental Biology Resource which collaborates with clinics in the UK to obtain aborted fetuses.[41]

The Procurement of Human Fetal Tissue for Research

Any research application for HFT begins with obtaining the tissue. *Primary* HFT consists of organs, tissues, or cells taken directly from a human fetus, almost always following induced abortion. While it is possible to collect such tissue from fetuses who have died of natural causes (*i.e.*, spontaneous abortion, also known as miscarriage, or stillbirth), this is not the typical practice.

There are several pathways through which a researcher can obtain fetal tissue, as detailed in the Final Report of the Select Investigative Panel convened by the U.S. House of Representatives Energy and Commerce Committee.[42] These include placing a request with a TPO and working directly with a nearby abortion provider. One research institution may also transfer fetal tissue to another research institution. Contracts or less formal arrangements may be established by individual researchers or by their research institutions, most of which are recipients of public funding. In some cases, university medical centers and clinics providing abortions share medical school faculty and residents, and/or the university grants faculty appointments to abortion clinic personnel.

A TPO has relationships with both abortion providers and researchers and serves to collect research-quality tissue from the clinic and provide it to the researcher, thus

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[38] Example:https://projectreporter.nih.gov/project_info_history.cfm?aid=9779708&icde=48031367.

[39] Accessed April 20, 2020, via search on "fetal tissue" at: *http://report.nih.gov/categorical_spending.aspx*.

[40] *https://www.sciencellonline.com/products-services/primary-cells/human.html*. Oral communication with technical staff confirmed cell isolation from aborted fetal tissue, although this information is not disclosed via their website. [Accessed February 19, 2020].

[41] *https://mrc.ukri.org/research/facilities-and-resources-for-researchers/human-developmental-biology-resource/*. [Accessed February 19, 2020].

[42] Final Report, Select Investigative Panel of the Energy & Commerce Committee. US House of Representatives. December 30, 2016. A compilation of activities available at *https://www.govinfo.gov/content/pkg/CPRT-114HPRT24553/html/CPRT-114HPRT24553.htm*. [Accessed February 19, 2020].

acting as a middleman between the two. Some examples from the investigations in 2015-2016 include non-profit organizations like ABR, as well as for-profit companies like StemExpress, Novogenix Laboratories, and DaVinci Biosciences. These can be free-standing entities, or they may be housed within an academic institution, such as the Human Fetal Tissue Repository at the Albert Einstein College of Medicine and the Birth Defects Research Laboratory at The University of Washington, which is the largest provider of HFT in the U.S. and is funded by NIH.[43] In a process similar to ordering supplies from other vendors, a researcher may place a request with a TPO for a desired tissue type and gestational age. To meet this demand for HFT, for-profit TPOs conduct commercial supply business operations; and designated non-profit TPOs conduct essentially the same supply operations. Depending upon the arrangements made between a particular TPO and an abortion provider, TPO employees may provide any or all of the following services: obtain consent from abortion patients regarding donation of the fetal remains for research; inspect the fetal remains and harvest research-quality fetal tissue; prepare and transport fetal tissue to the TPO facility or directly to the researcher; further process the tissue at the TPO facility (*e.g.,* isolate particular cells, test for quality or desired characteristics); store tissue and maintain tissue bank facilities; and perform administrative tasks related to both tissue collection from abortion providers and fulfillment of researcher requests for tissue, including making payments to the abortion provider and receiving payments from research institutions. Some TPOs place employees at the abortion facility to fulfill some of these tasks. TPOs may pay a fee to the abortion provider, either per patient (per consent) or per tissue specimen. When the TPO receives a request from a researcher, a specimen of the desired tissue type, gestational age, *etc.*, or even an entire fetus, is then delivered to the researcher. The researcher pays a fee to the TPO for this service; this appears to be a universal practice for all TPOs.

Fees may be collected by the abortion provider, TPO, or both. Similarly, transfers from abortion providers directly to researchers or institutions, or among research institutions, tissue banks, *etc.*, may involve payment of fees. By law, any money paid (whether to an abortion provider or to any middleman entity) must be only "reasonable payments associated with the transportation, implantation, processing, preservation, quality control, or storage of HFT"[44] and not for "valuable consideration."[45,46,47] However, reasonable payments can include net returns above the cost to for-profit TPOs for providing these services.

A significant, presently in practice downstream supply element of HFT procurement is an overlooked or ignored commercial activity that definitively exposes the present commodification of human fetuses. If a company uses HFT to create a processed product, such as isolated stem cells or continuous cell lines, there are currently no

[43] Ibid.
[44] 42 U.S. Code § 289g–2.
[45] National Organ Transplant Act.
[46] NIH Revitalization Act of 1993.
[47] 42 U.S. Code § 289g–2.

restrictions on selling these processed human materials for a profit. For example, there are large for-profit biotech companies, like American Type Culture Collection (ATCC), that sell human fetal cell lines and/or other abortion-derived human fetal products (*e.g.*, DNA, RNA, protein). So companies like these are making a significant downstream profit on products derived from HFT from elective abortions. Thus, a commercial market exists for the supply and demand of HFT and their processed products, and abortion clinics are the beginning of the supply chain.

Additional laws, regulations, and guidelines exist regarding the procurement and use of HFT in research and clinical applications. These involve informed consent from pregnant mothers, protection of patient privacy (HIPAA Privacy Rule), and approval and oversight from an Institutional Review Board. Furthermore, abortion procedures must not be modified for the purposes of procuring fetal tissue. Other relevant laws and regulations are in place regarding anatomical gifts, late-term abortion procedures, born-alive infants, and restrictions on the use of public funding for abortion.[48]

The Final Report of the Select Investigative Panel convened by the U.S. House of Representatives Energy and Commerce Committee[49] and the Minority Report of the same Panel[50] each contain their own analysis of these issues. The focus of the present paper is to demonstrate that these rules, even if adhered to, are insufficient for protecting the human dignity of human research subjects in the case of aborted fetuses and promoting the noblest aspirations of the scientific research enterprise: the advancement of human knowledge and the betterment of human health and well-being. These can never be achieved through the exploitation of marginalized vulnerable human beings, as science must always be in the service of all humanity including those "marginalized" within the womb.

Human Fetal Tissue Research Applications

In consideration of both the scientific and ethical dimensions of research using HFT, it is helpful to understand how and why this tissue is used, both historically and currently. **Figure 1** illustrates the multiple sources of prenatal human tissues available for different types of research, in the context of the continuum of human development. The harvest of these materials requires the death of the prenatal donor.

While the exploitation of any human being for the sake of scientific experimentation is ethically unacceptable, whether committed yesterday or years ago, there are some important distinctions to be made regarding the manner in which tissues are used and the ethical implications of various methods. These, in turn, will also impact pro-

[48] Final Report, Select Investigative Panel of the Energy & Commerce Committee. US House of Representatives. December 30, 2016. A compilation of activities available at *https://www.govinfo.gov/content/pkg/CPRT-114HPRT24553/html/CPRT-114HPRT24553.htm*. [Accessed February 19, 2020].

[49] Ibid.

[50] Final Report, Select Investigative Panel of the Energy & Commerce Committee. US House of Representatives. December 30, 2016. A compilation of activities available at *https://www.govinfo.gov/content/pkg/CPRT-114HPRT24553/html/CPRT-114HPRT24553.htm*. [Accessed February 19, 2020].

Figure 1

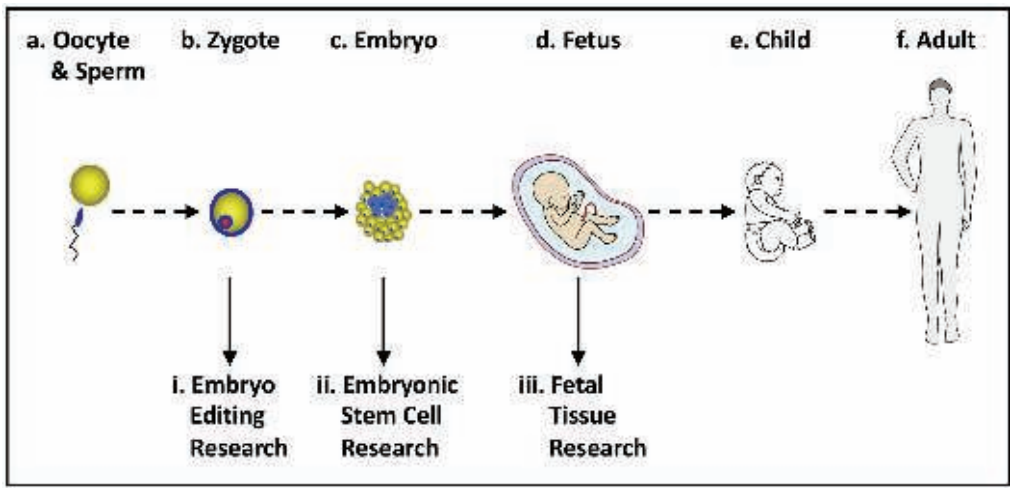

Figure 1. Types of research conducted with prenatal human tissues. The three major types of research that use prenatal human cells and tissues (i-iii) are illustrated at the stage of human development (a-f) when the targeted cells and tissues are harvested. Single-cell zygotes (b) produced by the fertilization of oocytes by sperm (a) are the primary focus of germline gene editing research (i). Multicellular developing embryos in their blastocyst phase are disrupted to form human embryonic stem cells (ii). Post-abortive fetuses are utilized for current human fetal tissue research (iii). Not indicated, perinatal and postnatal stem cells for research are harvested from consented living donors or their cadavers after death (e-f).

posed policy changes and their implementation. Chief among these distinctions is the difference between experiments that use primary tissue and those that use continuous derived cell lines.

As shown in **Figure 2**, certain research applications rely on the harvest of primary HFT from ongoing abortions, either using the organs or tissue itself (Fig. 2b) or keeping the primary (original) cells alive in culture for a limited amount of time (Fig. 2c). Other applications utilize successive generations of these cells, either as those that do not last for an extended period of time termed non-immortal, finite cell strains (Fig. 2d) or as immortalized, continuous cell lines (Fig. 2e), which last for extended periods of time. In these cases, a single abortion can give rise to large numbers of cultured cells that can be used for decades in labs around the world for a variety of purposes. They are bought and sold regularly, as are products derived from or produced by them (DNA, cellular proteins, viral proteins, *etc.*); and they can even be patented and licensed.

An important understated caveat to fetal tissue studies is that the physiologic and phenotypic properties of fetal human cells and tissues are not equivalent to those of mature adult human tissues that are the stated focus for a majority of biomedical research investigations. Though these biological differences are known and well understood, they are often not acknowledged. This inherent scientific design flaw can limit the success and applicability of many research studies based on the transplant of human fetal cells and tissues into mature adult tissues.

Figure 2

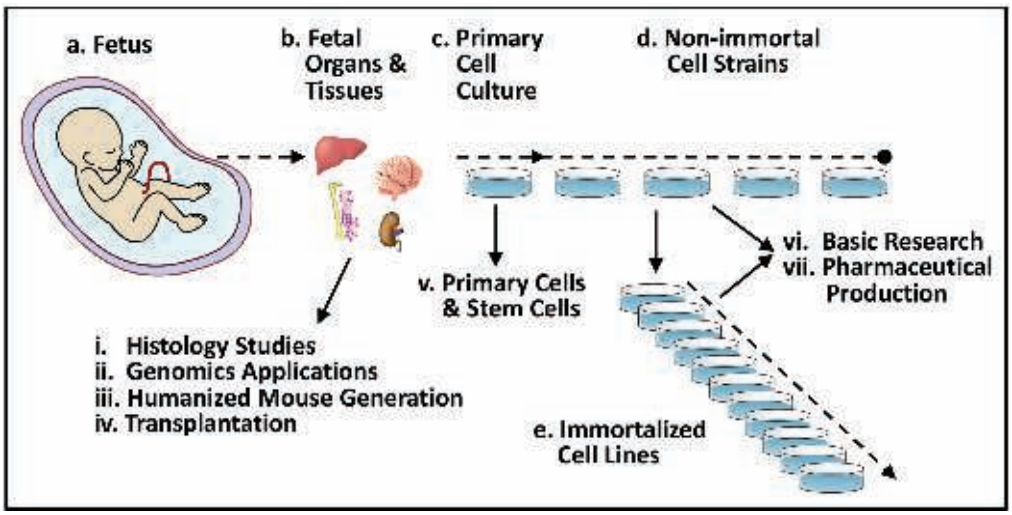

Figure 2. The uses of post-abortive fetal-derived tissue for human cell and disease research. The different types of research materials (b-e) derived from post-abortive human fetuses (a) are illustrated with respect to their main research applications (i-vii). Organs and tissue cells derived from aborted fetuses have been used directly for direct histological study (i), genome research applications (ii), generation of humanized mice (iii), and human transplantation research (iv). Fetal tissues have also been used to develop initial primary human cell cultures (c). Primary cell cultures can be used for direct experimentation and for the isolation of tissue stem cells for research (v). Primary cultures can be subsequently propagated as non-immortalized cell strains with continued passaging for a limited period of time (d), unless they are genetically modified to become continuous, immortalized cell lines, which can be passaged indefinitely in culture (e). Both non-immortal cell strains (d) and immortalized cell lines (e) of fetal origin have been used for direct biological study (vi), as well as for large-scale production of vaccines and biologic medicines (vii).

Primary Fetal Tissue

Primary HFT can be collected from the remains of aborted fetuses and transferred to the research laboratory in several ways, as described above. In some cases, the primary tissue (Fig. 2b) is used directly for observational or analytical studies (*e.g.*, Fig 2i-ii), or it may be a raw material used to generate humanized mice (Fig. 2iii), or it could be used clinically for transplantation (Fig. 2iv), which will be discussed in detail below. In other cases, the primary HFT is treated with enzymes or mechanical disruption to dissociate the tissue into its component cells (Fig. 2c), which can then be grown in laboratory cell culture conditions and used for experiments. Stem cells may be isolated from these cultures for certain applications. These primary cell cultures have limited lifespans before they undergo senescence, losing their ability to proliferate and ultimately dying. In 2014, the largest percentage of NIH-funded research projects involving primary HFT used it to study HIV/AIDS (39%), most likely to generate BLT ("bone marrow, liver, thymus") humanized mice using primary human fetal liver and thymus

tissues.[51] Other research areas for HFT research included developmental biology (18%); eye development and disease (14%); other infectious disease (*e.g.*, hepatitis C) (13%); miscellaneous (*e.g.*, type 1 diabetes) (8%); *in*-utero diseases, toxic exposures, and congenital conditions (7%); and fetal tissue repository (1%).[52]

There are a few historical examples for which either primary HFT or fetal-derived human cell strains or cell lines have been used in early vaccine discovery and/or development. There are also a limited number of vaccines and biologic medicines that are currently produced using fetal cell strains or cell lines. It is important to note that *NO* current vaccines or other medicines rely on primary HFT from present or future abortions; that is to say, any restrictions that may be placed on the use of abortion-derived primary HFT will *NOT* affect the availability of any medical treatments that are currently on the market. Due to its extensive media coverage and corresponding public misperceptions, the use of fetal tissue in vaccine development will be discussed in greater detail below.

As mentioned previously, another well-known example of primary HFT in research is the BLT humanized mouse model. Human bone marrow, liver, thymus, and other tissues from aborted fetuses are implanted into mice in order to create a more human-like immune system within the mice, which are then used to study various diseases, as well as to test new drug candidates.

Although given much attention in the media and in political rhetoric, the direct use of primary HFT, as defined above, constitutes a relatively small proportion of current biomedical research compared to *all* research funded by the NIH. In fiscal year 2014 (FY2014), HFT accounted for less than 0.2% of extramural grants funded by the NIH, and an even smaller amount for clinical trials.[53] Yet, clinical trials can also be performed and funded through private companies. Some examples include using human fetal eyes to study retinal transplant treatment for Age Related Macular Degeneration and Retinitis Pigmentosa (Ocular Transplantation, LLC), as well as human fetal brain to generate neural stem cells (huNSC) for treatment in Pelizaeus-Merzbacher disease (StemCells, Inc.) and stroke (ReNeuron, PISCES study with drug CTX0E03 DP).

It is an important consideration that a researcher using primary tissue requires ongoing tissue supply in order to collect more data, optimize methods, and produce publishable results. In the case of primary HFT, the research requires more abortions to occur, and at the required gestational age. For this reason, many legislative and regulatory efforts focus on ending the use of primary HFT from elective abortions. Below, we will discuss some of the plentiful alternatives available to enable important research efforts to continue in pursuit of greater understanding and treatment of human disease.

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[51] K. Sekar, et al., Congressional Research Service (CRS) report, Human Fetal Tissue Research: Frequently Asked Questions, *https://crsreports.congress.gov*, R44129 (2019); M. Wadman, The Truth About Fetal Tissue Research, *Nature* 528, 178 (2015).

[52] Ibid.

[53] Final Report, Select Investigative Panel of the Energy & Commerce Committee. US House of Representatives. December 30, 2016. A compilation of activities available at *https://www.govinfo.gov/content/pkg/CPRT-114HPRT24553/html/CPRT-114HPRT24553.htm*. [Accessed February 19, 2020].

Extending the Lifespan of Cultured Cells

After obtaining cells from primary tissue, it may be possible to subculture these primary cells a limited number of times by transferring them to new culture dishes with fresh culture medium (nutrient solution) and more space to proliferate, thus creating a *finite cell strain*, also known as an impermanent or non-immortal cell strain (Fig. 2d).[54] Each time this transfer process is done, it is numbered as a new "passage" in the cell strain's history. Passaging may also include "splitting," or distributing the transferred cells into multiple new dishes in order to expand the cell population.

Despite their finite lifespans, "by freezing cells at each subcultivation or every few subcultivations one could have cells available at any given time and in almost limitless numbers."[55] In fact, such strains first published in the 1960s are still in widespread use today. For example, cell strain WI-38 was derived from the lung tissue of a female fetus who was surgically aborted at 3 months gestation around the year 1962. These historic WI-38 cells are still used in vaccine production and biomedical research today, but even the founders admit that adult cell alternatives existed at the time they were derived.[56,57] In their original publication, Hayflick and Moorhead take care to note: "Although the subject of this report is confined to experiments involving human fetal cells, adult human cells have also been carried for similarly extensive periods of time with retention of the diploid configuration. Other workers have reported similar results with adult human diploid cells."[58]

Derivation and Use of Continuous Cell Lines

A *continuous cell line* is a population of cells that can survive and proliferate indefinitely under laboratory cell culture conditions (Fig. 2e). These lines may also be described as immortalized, established, or permanent. In short, derivation of a continuous cell line begins with primary tissue, which is treated with mechanical or enzymatic methods to dissociate the cells in order to maintain them in culture. These cells are then genetically manipulated by viruses, oncogenes, mutagens, or other agents in a process called immortalization or transformation. As the cells proliferate, portions are flash-frozen in liquid nitrogen and stored in a liquid nitrogen freezer or -130°C freezer indefinitely to be thawed for later use, at which time they will continue to grow and produce new generations. The frozen portions can also be transported to other laboratories, stored in repositories, *etc.*, and used around the world for many decades.

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[54] H. Lodish et al., Molecular Cell Biology. 4th edition. New York: W. H. Freeman (2000).

[55] L. Hayflick, P. S. Moorhead, The serial cultivation of human diploid cell strains. *Experimental cell research* 25, 585-621 (1961).

[56] L. Hayflick, The limited in vitro lifetime of human diploid cell strains. *Experimental cell research* 37(3), 614-636, (1965).

[57] Available for purchase from American Type Culture Collection: *https://www.atcc.org/products/all/CCL-75.aspx*. [Accessed February 19, 2020].

[58] L. Hayflick, P. S. Moorhead, The serial cultivation of human diploid cell strains. *Experimental cell research* 25, 585-621 (1961).

Continuous cell lines can be produced from a wide variety of sources: bacteria, yeast, plants, insects, or mammals—including humans. For both animals (henceforth referring specifically to non-human animals) and humans, the source material is primary tissue, which may be obtained at the embryonic, fetal, pediatric, or adult stages of development, indeed throughout the entire spectrum of development. For animals, tissue collection at any stage typically involves sacrificing the animal. For humans, tissue collection from embryonic or fetal subjects typically requires the death of the subject (Fig. 1). Embryonic cells (Fig. 1b, 1c) typically come from embryos created *in vitro*, either donated by couples following *in vitro* fertilization procedures, or created in the laboratory by performing somatic cell nuclear transfer (cloning) on eggs donated specifically for research purposes.[59] As described above, fetal tissue (Fig. 1d) almost always comes from fetuses terminated by elective abortion. For human subjects at all developmental stages after birth, tissue samples can be collected and donated to research following biopsies, surgeries, childbirth (*e.g.,* placenta, umbilical cord, amniotic fluid, *etc.*), or death by unrelated causes. Tissues may also be voluntarily donated for specific research studies, most commonly blood and biopsy specimens. It should be noted that cancer cells (both animal and human) are common sources for new cell lines, since they have often spontaneously transformed *in vivo*.

For both minor and adult human subjects, ethical guidelines have been thoroughly developed, implemented, and enforced such that tissues and/or cells are collected with informed consent and without undue harm. For animals, researchers must sufficiently justify their use and all procedures, subject to approval and oversight by institutional ethics review committees. However, fetal human subjects do not enjoy the same protections. Having been terminated by the abortion procedure, the useable portions of their remains are collected and distributed to researchers upon request. The mother receiving the abortion procedure provides the required consent. Though there are guidelines and institutional review boards in place for research using HFT, the standards applied do not provide the same protections as for minor or adult human research subjects. Protection of fetal human research subjects only applies when they would be injured non-electively as a consequence of the participation of pregnant research subjects. This contrast in the current requirements for the ethical conduct of human subjects research will be discussed in more detail below.

Historically, a certain number of continuous cell lines and finite cell strains have been derived from primary HFT, starting in the 1960s and continuing today; and each of these fetal-derived cell lines or strains originated from an individual, aborted fetus. Their use has become widespread and entrenched in many areas of biomedical research and pharmaceutical production.

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[59] R. Klitzman, M. V. Sauer, Payment of egg donors in stem cell research in the USA. *Reprod Biomed Online* 18(5), 603-608, (2009).

Driving Market Demand for Fetal Materials

The scientific utility of historical fetal cell sources has also motivated the generation of new finite cell strains and continuous cell lines from aborted fetuses. Thus, even "historical" cell strains and lines contribute to present and future experimentation on primary HFT from ongoing abortions. The following are just a few examples of how using historically derived fetal materials has created demand for newly aborted fetal remains.

In 1970, Jacobs, *et al.*, described the "value" of the fetal cell strain WI-38 as the reason that they "developed another strain of cells, also derived from foetal lung tissue, taken from a 14-week male foetus removed for psychiatric reasons from a 27 year old woman."[60] This cell strain, known as MRC-5, is still used today in vaccine production and other applications. In addition, frozen stocks of finite cell strains have eventually become depleted in cell repositories, motivating the creation of new cell strains from newly aborted fetuses over time,[61] including IMR-90 in 1977,[62] IMR-91 in 1982,[63] and Walvax-2 in 2015.[64] While the record shows that HFT is not the only viable source material for diploid cell strains or other cellular systems capable of supporting vaccine development and production, as well as basic research, their use has nevertheless been perpetuated and expanded, creating an artificial dependency on abortion that continues today.

Notably, government funds from the NIH's National Institute on Aging were paid to the Institute on Medical Research to produce "a planned series of human cell lines to be established, characterized, and banked in large quantity in support of the National Institute on Aging research and general cell biology," specifically "as a replacement for WI-38 (*1, 2*) as the NIH stock of low-passage WI-38 cells has become relatively limited for purposes other than vaccine manufacture."[65] In 1977, the new finite cell strain IMR-90 was published, which originated from the lung tissue of a female fetus aborted at 16 weeks gestational age.[66] To provide a male counterpart, IMR-91 was the second new strain, published in 1983: "The culture was established from a human male fetus obtained after a therapeutic abortion performed by hysterectomy at the time of steril-

[60] J. P. Jacobs, C. M. Jones, J. P. Baille, Characteristics of a human diploid cell designated MRC-5. *Nature* 227(5254), 168-170, (1970).

[61] H. M. Friedman, C. Koropchak, Comparison of WI-38, MRC-5, and IMR-90 cell strains for isolation of viruses from clinical specimens. *Journal of Clinical Microbiology* 7(4), 368, (1978).

[62] W. W. Nichols, et al. Characterization of a new human diploid cell strain, IMR-90. *Science* 196(4285), 60, (1977).

[63] W. W. Nichols, et al. Characterization of a new human diploid cell line—IMR-91. *In Vitro* 19(10), 797-804, (1983).

[64] B. Ma, et al. Characteristics and viral propagation properties of a new human diploid cell line, Walvax-2, and its suitability as a candidate cell substrate for vaccine production. *Hum Vaccin Immunother* 11(4), 998-1009 (2015).

[65] W. W. Nichols, et al. Characterization of a new human diploid cell strain, IMR-90. *Science* 196(4285), 60, (1977).

[66] Ibid.

ization" at approximately 12 weeks gestational age.[67] This fetus was removed from his mother's body alive and intact, inside her uterus, which had been otherwise healthy. Later, his remains were delivered to the researchers, who were waiting to collect cells from his lungs and skin. "Both lungs of the fetus were aseptically removed in a laminar flow hood and transferred to two sterile petri dishes," where the tissue was washed and minced, then placed into cell culture conditions.[68] Both IMR-90 and IMR-91 cultures are currently available to purchase from the Coriell Institute for Medical Research, through a partnership with the NIH's National Institute on Aging.[69]

Due to challenges in commercially obtaining WI-38 and MRC-5 cells of suitable quantity and quality to meet demand for vaccine production in China, the Yunnan Walvax Biotechnology Co. Ltd. undertook to derive its own human diploid cell strain from fetal tissue. To produce the Walvax-2 cell strain, nine fetuses were obtained, from which a single cell strain succeeded in meeting the established criteria. The authors state, "Walvax-2 was derived from a fetal lung tissue, similar to WI-38 and MRC-5, and was obtained from a 3-month old female fetus aborted because of the presence of a uterine scar from a previous caesarean birth by a 27-year old healthy woman."[70]

With the rise of gene therapy, the continuous HFT-derived human embryonic kidney 293 cell line (HEK293) (described in more detail below) found new utility as the only available packaging cell line for adenoviral vectors. However, this line carries significant limitations, and so another aborted fetus was procured in order to immortalize its retinal cells, now known as the continuous fetal cell line PER.C6.[71] One of its creators, Dr. Alex van der Eb, told the FDA: "PER.C6 was made just for pharmaceutical manufacturing of adenovirus vectors."[72] The PER.C6 human fetal cell line was genetically engineered to eliminate the risk of infecting patients with adenovirus. Thorough historical documentation was completed, including information about the donor, and pharmaceutical industry standards for sterility and containment were followed. PER.C6 is patented by Crucell and licensed by more than 75 companies. The fetus was 18 weeks gestational age, the pregnancy was normal, and it was a "socially indicated abortus, abortus provocatus, and that was simply because the woman wanted to get rid of the fetus" and because the father was unknown.[73]

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[67] W. W. Nichols, et al. Characterization of a new human diploid cell line—IMR-91. *In Vitro* 19(10), 797-804, (1983).

[68] Ibid.

[69] *https://www.coriell.org/0/Sections/Search/Sample_Detail.aspx?Ref=I91L-07&PgId=166*. [Accessed February 19, 2020].

[70] B. Ma, et al. Characteristics and viral propagation properties of a new human diploid cell line, Walvax-2, and its suitability as a candidate cell substrate for vaccine production. *Hum Vaccin Immunother* 11(4), 998-1009, (2015).

[71] F. J. Fallaux, et al. New helper cells and matched early region 1-deleted adenovirus vectors prevent generation of replication-competent adenoviruses. *Hum Gene Ther* 9(13), 1909-1917, (1998).

[72] US-FDA Meeting Transcript, FDA-CBER Vaccines and Related Biological Products Advisory Committee, (2001). Available at: *https://wayback.archive-it.org/7993/20170404095417/https:/www.fda.gov/ohrms/dockets/ac/01/transcripts/3750t1_01.pdf*. [Accessed February 6, 2020].

[73] Ibid.

Such patents and licensing deals can lead to significant financial benefits to inventors, universities, and companies. Further financial benefit comes when these cell lines are optimized and scaled to produce biologic medicines, such as Pulmozyme, Enbrel, and multiple vaccines produced by Merck, GSK, Sanofi Pasteur, and others.[74] Sophisticated engineering techniques have emerged for the creation of designer cell lines, as well as for further genetic manipulation and selection to create highly specialized sub-lines of existing cell lines.[75]

Human fetal cell strains date at least to the 1960s.[76,77] New human fetal cell lines have been published as recently as 2018.[78] Efforts in this area are ongoing and will continue into the future, especially if they remain legally unrestricted. There is great interest in creating human-cell-based models of specific disease states and specific cell types. HFT is one material used in these pursuits, and the "gold standard" status of some abortion-derived historical cell lines/strains makes it an attractive option. Thus, ethical evaluation of the use of historical cell lines/strains must also take into account the ongoing abortions that are necessary for the development of new cell lines/strains, as well as the financial and professional incentives that exist in this area of study.

HEK293 Fetal Cell Line

Published in 1977, the continuous cell line HEK293 was derived as follows: "Using procedures similar to those used successfully to transform rat and hamster kidney cells (Graham *et al.* 1974) a total of 8 transformation experiments have been carried out with, on average, 20 cultures of HEK cells per experiment."[79] HEK stands for human embryonic kidney, and the successful immortalization originated from experiment number 293.[80] While the efficiency was low, sheared fragments of adenovirus type 5 DNA did successfully immortalize the fetal cells to produce the HEK293 continuous cell line, sometimes referred to as simply 293 cells, or multiple other names, along with many sub-lines in common use.

The primary tissue used to derive HEK293 originated from a female fetus aborted in the Netherlands, probably in 1972. Many details have been lost to time, including

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[74] Children of God for Life (2018) U.S. Aborted Fetal Products. Available at: *https://cogforlife.org/wp-content/uploads/fetalproductsall.pdf*. [Accessed February 8, 2020].

[75] Y. Genzel, Designing cell lines for viral vaccine production: Where do we stand? *Biotechnol J* 10(5), 728-740 (2015).

[76] L. Hayflick, P. S. Moorhead, The serial cultivation of human diploid cell strains. *Experimental cell research* 25, 585-621 (1961).

[77] L. Hayflick, The limited in vitro lifetime of human diploid cell strains. *Experimental cell research* 37(3), 614-636 (1965).

[78] K. Umehara, et al. A New Conditionally Immortalized Human Fetal Brain Pericyte Cell Line: Establishment and Functional Characterization as a Promising Tool for Human Brain Pericyte Studies. *Molecular Neurobiology* 55(7), 5993-6006 (2018).

[79] F. L. Graham, J. Smiley, W. C. Russell, R. Nairn , Characteristics of a Human Cell Line Transformed by DNA from Human Adenovirus Type 5. *Journal of General Virology* 36(1), 59-72 (1977).

[80] F. L. Graham, Cell line transformation. *Curr. Contents* 8(8):2 (1992).

gestational age, but it seems that the mother and fetus were both in good health.[81] The researchers used tissue harvested from the fetus' kidney, but HEK293 cells have significant neuronal and adrenal characteristics, leading to controversy over the exact cell type that gave rise to the immortalized line.[82]

The researchers who derived the HEK293 line were primarily interested in studying adenoviruses and in determining whether human cells could be transformed in a way similar to rodent cells, and, if so, learning more about how this change takes place.[83] Accordingly, the cells have been used "almost everywhere adenoviruses are studied."[84] In addition, HEK293 cells replicate well in culture, are easily transfected with DNA, produce high levels of proteins and viral materials, and have been found amenable to many experimental applications. "The human embryonic kidney (HEK) 293 cell line and its derivatives are used in experiments ranging from signal transduction and protein interaction studies over viral packaging to rapid small-scale protein expression and bio-pharmaceutical production."[85] They are ubiquitous in both research and industry: "293 cells are second only to HeLa cells in the frequency of their use in cell biology (a search in PubMed for this cell line and its most popular derivatives yields 20,000 hits). They are second only to CHO [Chinese Hamster Ovary] cells for their use in biopharmaceutical production (and take the prime spot for use in small-scale protein production and in viral vector propagation)."[86]

Therapies manufactured using HEK293 include, but are not limited to, the gene therapy LUXTURNA to treat retinal dystrophy; CAR-T cell immunotherapy to treat specific types of blood cancer; and therapeutic proteins for hemophilia and cystic fibrosis. While this is an established human cell line that is used in bio-manufacturing, HEK293 poses important scientific shortcomings. Notwithstanding that the cell is ethically controversial because it was derived from an aborted first-trimester fetus back in the 1970s,[87] HEK293 cells have an abnormal number of chromosomes.[88] HEK293 cells were virally transformed by the introduction of cultured human embryonic kidney cells with a large genetic segment of adenovirus.[89]

[81] US-FDA Meeting Transcript, FDA-CBER Vaccines and Related Biological Products Advisory Committee, (2001). Available at: *https://wayback.archive-it.org/7993/20170404095417/https:/www.fda.gov/ohrms/dockets/ac/01/transcripts/3750t1_01.pdf.* [Accessed February 6, 2020].

[82] Y.-C. Lin, et al. Genome dynamics of the human embryonic kidney 293 lineage in response to cell biology manipulations. *Nature Communications* 5(1), 4767 (2014).

[83] US-FDA Meeting Transcript, FDA-CBER Vaccines and Related Biological Products Advisory Committee, (2001). Available at: *https://wayback.archive-it.org/7993/20170404095417/https:/www.fda.gov/ohrms/dockets/ac/01/transcripts/3750t1_01.pdf.* [Accessed February 6, 2020].

[84] F. L. Graham FL, Cell line transformation. *Curr. Contents* 8(8), 2 (1992).

[85] Y.-C. Lin, et al. Genome dynamics of the human embryonic kidney 293 lineage in response to cell biology manipulations. *Nature Communications* 5(1), 4767 (2014).

[86] Ibid.

[87] A. Wong, The Ethics of HEK 293. *The National Catholic Bioethics Quarterly* 6(3), 473-495 (2006).

[88] Y.-C. Lin, et al. Genome dynamics of the human embryonic kidney 293 lineage in response to cell biology manipulations. *Nature Communications* 5(1), 4767 (2014).

[89] F. L. Graham, J. Smiley, W. C. Russell, R. Nairn , Characteristics of a Human Cell Line Transformed by DNA from Human Adenovirus Type 5. *Journal of General Virology* 36(1), 59-72 (1977).

Subsequent analysis has shown that the genetic transformation was formed by inserting 4,500 base pairs of this virus into chromosome 19.[90] HEK293 poses a small risk of introducing a virus capable of replicating when producing viral vectors that can produce a serious viral infection. Also, there is a risk for trace amounts of contaminating viral proteins when producing a biologic or vaccine. Furthermore, there are differences in glycosylation pattern in proteins between HEK293 cells and human plasma, in which the decoration of sugar molecules on proteins regulate the efficacy and safety of therapeutic proteins.[91] For example, the glycosylation pattern for factor VII (a therapy for hemophilia) when produced from HEK293 cells differs significantly from plasma-derived factor VII.[92] Thus, there is not only a moral reason, but also a scientific need to create reproducible and well-defined human cell lines that are derived without viral elements. Moreover, there is a genuine scientific need to develop a dependable, robust, and safe supply chain of human cells for bio-manufacturing.

Scientists at the John Paul II Medical Research Institute (JP2MRI), under the leadership of Dr. Alan Moy, are working to develop an ethical human cell line to replace the HEK293 fetal cell line. According to Dr. Moy, human cell lines must be reproducible, safe, and easily replenished. These criteria are not reliably achieved within the abortion industry. The health of the mother and fetus must be verified and well documented. There must be rigid quality controls in tissue procurement and transportation. Lastly, the tissue source must be reproducible. The abortion industry cannot meet these requirements. For example, JP2MRI has identified a select human adult stem cell called CET-JP2-2007, which does not require aborted fetal tissue or human embryos and has "the potential to serve as a cell therapy, gene therapy, biologic producer and vaccine."[93]

All natural human tissue cell cultures, regardless of their tissue of origin, have a limited culture life span. To gain an infinite proliferation potential, cells in a culture must be immortalized. Prior human cell lines derived from abortion were created with crude methods by today's standards (*e.g.*, viral transformation). Now, fifty years of biomedical research on the molecular basis of cell immortalization and cell transformation has yielded a vast repertoire of cellular genes whose genetic alteration can yield immortalized cell lines from essentially any type of proliferative human tissue cell, including ethically obtained tissue cells from consented children and adults (*e.g.*, p53 gene alterations). Moreover, progress in the development of facile molecular genetics technologies like CRISPR-Cas9 gene editing allow ever-increasing precision in the genetic engineering of human cells. Together, these biotechnological advances could be

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[90] N. Louis , C. Evelegh, F. L. Graham, Cloning and Sequencing of the Cellular–Viral Junctions from the Human Adenovirus Type 5 Transformed 293 Cell Line. *Virology* 233(2), 423-429 (1997).

[91] A. Croset, et al. Differences in the glycosylation of recombinant proteins expressed in HEK and CHO cells. *Journal of Biotechnology* 161(3), 336-348 (2012).

[92] E. Böhm, et al. Differences in N-glycosylation of recombinant human coagulation factor VII derived from BHK, CHO, and HEK293 cells. *BMC Biotechnol* 15, 87-87 (2015).

[93] John Paul II Medical Research Institute. Available at: *https://www.jp2mri.org/universal-off-the-shelf-gen-backgrd.* [Accessed April 21, 2020].

deployed straightforwardly to not only develop ethical replacements for HEK293, but also new lines that would improve on HEK293 cells' shortcomings in manufacturing and safety.

Concerns with Widespread Use of Continuous Fetal Cell Lines and Strains

The ethical evaluations for use of both primary fetal tissue and fetal cell lines/strains involve many of the same considerations. The most significant difference, from an ethical perspective, is that research using fetal cell lines/strains does not inherently require future abortions to occur in order to continue the specific work underway. This is one important reason that many legislative efforts focus on ending the use of primary HFT. However, as just demonstrated above, regular use of fetal cell lines/strains does, in fact, motivate the generation of new cell lines/strains, with newly aborted fetuses sought again as a source. Even if there were no pressure to create new lines/strains, each existing cell line/strain indeed originated from a fetus who was terminated *in utero*, raising all of the same ethical concerns that surround primary fetal tissue. In fact, in the past, many efforts to develop a new cell line required multiple attempts, *i.e.,* multiple abortions. For example, the now-ubiquitous cell line HEK293 required eight experiments before a viable clone was isolated and grown to sufficient cell numbers to establish a permanent line.[94] Albeit, today's technologies for continuous cell line derivation are much more efficient. The fact that these abortions occurred in the 1970s does not diminish the moral considerations surrounding the origin of these cells.

Widely used cell lines like HEK293 and cell strains like WI-38 pose the greatest challenge to researchers who wish to avoid complicity with the act of elective abortion. Lines and strains like these are long and well engrained in cell biology and biomedical research. In many examples, they have been employed as the only practical option for specific applications in areas like virology and gene editing, and, in the case of non-immortal cell strains, as essential normal human cell controls. Even if one manages to avoid using HEK293 cells directly, for example, many research reagents, such as viral vectors, antibodies and other proteins, are produced in HEK293. Collaboration with colleagues and dependence on institutional core facilities often limits cell choices. There are also pressures to match conditions used in previously published work and to meet expectations of manuscript and grant reviewers regarding materials and methods. Transparency is sorely lacking in the labeling and advertising of certain products, further impeding the conscience rights of scientists who wish to avoid these materials. Some promising new therapies with significant potential benefit, such as CAR-T cells and CRISPR-Cas9 gene editing techniques, may utilize HEK cells to package the necessary vectors.

In this landscape, researchers with conscientious objections to abortion-derived materials must rigorously search for the origins of all proposed research materials: trac-

[94] F. L. Graham, J. Smiley, W. C. Russell, R. Nairn , Characteristics of a Human Cell Line Transformed by DNA from Human Adenovirus Type 5. *Journal of General Virology* 36(1), 59-72 (1977).

ing through the published literature, checking product information sheets from ATCC and other vendors, consulting databases like Cellosaurus,[95] and calling technical support for additional information when needed. When ethical conflicts arise, these researchers must work to find and implement alternative materials from ethical sources, when available, and to develop them when they are not. This is a difficult path and may not be supported by supervisors, colleagues, home institutions, or funding agencies. Some scientists may feel forced to leave the field or to make moral compromises. However, there are some promising initiatives in this area. On an institutional level, JP2MRI and Sound Choice Pharmaceutical Institute are examples of companies focused on developing ethical replacements for abortion-derived materials. In the realm of clinical treatments, the Midwest Stem Cell Therapy Center at The University of Kansas was created by the Kansas legislature in 2013 and focuses solely on non-controversial materials, adhering to the highest ethical standards while advancing the most promising clinical applications for stem cell research. Efforts like these will pave a future where all scientists, physicians, and patients can develop and accept treatments in good conscience.

The Case of Vaccines

Several strategies are used to make vaccines against viral and bacterial infection. As part of the manufacturing process, vaccines are first produced by growing large quantities of the targeted pathogen in a controlled laboratory environment. The pathogen is harvested and parts (e.g., one or more isolated proteins) or the whole pathogen—killed or "attenuated" (weakened)—are injected as a vaccine, to elicit an immune response including formation of antibodies as well as immune memory cells, capable of reacting against future invasions of the pathogen. Specific pathogen proteins can also be produced via recombinant genetics techniques, wherein the target protein is produced alone, without need for the whole, growing pathogen. While bacterial pathogens can usually be grown free-living in culture medium or other supportive environments, viruses require a living cell in which to grow. Viruses can be grown inside cells using various techniques, including: (1) cultured human cell lines (e.g., WI-38, HEK293, HeLa, Jurkat, etc.); (2) cultured animal cell lines (e.g., Vero monkey cells, CHO hamster cells, Sf9 insect cells, etc.); (3) embryonated eggs; (4) live animals (e.g., mouse, rabbit).

The historical fact is that primary aborted fetal tissue has never been used in vaccine production. The original Salk and Sabin polio vaccines used monkey tissue to grow virus. While there are a couple of historical cell lines that were grown from abortions in the 1960s, kept in cell culture, and used for some vaccines, even these cell lines are obsolete and no longer used for most vaccines today. For example, much of the polio vaccine today is made using the Vero monkey cell line.

Some of the earliest attempts at growing viruses sometimes used cultures of mixed HFT. For example, the proof-of-principle experiment showing that polio virus could be

[95] Bairoch A, The Cellosaurus, a Cell-Line Knowledge Resource. *J Biomol Tech* 29(2):25-38 (2018).

grown in non-nervous tissue culture in 1949 used HFT.[96] But it is decidedly not true that the 1954 Nobel prize given to Enders et al. was for production of polio vaccine, as some have claimed, nor even for growth of enough virus used to produce the polio vaccine. The Nobel prize was awarded "for their discovery of the ability of poliomyelitis viruses to grow in cultures of various types of tissue."[97] There remains uncertainty and a lack of transparency as to whether some of Enders' fetal tissue was even from induced abortion. The 1949 published paper on growth of virus in fetal tissue thanks the provider of the tissue by name but does not indicate if the source of fetal tissue was from induced abortion. This may suggest that the fetal tissue used in the study was from spontaneous abortion, *i.e.,* miscarriage, and not from induced abortion. At the time, induced abortion was illegal in the United States, and thanking the colleague by name, in print, who supplied the tissue would have been incriminating.

As far as production of poliovirus for vaccine, the fact is that the original Salk and Sabin vaccines were both produced using laboratory-cultured monkey tissue.[98] Later, some poliovirus was produced in human fetal cell lines (WI-38,[99] fetal female lung; MRC-5,[100] fetal male lung) and some continues to this day.[101] But it deliberately misrepresents the science to say that polio vaccine was produced in "fetal tissue." HeLa cells were also used in the past to make some polio vaccine,[102] but it would be likewise misleading to say that polio vaccine was produced in human cervical carcinoma tissue, from which HeLa cells were derived.

Nonetheless, even the American Society for Cell Biology has passed on mistaken information regarding use of fetal tissue vs. historical fetal cell lines for vaccines. "Fetal

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[96] J. F. Enders, et al., Cultivation of the Lansing strain of poliomyelitis virus in cultures of various human embryonic tissues, *Science* 109, 85 (1949).

[97] The Nobel Prize in Physiology or Medicine 1954. NobelPrize.org. Nobel Media AB 2020. Available at: *www.nobelprize.org/prizes/medicine/1954/summary/*. [Accessed 16 Feb 2020].

[98] J. E. Salk, Recent Studies on Immunization against Poliomyelitis, *Pediatrics* 12, 471 (1953); and J. E. Salk, et al., Formaldehyde Treatment and Safety Testing of Experimental Poliomyelitis Vaccines, *Am. J. Public Health* 44, 563 (1954); and J. E. Salk, et al., Studies in Human Subjects on Active Immunization Against Poliomyelitis II. A Practical Means for Inducing and Maintaining Antibody Formation, *Am. J. Public Health* 44, 994 (1954); and A. B. Sabin, Present status of attenuated live-virus poliomyelitis vaccine, *JAMA* 162, 1589 (1956).

[99] Original fetal cell cultivations 1961, original poliovirus growth 1962 in WI-1, standardized in WI-38; L. Hayflick, P. S. Moorhead, The serial cultivation of human diploid cell strains, *Experimental Cell Research* 25, 585 (1961); L Hayflick, et al., Preparation of poliovirus vaccines in a human fetal diploid cell strain, *Am. J. Hyg.* 75, 240 (1962); L. Hayflick, The limited in vitro lifetime of human diploid cell strains, *Exp. Cell Res.* 37, 614 (1965).

[100] J. P. Jacobs, et al., Characteristics of a Human Diploid Cell Designated MRC-5, *Nature* 227, 168 (1970).

[101] See, e.g., CDC, Appendix B: Vaccine Excipient & Media Summary, Epidemiology and Prevention of Vaccine-Preventable Diseases, The Pink Book: Course Textbook—13th Edition, 2015; accessed at: http://www.cdc.gov/vaccines/pubs/pinkbook/index.html.

[102] W. F. Scherer, et al., Studies on the propagation in vitro of poliomyelitis viruses. IV. Viral multiplication in a stable strain of human malignant epithelial cells (strain HeLa) derived from an epidermoid carcinoma of the cervix, *J. Exp. Med.* 97, 695 (1953).

tissue already has proved its value in a wide range of life-saving vaccines against diseases that include measles, mumps, rubella, chickenpox, polio, hepatitis A, hepatitis B, rabies, and shingles, she said." Correction (4/22/2016, 2:57 p.m.): This article originally quoted Rep. Janice Schakowsky as naming diphtheria, tetanus, and whooping cough among a group of vaccines developed with the help of fetal tissue. She was relying on information provided by the American Society for Cell Biology, which has corrected its list to remove those vaccines. This article has been revised to reflect the correction.[103]

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."[104] Nonetheless, primary fetal tissue has *never* been used for vaccine production, and currently most vaccines do not even use the continuous fetal-derived cell lines, e.g., much of the polio vaccine is made using the Vero (monkey) cell line.

Ethical Research Alternatives

Numerous, non-controversial alternatives are available to researchers that do not rely on elective abortions (**Figure 3**). Many of these alternatives are available now and sufficient for many research studies. Others are still in development.

A common argument for continuing use of aborted human fetuses for research is that alternatives are not as good as fetal tissue, because of underlying limitations that undermine their usefulness. Another argument is that although these alternatives may one day replace the need for fetal tissue, presently these technologies are still in development; and therefore researchers must rely on fetal tissue as a reference material.[105] The fact is that no model human tissue cell system, whether derived from HFT or ethical alternatives, is devoid of technical, experimental, and scientific limitations. None are perfect to the ideal. Furthermore, ethical alternatives have their own inherent distinct qualities and are, in many ways, more advantageous, efficient, and cost effective compared to aborted fetal tissue. Plus, they can be harvested from consenting individuals who are living or have died of natural causes; thus, they pose no ethical concerns.

Many alternative postnatal human tissues are routinely available from living individuals. These tissues are donated with proper consent and processed immediately for research and, in many cases, clinical applications (*e.g.*, allogeneic bone marrow cell transplant). Because there are so many useful alternatives available to researchers today, considering all of them here is neither possible nor necessary. Instead, a close exam-

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[103] Paul Basken, The Chronicle of Higher Education.

[104] From: "Talking Points," Fetal Tissue Research, Second in an occasional series of pocket-sized briefing papers from the American Society for Cell Biology, April 2001. NOTE: this talking point sheet was removed from the ASCB website in 2015, and replaced with a new set of talking points that did not mention this CDC quote.

[105] K. Sekar, et al., Congressional Research Service (CRS) report, Human Fetal Tissue Research: Frequently Asked Questions, *https://crsreports.congress.gov*, R44129 (2019).

Figure 3

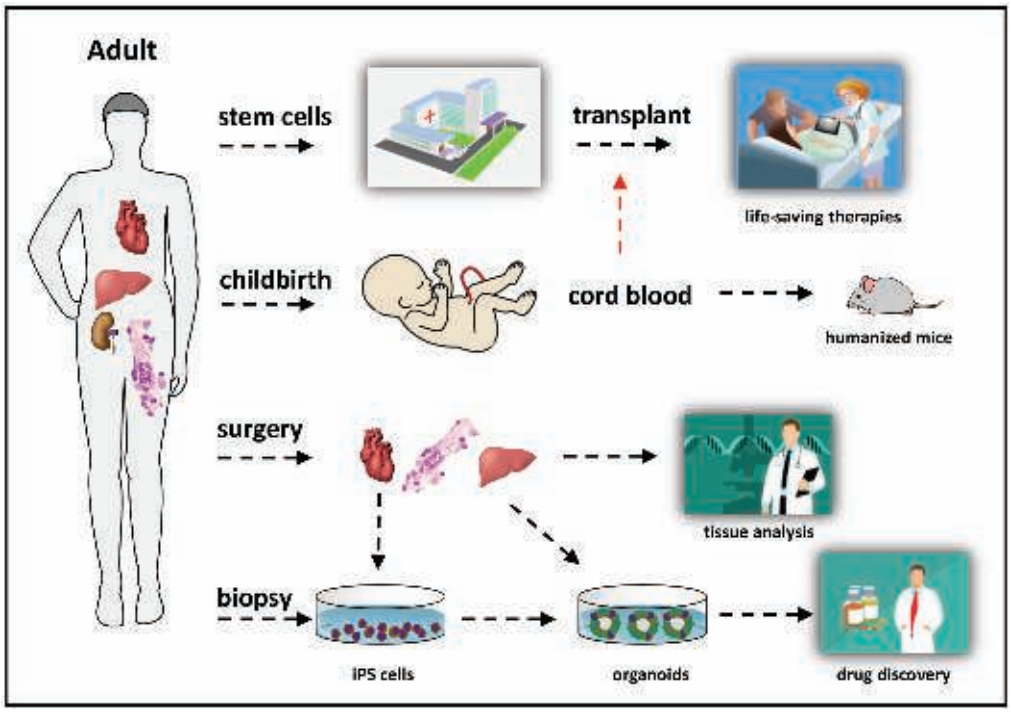

Figure 3. Alternative, ethical sources of human cells and tissues for research and medical therapeutics. The four major ethical procedures currently available for procurement of human organs and tissues from live donors are diagrammed. Adult tissue stem cells are often harvested in clinical centers for use in HSC transplant therapies. For-profit companies also recruit volunteer donors, with informed consent, to provide HSC preparations for research. Many perinatal tissues like umbilical cord blood are available after informed consent for both research (e.g., derivation of mice with humanized immune systems) and use in HSC transplant therapies. Surgically removed organs and tissues are ethically consented for organ transplant therapies, and unused surgical discards are made available for tissue cell research, including being a source of adult tissue stem cells and starting materials for organoid cultures for research and drug discovery. There is also a long history of pathological and normal biopsy materials being consented for research after diagnostic and prognostic needs are met. Induced pluripotent stem (iPS) cells can be derived from biopsy specimens or surgical discard tissues, and used to produce organoid cultures for pharmaceutical drug evaluations.

ination of several of the most valuable and most prevalent examples is provided for the purpose of this discussion.

Adult Stem Cells

Adult stem cells are not the same as embryonic stem cells from an embryo or fetal stem cells from a fetus. Therefore, a brief explanation of these unique stem cells' differences is important. At the earliest stage of fertilization, a human organism contains all of the genetic programming it needs to develop and form a fully functioning baby. The earliest epiblast cells, present within the inner cell mass of a day-5 embryo blastocyst,

are particularly important in early human development. *In vivo*, or in their natural state, epiblast cells are the progenitors for all cell types (>200) present in the fully developed human body. Epiblast cells are extracted from blastocysts and used to derive human embryonic stem cells (hESCs; Fig. 1.c.ii). hESCs can both self-renew (replicate themselves) and differentiate into more specialized cells. This form of "stemness" is a key feature that distinguishes hESCs from "adult stem cells." It is noteworthy that, when outside of a natural embryo, derived hESCs are restricted in their capacity, so that they can only form immature fetal phenotypes. In order for a researcher to obtain hESCs, the embryo is disrupted and destroyed. As a result of this troubling feature of their production, the ethics of hESC research became an issue of pointed debate soon after its initiation in the late 1990s and continues today. Fetal cells isolated from an aborted fetus are more tissue-specific in nature than hESCs, but with a varying degree of differentiation depending on the origin organ and the gestational age of the fetus.

Adult cells, on the other hand, can be obtained ethically, without any undue harm coming to the donating person. Adult stem cells include stem cells found in late fetal development, in perinatal tissues (*e.g.*, umbilical cord blood, amniotic fluid, placenta) and postnatal tissues (*e.g.,* peripheral blood, bone marrow, skin, fat, heart, liver, *etc*.). Unlike hESCs, when adult stem cells produce differentiated cells, they do not undergo differentiation themselves. By a division process called asymmetric self-renewal, they retain their undifferentiated "stemness" state while simultaneously dividing to produce cells that become the mature functional cells of human organs and tissues. This unique function is essential for the maintenance and repair of tissues in children and adults. Neither hESCs nor early fetal stem cells have this capability.[106] Because of their tremendous therapeutic potential, adult stem cells have for decades been used as the gold standard in clinical medicine to treat various blood disorders and cancers in over two million individuals worldwide.[107]

Adult stem cells are present in virtually every tissue of the human body and are important for tissue maintenance, regeneration, and repair. Adult stem cells can be either unipotent, producing only one type of differentiated cell (*e.g.*, the crystallin cells of the lens of the eye) or multipotent, producing many different lineages of differentiated cells in a given tissue (*e.g.*, hematopoietic cells of the blood). This tissue-specific potency of adult stem cells is often contrasted to the tissue pluripotency of hESCs as a failing for therapeutic development. However, the ability of hESCs to differentiate into tissues from any embryonic germ layer has itself proved more problematic for therapeutics development, because it leads to the formation of tumors when hESCs are transplanted

[106] J. L. Sherley, "Asymmetric self-renewal: the mark of the adult stem cell," in Stem Cell Repair and Regeneration, N. A. Habib, M. Y. Gordon, N. Levicar, L. Jiao, and G. Thomas-Black, Eds. (Imperial College Press, 2005), pp. 21-28.

[107] D. A. Prentice, Adult Stem Cells: Successful Standard for Regenerative Medicine. *Circ Res*. 124, 837-839 (2019); A. Gratwohl et al., For the Worldwide Network of Blood and Marrow Transplantation WBMT. One million haemopoietic stem- cell transplants: a retrospective observational study. *Lancet Haematol* , e91–100 (2015).

into mature human tissues. In contrast, adult stem cells integrate naturally into mature human tissues for replacement and repair therapies without tumor formation.[108]

Cord Blood

Labor and delivery procedures generate perinatal tissues (umbilical cord, umbilical cord blood, amniotic fluid, amniotic membranes, placenta) that are routinely discarded after a baby is born. Adult stem cells unique to umbilical cord blood warrant special attention, because they are particularly rich in multipotent hematopoietic (blood) adult stem cells and have a high capacity to regenerate damaged tissues.[109] As such, cord blood is arguably one of the most valuable resources available to researchers today. Unless planned for collection immediately after birth for storage, the cord blood is usually thrown away as a medical waste product.

Umbilical cord blood is an important transplant treatment option for a number of diseases, including blood disorders and childhood cancers. An estimated 700,000 umbilical cord blood units have been donated for public use and over 25,000 patients have been cured with this approach.[110] Cord blood is collected safely and painlessly, withstands long-term cryopreservation, and carries a low risk of transmitting viral infections and somatic mutations that could complicate the patients' course after transplantation.[111] A perfect HLA match for transplantation is also not required with cord blood, compared to other blood stem cell sources, such as bone marrow.[112]

Many cellular therapies approved by the FDA or under FDA jurisdiction use bone marrow, mobilized peripheral blood, cord blood-derived adult hematopoietic stem cells (HSCs), or a patient's own cells for treatment. Some examples of FDA-approved cord blood cellular therapy products include ALLOCORD, CLEVECORD, Ducord, HEMACORD, HPC, Cord Blood—Bloodworks, etc.[113]

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[108] J. L. Sherley, The importance of valid disclosures in the human embryonic stem cell research debate. *Cell Prolif*. 41 (Suppl. 1), 57-64 (2008).

[109] S. Roura, et al. The role and potential of umbilical cord blood in an era of new therapies: a review. *Stem Cell Research & Therapy* 6, 123 (2015); B. Baudin, et al. A protocol for isolation and culture of human umbilical vein endothelial cells. *Nat. Protoc*. 2,481 (2007); R. S. Song, et al. Generation, expansion, and differentiation of human induced pluripotent stem cells (hiPSCs) derived from the umbilical cords of newborns. *Curr. Protoc. Cell Biol*. 29:1C16.1 (2014).

[110] K. Ballen, Update on umbilical cord blood transplantation, *F1000Research*, 6(F1000 Faculty Rev), 1556 (2017) [Last updated: 17 JUL 2019].

[111] S. Roura, et al. The role and potential of umbilical cord blood in an era of new therapies: a review. *Stem Cell Research & Therapy* 6, 123 (2015); K. K. Ballen et al., Umbilical cord blood donation: public and private? *Bone Marrow Transplantation*, 50, 1271 (2015).

[112] Ibid.

[113] *https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products*. [Accessed February 19, 2020].

Cord blood is also a useful source of non-hematopoetic cell types in research that can be readily isolated *ex vivo* using established methods.[114] These cell populations include mesenchymal stem cells and endothelial-like vascular progenitors that can be expanded into finite cell lines that maintain basic characteristics representative of their cell type. For example, human umbilical vein endothelial cells (HUVECs) are a well-established cell strain used to study basic biology and vascular-related diseases.[115] In addition, HUVECs originating from umbilical cords of newborns can be reprogrammed into human induced pluripotent stem cells (hiPSCs), which are a valuable cell source in research because of their ability to "differentiate into multiple cell types."[116]

Surgical Specimens and Tissue Banks

In addition to labor and delivery, there are other routine medical procedures that require the sampling or removal of tissues, as a part of the surgical procedure, which are excellent resources for researchers. In some cases, surgical biopsy samples are collected and sent to a pathology laboratory for pathological examination and diagnosis. With proper consent and institutional approval, these tissue biopsies can be stored in a repository and accessed by researchers without charge or, at most, with a nominal fee to cover storage costs.

Tissue banks at academic institutions may house human tissue specimens from medical procedures in a secure storage facility that collects, processes, and distributes blood and tissue for researchers on campus.[117] They often take care of the consenting process and perform collection of blood products and otherwise-discarded tissue from surgeries, including bone marrow, tumor and control tissue. Tissue banks usually work directly with internal medical staff to make tissues available to researchers within their own institution. With tissues readily available, researchers can propose a study and request prepared samples from the tissue bank as soon as the research has been approved. These tissue banks save time and money, while enabling invaluable research studies.

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[114] S. Roura, et al, The role and potential of umbilical cord blood in an era of new therapies: a review. *Stem Cell Research & Therapy* 6, 123 (2015).

[115] B. Baudin, et al, A protocol for isolation and culture of human umbilical vein endothelial cells. *Nat. Protoc*. 2,481 (2007).

[116] R. S. Song R.S., et al, Generation, expansion, and differentiation of human induced pluripotent stem cells (hiPSCs) derived from the umbilical cords of newborns. *Curr. Protoc. Cell Biol*. 29, 1C16.1 (2014).

[117] Examples: Medical College of Wisconsin Tissue Bank: https://www.mcw.edu/departments/pathology-and-laboratory-medicine/research/mcw-tissue-bank; Harvard Brain Tissue Resource Center: *https://hbtrc.mclean.harvard.edu*; University of Chicago Human Tissue Resource Center: *https://htrc.uchicago.edu*; University of Arkansas Tissue Biorepository and Procurement Resources: *https://pathology.uams.edu/pathology-services/pathology-research/translational-pathology-shared-resource/uams-tissue-procurement-facility/*; University of Kansas Medical Center Biospecimen Repository Core Facility: http://www.kumc.edu/school-of-medicine/biospecimen.html.

If a lab desires to work with tissue that is not available through a repository or tissue bank, the researcher may establish their own patient consent and tissue collection procedures with proper institutional review board approval. Such an independent process will often involve working closely with medical and surgical staff, so that the tissue is collected and processed immediately after the procedure.

Several studies have demonstrated that various resected specimens from children and adults undergoing routine surgery and biopsy procedures can be used in research, such as human cardiac valve, abdominal artery, bladder, adipose, tonsil, liver, and tumor.[118] In fact, a recent report showed that surplus human thymus tissue from newborn babies obtained during surgical procedures to repair congenital heart defects can be used to generate NeoThy humanized mice.[119] Unused discards from explanted organs from organ transplant procedures are also an important source of human tissue for research.

National and international tissue banks also exist worldwide, including The National Marrow Donor Program (NMDP)- "Be The Match"- which is the largest repository for cord blood. NMDP has established relationships with public cord blood banks throughout the United States and internationally. More than 765,000 cord blood units are available to clinicians and researchers worldwide for transplantation, cellular therapy, and research.[120] In addition, the NMDP-Be the Match repository processes and stores tissue and DNA samples from donors and recipients who are in the process of providing or receiving stem cells for transplant, with more than 9 million total samples in storage.[121] They also house samples from more than 22,000 donor/recipient pairs that are available for use in research, as well as >1 million stored samples available for retrospective studies to determine transplant outcomes.

Finally, donated organs not suitable for transplantation can be obtained from designated procurement organizations and used in research. In one study, donated livers from deceased neonates, children, and adults (not suitable for orthotopic liver

[118] E. N. Johnson, Y.M. Lee, T. L. Sander, S. Kaushal, E. Rabkin, F. J. Schoen, J. Bishoff. An NFATc1-dependent pathway for VEGF-mediated proliferation in human pulmonary valve endothelial cells. *J Biol Chem*. 278(3), 1686-92 (2003); D.B. Klinkner, J. C. Densmore, S. Kaul, L. Noll, H. J. Lim, D. Weihrauch, K. A. Pritchard, K. T. Oldham, T. L. Sander. Endothelium-derived microparticles (EMPs) inhibit human cardiac valve endothelial cell function. *Shock* 25(6),575-80 (2006); J. A. Hipp, J. D. Hipp, J. J. Yoo, A. Atala, K.-E. Andersson, Microarray analysis of bladder smooth muscle from patients with myelomeningocele, *BJU International*. 102, 741-746 (2008); J. P. Meekel, et al., An in vitro method to keep human aortic tissue sections functionally and structurally intact. *Scientific Reports*. 8, 8094 (2018); J. Paupert et al., Rapid and Efficient Production of Human Functional Mast Cells through a Three-Dimensional Culture of Adipose Tissue-Derived Stromal Vascular Cells, *J Immunol* 201, 3815-3821 (2018); N. Leelatian, et al., Single cell analysis of human tissues and solid tumors with mass cytometry. Cytometry B Clin Cytom. 92(1), 68–78 (2017); X.Wu et al., Precision-cut human liver slice cultures as an immunological platform, *J Immunol Methods*. 455, 71–79 (2018).

[119] M. E. Brown, et al., A Humanized Mouse Model Generated Using Surplus Neonatal Tissue, *Stem Cell Reports*, 10(4),1175-1183 (2018).

[120] *https://bethematch.org/about-us/how-we-help-patients/be-the-match-registry/*. [Accessed February 19, 2020].

[121] *https://bethematch.org/about-us/careers/career-opportunities/research-and-science/; https://bethematch.org/about-us/how-we-help-patients/research--advancing-transplant-science/*. [Accessed February 19, 2020].

transplantation) were obtained from federally designated organ procurement organizations and the stem cells isolated from the liver. The liver cells from these pediatric and adult tissues were isolated alongside fetal livers. Fetal livers contained more pluripotent cell types, but as the authors note, "the pluripotent hepatic progenitors are evident in both fetal and postnatal livers and remain stable in their phenotypes throughout life, particularly the hepatic stem cells, which persist in relatively constant numbers in livers at all donor ages."[122]

Human Induced Pluripotent Stem Cells (hiPSCs)

Induced pluripotent stem cells (hiPSCs) are adult somatic cells (any cell other than reproductive cells) that have been genetically reprogrammed into pluripotent cells with basic biologic properties similar to hESCs. The first reports of their discovery were published by two independent groups in 2007 and ultimately resulted in a Nobel prize.[123]

A major advantage of this technology is that hiPSCs can be generated from virtually any adult somatic cell type without destruction of human embryos or fetuses. Once generated, hiPSCs can differentiate into different types of cells, similar to human embryonic stem cells, and thus hold similar promise for cell-based therapies, disease modeling, and regenerative medicine.[124] For example, several clinical trials are testing the application of hiPSCs for development of cell replacement therapies for a number of diseases, including macular degeneration, ischemic heart disease, diabetes, and spinal cord injury.[125]

Human iPSC technology also provides a unique opportunity to establish cellular models of human diseases. Scientists can develop experimental models of nearly any disease by reprogramming somatic cells from a patient with disease (*e.g.*, skin cells from a Parkinson's patient). These disease models are immensely valuable to researchers for understanding basic mechanisms of disease, performing experiments that aim to correct the disease via gene therapy, as well as high-throughput screening of compounds for drug discovery. In fact, hiPSC-based drug discovery has identified novel compounds that can reverse disease-associated phenotypes *in vitro* and are currently under clinical investigation to treat diseases such as amyotrophic lateral sclerosis, Alzheimer's disease, progressive supranuclear palsy and spinal muscular atrophy.[126]

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[122] E. Schmelzer, E. Wauthier, L. M. Reid, The Phenotypes of Pluripotent Human Hepatic Progenitors, *Stem Cells* 24, 1852–1858 (2006).

[123] K. Takahashi, K. et al. Induction of pluripotent stem cells from adult human fibroblasts by defined factors. *Cell*. 131, 861-872 (2007); J. Yu, et al. Induced pluripotent stem cell lines derived from human somatic cells. *Science* 318, 1917–1920 (2007).

[124] K. Takahashi K, S. Yamanaka, A decade of transcription factor-mediated reprogramming to pluripotency. *Nat Rev Mol Cell Biol*. 17(3), 183-193 (2016).

[125] F. Soldner, R. Jaenisch. Stem cells, genome editing and the path to translational medicine. *Cell* 175(3), 615-632 (2018).

[126] Ibid.

It is noteworthy that hiPSCs were developed during the time that U.S. President George W. Bush introduced a ban on federal funding for research on newly derived human ESC lines. This policy was enacted in 2001, in an effort to move away from research that required the destruction of embryos and to focus on ethical alternatives. A Yale journal article openly admits—"Subsequent U.S. progress in iPS cell research may have well enjoyed unique encouragement under Bush's policies."[127] This shift away from ES cells occurred in part, because some of the earliest work with iPSCs involved analyzing *mouse* ES cells. As Takahashi and Yamanaka would later recount, mouse ES cells are "much easier to use and are robustly expandable in comparison to fertilized eggs."[128]

Therefore, federal and state policies that introduce bans on any research using unethical sources, such as embryos or aborted fetuses, are not a hindrance to science. Instead, these measures have encouraged scientific advancement within ethical boundaries and provided substantive incentive for researchers to develop even better alternatives that can lead to remarkable discoveries. Mummary perhaps says it best: "Until recently, these [ES cells] were the only stem cells able to make all of the 200 or so specialized cells of the body. Yet just when we thought this was an intractable problem, with ethical objections countering the potential benefit to very sick patients, stem cell research took a new and completely unexpected turn. This was the discovery of induced pluripotent stem cells."[129]

Finally, it is important to note that hiPSCs can be generated using any somatic cell, including embryonic or abortion-derived fetal cells. As a result, some hiPSC cell lines, themselves, have been derived using fetal cell-derived cell lines (*i.e.,* HEK293) for use in packaging lentiviral vectors for gene therapy development. Therefore, complete avoidance of ethically questionable cell lines requires ensuring that hiPSCs are generated from cells from adults, perinatal tissues (cord blood, placenta, *etc.*), or prenatal tissues that did not require the destruction of embryos or the elective abortion of fetuses.

Human Organoids

Organoids, also known as organs "in a dish," are a viable alternative when created from stem cells, like iPS cells, derived from ethically donated primary living cell and tissues. Organoids are three-dimensional models of human organs. They are cellular clusters that have been shown to replicate normal function and development *in vitro* for various organs including brain, liver, pancreas, intestine, stomach, lung, kidney, and eye. Organoid constructs provide superior models to study tissue organization and disease, as well as starting points for potential transplantation. One simple example is aggregation of hepatocytes into "mini-livers," actually just 3-D monocultures in suspension that are small enough to survive by diffusion of nutrients. Such mini-livers can

[127] V. Murugan, Embryonic Stem Cell Research: A Decade of Debate from Bush to Obama. *Yale Journal of Biology and Medicine* 82, 101-103 (2009).

[128] K. Takahashi K, S. Yamanaka, A decade of transcription factor-mediated reprogramming to pluripotency. *Nat Rev Mol Cell Biol*. 17(3), 183-193 (2016).

[129] C. Mummery C, A. van de Stolpe, B. A. J. Roelen, H. Clevers, *Stem Cells (Second Edition)*, Preface. (Academic Press, Boston) (2014).

potentially serve as laboratory models for liver function, as bioartificial livers for toxicity testing, and may even be useful for transplantation for liver regeneration. The laboratory of McGuckin and Forraz has shown that hepatocytes can be produced in culture from umbilical cord blood stem cells, a readily-available source of multipotent stem cells, and have recently reviewed the field of hepatocyte production and liver repair.[130]

More complex organoids with specific architectures have also been constructed. One example is development of a tissue-engineered colon, which is also innervated similar to normal colon tissue.[131] An Australian team has generated kidney organoids that contain kidney-specific cell types and structures—nephrons associated with a collecting duct network. The individual nephrons showed differentiated structural organization into tubules and glomeruli, similar to that observed in adult kidneys.[132] Cerebral organoids have also been used to discern the mechanism of action of Zika virus on developing brains that results in microcephaly,[133] as well as to model the developing brain to test potential treatments and preventative measures.[134] Construction of cerebral organoids has become very sophisticated, e.g., able to form the complete cellular complexity of the human cortex.[135] These are only a few brief examples from the explosive growth of this field, with much more to come both in terms of modeling embryological and tissue development, drug screening, and specific engineering of organoids.[136]

Postmortem Tissues

Postmortem tissues from both prenatal and postnatal deaths that occur naturally are an ethical alternative source of tissue for research. And unlike fetal tissue obtained from elective abortions, postmortem tissues from natural death (*i.e.*, miscarriages) are more widely accepted and approved for use in research, with no apparent state statutory restrictions.[137]

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[130] Saba Habibollah, Nico Forraz, and Colin P. McGuckin, "Application of Umbilical Cord and Cord Blood as Alternative Modes for Liver Therapy," *in*: N. Bhattacharya, P.G. Stubblefield (eds.), Regenerative Medicine: Using Non-Fetal Sources of Stem Cells (Springer-Verlag, London, 2015), 223-241, doi: 10.1007/978-1-4471-6542-2_22.

[131] M. M. Wieck et al., "Human and murine tissue-engineered colon exhibit diverse neuronal subtypes and can be populated by enteric nervous system progenitor cells when donor colon is aganglionic," *Tissue Engineering Part A* 22, 53-64 (2016), doi: 10.1089/ten.TEA.2015.0120.

[132] M. Takasato et al., "Kidney organoids from human iPS cells contain multiple lineages and model human nephrogenesis," *Nature* 526, 564-568 (2015), doi:10.1038/nature15695.

[133] P. P. Garcez, et al., Zika virus impairs growth in human neurospheres and brain organoids. *Science* 352, 816-818 (2016).

[134] M. Watanabe, et al., Self-Organized Cerebral Organoids with Human-Specific Features Predict Effective Drugs to Combat Zika Virus Infection, *Cell Reports* 21, P517-532 (2017).

[135] S. Velasco, et al., Individual brain organoids reproducibly form cell diversity of the human cerebral cortex, *Nature* 570, 523–527 (2019); doi: 10.1038/s41586-019-1289-x.

[136] T. Takebe, J. M. Wells, Organoids by design, *Science* 364, 956–959 (2019); doi: 10.1126/science.aaw7567.

[137] L. Borgatta, D. Kaufman, J. P. Kelly, D. Babaian, M. Banks. Applications for Research Concerning Fetal or Placental Tissue and Expected Institutional Review Board Responses. *Journal of Empirical Research on Human Research Ethics* 12(3), 150–160 (2017).

Some of the earliest studies using prenatal miscarried tissue date back to the 19th century, including an anatomy study in 1843 using a six-week old fetus that died a natural death *in utero*.[138] In 1912, Harvey Cushing, a pioneer in neurological surgery, performed two of the first documented pituitary gland transplantations, inserting pituitary gland tissue from full-term stillborn infants into an adult male's cerebral cortex.[139] While the transplantation was ultimately unsuccessful, Cushing contemplated ways to avoid fetal tissue transplantation altogether and proposed using tissues cultivated outside a living organism (future field of tissue regeneration).[140]

Others continued to explore and examine the use of miscarriage tissue to study cell viability, disease mechanisms, and even hematopoietic cell transplantation. In 1966, cell studies were conducted to determine whether aborted tissue from Finland and miscarriage tissue from local hospitals in Philadelphia could be used to establish finite cell strains and study viral infection as a potential cause of miscarriage.[141] Cell lines were successfully established from both elective abortion and miscarriage tissue and the "failure to grow cells from explants occurred in the same proportion in embryos from surgical abortions as in embryos obtained from spontaneous abortions."[142]

More recent studies have examined larger and more defined cohorts from miscarriages and ectopic pregnancies. A study conducted by Low, *et al.*, in 1994, collected fetal tissue from 137 miscarriages and 27 ectopic pregnancies within 12 hours of death.[143] They found that 63% of identifiable embryos/fetuses were rated Grade I and Grade II quality with viable cells and tissues from liver, thymus, spleen, bone marrow, pancreas, brain, spinal cord, kidneys, lungs, and skin. Based on these numbers, they predicted that over 100,000 miscarriages with Grade I/II quality tissue could be available per year based on the estimated 750,000 miscarriages in the U.S. annually.[144]

Authors of a 1995 JAMA article then reported on the suitability of fetal tissues from a large number of miscarriages and ectopic pregnancies, specifically for transplantation.[145] This study obtained over 1,000 spontaneously aborted embryos and ectopic pregnancies (<8 and >8 weeks of gestational age). The authors reported that a limited

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[138] J. M. Dittmar, P. D. Mitchell. From cradle to grave via the dissection room: the role of foetal and infant bodies in anatomical education from the late 1700s to early 1900s. *J Anat* 229, 713-722 (2016).

[139] C. Pendleton, A. Quinones-Hinojosa, Tissue and progenitor cell transplantation for the management of pituitary disorders: from Harvey Cushing to the next frontier in Human Fetal Tissue Transplantation, N. Bhattacharya, P. Stubblefield, Eds (Springer 2013) pp:179-180.

[140] Ibid.

[141] A. Boue, C. Hannoun, J. Boue, S. A. Plotkin et al, Cytological and Chromosomal Studies of Cell Strains from Aborted Human Fetuses. *Exp Biology* 122, 11-16 (1966).

[142] Ibid.

[143] Low et al., Human fetal tissue from spontaneous abortions as potential sources of donor tissue for cell transplantation therapy. *Transplantation Proceedings* 26 (6), 3500 (1994).

[144] Ibid.

[145] D. W. Branch, et al. Suitability of fetal tissue from spontaneous abortions and from ectopic pregnancies for transplantation. *JAMA* 273, 66 (1995).

amount of miscarriage tissue would be suitable for clinical transplants.[146] But this result was challenged by Dr. Maria Michejda at Georgetown University School of Medicine, who reported that over 15% of the 300,000 second-trimester miscarriages in her studies were suitable for transplantation when collected and preserved properly.[147] Accordingly, spontaneous miscarriages were a useful and ethical alternative source of fetal stem cells for hematopoietic cell transplantation and other labs agreed with her findings.[148] A small cell bank (Protocell) was established to provide hematopoetic stem cells from second-trimester miscarriages for these studies.[149]

Additional reports using miscarriage tissue have demonstrated that researchers can transplant fetal bone marrow HSCs into sheep,[150] telecephalon can be isolated from fetal brain to detect astroglia cells,[151] and human midbrain-derived neural progenitors (hmNPCs) can be generated from fetal central nervous system tissue.[152] And finally, two different groups have isolated human neural stem cells (hNSCs) from miscarriage tissue; one of these studies even describes using these cells as a test of safety for cell therapy in a phase I trial which could then lead to later-phase clinical trials for the treatment of patients with ALS.[153]

In regard to genetic concerns with miscarriage tissue, the majority of chromosomal aneuploidies (abnormal number) occur in the first trimester. But according to a 2014 report by the CDC, only 10% of fetal deaths in the second trimester at greater than 20 weeks' gestation are attributed to congenital malformations and chromosomal abnormalities.[154] Most fetal deaths were found to be a result of things such as placenta or cord complications, maternal complications or conditions related to pregnancy.[155] Furthermore, some researchers go out of their way to collect fetal tissue from abortions that

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[146] Ibid.

[147] M. Michejda, Spontaneous miscarriages as a source of fetal stem cells. *The National Catholic Bioethics Quarterly* 2, 401 (2002); A. G. Wu, et al. Analysis and characterization of hematopoietic progenitor cells from fetal bone marrow, adult bone marrow, peripheral blood, and cord blood. *Pediatric Research* 46, 163 (1999).

[148] Ibid.

[149] M. Michejda, Spontaneous miscarriages as a source of fetal stem cells. *The National Catholic Bioethics Quarterly* 2, 401 (2002).

[150] G. Noia, et al., Source of cell injected is a critical factors for short and long engraftment in xeno-transplantation. *Cell Prolif*. 41 (Suppl. 1), 41–50 (2008).

[151] D. Virgintino, et al. , Astroglia-microvessel relationship in the developing human telencephalon, I*nt. J. Dev. Biol*. 42:1165-1168 (1998).

[152] J. Moon, et al., Preclinical Analysis of Fetal Human Mesencephalic Neural Progenitor Cell Lines: Characterization and Safety In Vitro and In Vivo. *Stem Cells Translational Medicine*. 6, 576-588 (2016).

[153] L. Mazzini, et al., Human neural stem cell transplantation in ALS: initial results from a phase I trial. *Journal of Translational Medicine* 13, 17 (2015); P. Yang, et al, Icariin promotes cell proliferation and regulates gene expression in human neural stem cells *in vitro*. *Molecular Medicine Reports* 14, 1316-1322 (2016).

[154] D. L. Hoyert, E. C. W. Gregory, Cause of Fetal Death: Data From the Fetal Death Report, 2014. *National Vital Statistic Report* 65, 7 (2016).

[155] Ibid.

contain congenital birth defects (*e.g.*, Down syndrome, neural tube defects like Spina Bifida). So, considering that anomalies exist in a subset of the miscarriage population, one would expect miscarriage tissue to be a highly sought after resource for investigators wishing to study specific disorders. And in fact, the largest NIH-funded fetal tissue repository in the U.S. (The Birth Defect Laboratory at the University of Washington), receives fetal tissue from Pacific Northwest Facility and Seattle Reproductive Medicine from pregnancy losses, in addition to elective abortions.[156] Currently, miscarriage tissue is not as easily accessible or commercially available as aborted fetal tissue. Therefore, future efforts could involve, (1) creating awareness and informing parents regarding the donation of their child's remains to research as an anatomical gift and (2) redirecting funds to establish fetal tissue banks to include a mechanism for obtaining tissue from miscarriages and ectopic pregnancies in a timely manner.

Further, postnatal cadavers from deaths due to natural and unexpected causes are suitable for several research applications. In a retrospective review, Hodgetts *et al*. found that stem cells could be isolated after death from neonates to adults 95 years of age from various organs including eye, brain, muscle, arteries, and pancreatic islet.[157] There are other examples of postnatal cadaveric specimens examined, side-by-side, and compared to fetal tissue from elective abortions, especially in large developmental genomic and proteomic studies.[158] For example, in 2018, Li *et al*. collected bulk tissue and cells from 60 de-identified postmortem brains, ranging from five post-conception weeks (PCW) to 64 postnatal years (PY), in which 50% were postnatal cadaveric tissue. If cadaveric tissue from infants, children, and adults that die of natural causes is suitable for these large studies, then cadaveric tissue from fetuses that die of natural causes should be suitable as well.

Finally, studies have been performed using tissues from infants that have died unexpectedly to better understand the mechanisms involved in sudden infant death syndrome (SIDS) and sudden unexplained infant death syndrome (SUIDS).[159] And similar to surgically discarded tissues as described above, cadaveric tissues may be found in tissue banks, repositories, and morgues and can be acquired with proper consent and IRB approval.

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[156] Final Report, Select Investigative Panel of the Energy & Commerce Committee. US House of Representatives. December 30, 2016. A compilation of activities available at *https://www.govinfo.gov/content/pkg/CPRT-114HPRT24553/html/CPRT-114HPRT24553.htm*. [Accessed February 19, 2020].

[157] S. I. Hodgetts, et al., Long live the stem cell: The use of stem cells isolated from post mortem tissues for translational strategies. *The International Journal of Biochemistry & Cell Biology*, 56, 74–81 (2014).

[158] M. Li, et al., Integrative functional genomic analysis of human brain development and neuropsychiatric risks. *Science* 362, 6420 (2018); M.-S. Kim, et al., A draft map of the human proteome. *Nature* 509(7502), 575-581 (2014).

[159] R. Männikkö, et al., Dysfunction of NaV1.4, a skeletal muscle voltage-gated sodium channel, in sudden infant death syndrome: a case-control study. *Lancet* 391, 1483–92 (2018).

Humanized Mice

Humanized mice constructed to contain a human immune system are used in research to study immunity and immune development, vaccines, immunotherapies, and cancer. Humanized mice can be generated using ethical alternatives, such as peripheral blood mononuclear cells (PBMCs) collected from living adults, often referred to as the "hu-PBMC" or "hu-PBL" mouse. Another model is called the "hu-HSC" mouse, generated using $CD34^+$ hematopoietic (blood) stem cells (HSCs), which can be obtained from adult bone marrow, umbilical cord blood, and peripheral blood. Stem Express, the company that previously supplied human aborted fetal tissues for this purpose, now only supplies $CD34^+$ HSCs derived from the bone marrow and blood of consented adult human donors. In addition, genetically engineered NSG-SGM3 mice engrafted with $CD34^+$ stem cells from cord blood are also available. These mice have increased $CD33^+$ myeloid cell and $CD4^+$ $CD25^+$ $FoxP3^+$ Treg cell numbers, which are key factors necessary for better engraftment of hematopoietic progenitor cells.[160] Many of these ethical alternatives are available commercially from U.S. vendors, such as The Jackson Laboratory, so that researchers do not have to manage technical challenges of generating humanized mice.[161]

A more recent option, called the "NeoThy" humanized mouse, is a viable alternative generated with surplus human thymus tissue from newborn babies obtained during surgical procedures to repair congenital heart defects and $CD34^+$ stem cells from donated cord blood.[162] Neonatal thymus tissue is "abundant" and "more than 1,000 fragments suitable for transplantation can be obtained from a single thymus" compared to the 20 fragments obtained from aborted fetal tissue. Therefore, neonatal thymus tissue is 50 times more efficient than aborted fetal tissue for generating the same number of mouse models. In their paper, the authors discuss their drive to develop this mouse based on known limitations with fetal tissue humanized mice, including limited fetal specimen size, which leads to "significant experimental variability and discourages robust characterization," and "BLT models [that] may not reliably represent clinical patient immune responses."[163]

Indeed, there are various humanized mouse models and the advantages and limitations of each model have been thoroughly considered by the research community. Humanized mice generated with fetal tissue tend to be more technically difficult, costly,

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[160] E. Billerbeck, et al., Development of human CD4+FoxP3+ regulatory T cells in human stem cell factor-, granulocyte-macrophage colony-stimulating factor-, and interleukin-3-expressing NOD-SCID IL-2R{gamma}null humanized mice. *Blood*, 117(11), 3076-86 (2011).

[161] *Jackson Labs website for humanized mice*: *https://www.jax.org/jax-mice-and-services/in-vivo-pharmacology/humanized-mice* [Accessed February 19, 2020].

[162] M E. Brown, et al., A Humanized Mouse Model Generated Using Surplus Neonatal Tissue, *Stem Cell Reports* 10(4):1175-1183 (2018).

[163] Ibid.

time consuming, and not as efficient as the other models.[164] And even at a "Meet the Experts" workshop held by the NIH/NIAID in 2015 to discuss improvements to and limitations of Humanized Mouse Models for HIV Research, some advantages of alternative models (*e.g.*, Hu-HSC mice) over BLT mice were identified as including that they are easier to prepare at lower cost, more animals can be generated per cohort, there is negligible graft-versus-host disease and longer life span, chronic HIV infection is longer-lasting, and long-term safety and toxicity assessments are possible.[165]

While there are limitations to *all* available humanized mice models, recent reports highlight the need for better systems. For example, Kenney *et al.* state that "The development of GVHD [graft versus host disease] in almost all of the model systems represents a constraint on the experimental window available for the study of graft survival" and mention room for improvement in other areas including immune system engraftment and immune function.[166] In another report, Skelton *et al.* state that "…there is still need for more development within all of the models to create an immune cell composition similar to that observed in humans."[167] Therefore, in this rapidly evolving field on the cusp of exciting developments, it would behoove scientists and funding agencies to focus on developments that do not rely on HFT, thus guaranteeing the discovery of both the best and most ethical models.

Fetal Tissue Claims Versus Facts

Several false and misleading claims have been made regarding the use of HFT in research. Below we address the most common claims made in support of harvesting these tissues, followed by available and relevant factual information. In short, the use of HFT is not necessary to study some of the most debilitating diseases of our time. As described in the previous section, excellent alternatives exist that are currently available and being used worldwide for research and clinical studies. Below, commonly advanced claims to rationalize and justify the use of aborted fetuses for biomedical research are considered in greater depth.

Development of Vaccines

Claim: *The use of fetal tissue has saved millions of lives with vaccines, so continued harvesting of newly aborted fetuses is required in order to develop new vaccines.*

Fact: *Neither primary HFT nor fetal-derived cell lines from abortions are needed to make vaccines.*

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[164] L. Cheng et al., Humanized mice engrafted with human HSC only or HSC and thymus support comparable HIV-1 replication, immunopathology, and responses to ART and immune therapy. *Front. Immunol* 9, 817 (2018).

[165] R. Akkina, et al., Improvements and limitations of humanized mouse models for HIV research: NIH/NIAID "meet the experts" 2015 workshop summary. *AIDS Res Hum Retroviruses* 32, 109 (2016).

[166] L. L. Kenney, et al., Humanized mice and tissue transplantation, *Am J Transp*l 16(2), 398-397 (2016).

[167] J. K., Skelton, et al., A Hitchhiker's guide to humanized mice: new pathways to studying viral infections, *Immunology* 154, 50-61 (2018).

Although fetal cell lines from past abortions were used to develop and manufacture some vaccines, primary fetal tissue from ongoing abortions is not used to produce any vaccine products today. In fact, even continuous cell lines and finite cell strains derived from aborted fetal tissue collected decades ago have never been the exclusive means necessary for development or production of any vaccine. Only 11 vaccines currently available in the United States use these historic cell lines (directed against zoster, varicella, rabies, rubella, hepatitis A, polio and adenovirus),[168] but each of these could be produced in non-fetal cell lines. In fact, for most of these diseases, there are already vaccine formulations available in the U.S. that do not use fetal-derived cell lines. Only four diseases without non-fetal versions remain on the U.S. market (adenovirus, hepatitis A, rubella, and varicella),[169] and there is no scientific reason that these vaccines could not be produced in non-fetal cell lines. In fact, three different manufacturers in Japan produce rubella vaccines using either rabbit kidney or quail embryo fibroblast cells.[170] Ending the harvest of primary tissues from aborted fetuses today will not disrupt ongoing vaccination therapies, nor will it inhibit the development of new vaccines going forward.

One of the newest vaccines on the market protects against shingles. The Shingrix vaccine is made using CHO (hamster) cells, and it is far superior to the older vaccine made with cell lines derived from aborted fetuses.[171] Shingrix, a modern recombinant subunit vaccine produced in engineered hamster cells, also shows greater than 90% effectiveness, while providing better protection than the historical vaccine produced with fetal-derived cells.

Another example is the recent success of a field test of a vaccine against Dengue virus, a close relative of Zika.[172] The vaccine provided 100% protection[173] and was developed using monkey cells and a mosquito cell line.[174]

Yet another example is development of the vaccine rVSV-ZEBOV against Ebola virus. This successful Ebola vaccine was not developed using either primary fetal tissue or continuous fetal-derived cell lines, but rather with Vero, a monkey cell line, demon-

[168] Final Report, Select Investigative Panel of the Energy & Commerce Committee. US House of Representatives. December 30, 2016.

[169] Ibid. Updated to remove zoster from this list following the introduction of the Shingrix vaccine in 2017.

[170] Reef SE & Plotkin SA (2018) 53—Rubella Vaccines. *Plotkin's Vaccines (Seventh Edition)*, eds Plotkin SA, Orenstein WA, Offit PA, & Edwards KM (Elsevier), pp 970-1000.e1018.

[171] Package insert, https://www.fda.gov/downloads/biologicsbloodvaccines/vaccines/approvedproducts/ucm581605.pdf.

[172] B. D. Kirkpatrick, et al., The live attenuated dengue vaccine TV003 elicits complete protection against dengue in a human challenge model, *Sci. Transl. Med.* 8, 330ra36 (2016).

[173] E. C. Hayden, Dengue vaccine aces trailblazing trial, *Nature*, 2016, doi: 10.1038/nature.2016.19576.

[174] R. Men, et al., Dengue Type 4 Virus Mutants Containing Deletions in the 39 Noncoding Region of the RNA Genome: Analysis of Growth Restriction in Cell Culture and Altered Viremia Pattern and Immunogenicity in Rhesus Monkeys, *J. Virology* 70, 3930 (1996); and F. Medina, et al., Dengue Virus: Isolation, Propagation, Quantification, and Storage, *Current Protocols in Microbiology* 15D.2.1-15D.2.24, (November 2012).

strating again that medical science has moved beyond any need for fetal tissue in useful, lifesaving vaccine research.[175]

Finally, the race is on to develop a vaccine against a newly recognized disease threat, the coronavirus SARS-CoV-2 that causes COVID-19. Examples include vaccines that use synthetic nucleic acid (DNA or RNA) produced in cell-free systems, recombinant proteins using non-human cultured cells (i.e., insect, monkey), recombinant proteins using non-controversial human cells (cord blood and placenta), and antibodies produced in genetically engineered mice (i.e., VelocImmune mouse model).[176] In fact, the VelocImmune mouse has proven success in generating antibodies to the Ebola virus, which is undergoing current testing in normal healthy volunteers in preparation for potential use in future Ebola epidemics.[177]

Fetal Transplants

Claim: Fetal tissue is critical for potential transplant treatments.

Fact: Fetal tissue transplants have a history of failure.

First, no fetal tissue transplant clinical trials have been federally funded since FY 2003, and fetal tissue transplants have historically failed. Between 1988 and 1994, roughly 140 Parkinson's disease patients received fetal tissue (up to six fetuses per patient), with varying results.[178] Subsequent reports showed that severe problems developed from fetal tissue transplants. One patient who received transplant of fetal brain tissue (from a total of 3 fetuses) died subsequently, and at autopsy was found to have various non-brain tissues (*e.g.,* skin-like tissue, hair, cartilage, and other tissue nodules) growing in his brain.[179]

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[175] S. T. Agnandji, et al., Phase 1 Trials of rVSV Ebola Vaccine in Africa and Europe — Preliminary Report, *NEJM* published on April 1, 2015; doi: 10.1056/NEJMoa1502924; originally developed by the Public Health Agency of Canada, which patented it in 2003, http://www.google.com/patents/WO2004011488A2?cl=en.

[176] Draft landscape of COVID-19 candidate vaccines—26 March: *https://www.paho.org/en/documents/draft-landscape-covid-19-candidate-vaccines-26-march*; COVID-19 Vaccine Tracker Posted 27 March 2020: *https://www.raps.org/news-and-articles/news-articles/2020/3/covid-19-vaccine-tracker*; JP2MRI: *https://mailchi.mp/jp2mri.org/are-there-current-vaccines-in-development-for-covid-19-that-are-using-cell-lines-from-aborted-fetal-cells-1018081?e=f31d478c00*. [Accessed April 21, 2020].

[177] *https://www.pharmafocusasia.com/clinical-trials/human-antibody-discovery*; K.E. Pascal et al., Development of Clinical-Stage Human Monoclonal Antibodies That Treat Advanced Ebola Virus Disease in Nonhuman Primates, *The Journal of Infectious Diseases* 218, 5612-5626 (2018).

[178] Reviewed in: Fine A, Transplantation of fetal cells and tissue: an overview, *Can Med Assoc J* 151, 1261 (1994).

[179] R. D. Folkerth, R. Durso, Survival and proliferation of nonneural tissues, with obstruction of cerebral ventricles, in a parkinsonian patient treated with fetal allografts, *Neurology* 46, 1219 (1996).

In 2001, the first report of a full clinical trial[180] (funded by NIH) using fetal tissue for Parkinson's disease patients was prominently featured in the *New York Times*,[181] with doctors' descriptions of patients writhing, twisting, and jerking with uncontrollable movements; the doctors called the results "absolutely devastating," "tragic, catastrophic," and labeled the results "a real nightmare."

A second large, controlled study published in 2003 showed similar results (funded by NIH), with over half of the patients developing potentially disabling tremors caused by the fetal brain tissue transplants.[182] The results of these two large studies led to a moratorium on fetal tissue transplants for Parkinson's. Long-term follow-up of a few of the patients in these large studies showed that even in fetal tissue that grew in patients' brains, the grafted tissue took on signs of the disease and were not effective.[183]

Developing Advanced Therapies

Claim: Fetal tissue was essential for developing advanced and approved therapies, like Truvada for HIV.

Fact: Fetal tissue has never been the exclusive means necessary for development and approval of advanced therapies.

Humanized mice are an important model for testing unproven anti-HIV-1 drugs and proven drugs for new applications. BLT humanized mice generated with fetal bone marrow/liver/thymus tissue have been used to study HIV infection, human immune response, antiretroviral treatments, and to test new therapies (*e.g.*, Truvada). However, the BLT mouse is only one model amongst many other animal and non-fetal models that have been used to study diseases, like HIV, and develop therapies.

Berges and Rowen reviewed the history and utility of humanized mice to study HIV-1 infection. At the time of their report, six different humanized mouse strains generated with human HSCs had been used to analyze HIV-1 infection, of which two used cord blood.[184] These include (1) RAG-hu mouse humanized with purified $CD34^+$ HSCs derived from cord blood or fetal liver (2) hNOG or hNSG mice humanized with cord blood derived $CD34^+$ cells; (3) hNOG or hNSG mice humanized with fetal liver derived $CD34^+$ cells; (4) NOD/SCID BLT mice; (5) hNSG BLT mice; and (6) Balb/c $Rag1^{-/-}gc^{-/-}$ mice humanized with purified $CD34^+$ HSCs from fetal liver. The review goes on to describe how *several* anti-HIV-1 drugs have been tested for efficacy in HSC-engrafted

[180] C. R. Freed, et al., Transplantation of embryonic dopamine neurons for severe parkinson's disease, *N Engl J Med* 344, 710 (2001).

[181] G. Kolata, "Parkinson's Research Is Set Back by Failure of Fetal Cell Implants," *New York Times* March 8, 2001; accessed at: http://www.nytimes.com/2001/03/08/health/08PARK.html.

[182] C. W. Olanow, et al., A Double-blind Controlled Trial of Bilateral Fetal Nigral Transplantation in Parkinson's Disease, *Ann Neurol* 54, 403 (2003).

[183] H. Braak, K. Del Tredici, Assessing fetal nerve cell grafts in Parkinson's disease, *Nature Medicine* 14, 483 (2008).

[184] B. Berges, M. Rowan, The utility of the new generation of humanized mice to study HIV-1 infection: transmission, prevention, pathogenesis, and treatment. *Retrovirology*, 8:65 (2011).

mice, using both the BLT model, which uses HFT, and RAG-hu models that use HFT or cord blood. Furthermore, others have compared the efficacy of human cell engraftment using HSCs from cord blood, adult bone marrow, fetal liver, and peripheral blood and found that human cord blood is the best scientific and ethical source for optimal human cell engraftment.[185] Therefore, ethically derived HSCs from cord blood have been used to study HIV-1 and are a useful model for testing advanced therapies.

A report by Akkina in 2013 further reviewed the history of HIV research using humanized mice models and stated that "BLT mice received more attention until recently due to its early application."[186] Indeed, data presented at a 2015 NIH workshop to discuss improvements and limitations of humanized mouse models for HIV research would later show that the alternative hu-HSC humanized mouse model is "equally amicable for testing microbicide and oral pre-exposure prophylaxis (PrEP) strategies against vaginal HIV-1 transmission."[187]

Cheng *et al*. then demonstrated in 2018 that the hu-HSC humanized mouse model is sufficient for the study of HIV infection, pathogenesis, and therapy,[188] meaning fetal tissue is not needed. In their study, they used $CD34^+$ HSCs purified from fetal liver, but in their conclusion, emphasize that "the source of HSCs to construct NRG-hu HSC mice is not restricted to fetal liver derived $CD34^+$ cells. $CD34^+$ HSCs from cord blood or human BM can also support the systemic development of human immune system."[189] Furthermore, HSC transplantation alone has also been shown to be adequate to achieve human cell mucosal engraftment in mice, confirming that transplantation of human fetal thymus tissue (as done with BLT mice) is not necessary.[190]

As described earlier, a more recent report in 2019 demonstrated that surplus human thymus tissue from newborn babies obtained during surgical procedures to repair congenital heart defects, combined with HSCs from cord blood, can also be used to

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[185] C. M. Lepus, et al., Comparison of human fetal liver, umbilical cord blood, and adult blood hematopoietic stem cell engraftment in NOD-scid/gammac-/-, Balb/c-Rag1-/-gammac-/-, and C.B-17-scid/bg immunodeficient mice. *Human Immunology* 70(10), 790–802 (2009).; T. Matsumura, et al., Functional CD5+ B cells develop predominantly in the spleen of NOD/SCID/gammac(null) (NOG) mice transplanted either with human umbilical cord blood, bone marrow, or mobilized peripheral blood CD34+ cells. *Experimental Hematology* 31(9), 789–797 (2003). Also reviewed in R. Ito, et al., Humanized mouse models: Application to human diseases, *J Cell Physiol* 233:3723–3728 (2018).

[186] R. Akkina, et al. New generation humanized mice for virus research: Comparative aspects and future prospects. *Virology* 435, 14 (2013).

[187] R. Akkina, et al., Improvements and limitations of humanized mouse models for HIV research: NIH/NIAID "meet the experts" 2015 workshop summary. *AIDS Res Hum Retroviruses* 32, 109 (2016).

[188] L. Cheng et al., Humanized mice engrafted with human HSC only or HSC and thymus support comparable HIV-1 replication, immunopathology, and responses to ART and immune therapy. *Front. Immunol* 9, 817 (2018).

[189] Ibid

[190] B. K. Berges, M. R. Rowan, The utility of the new generation of humanized mice to study HIV-1 infection: transmission, prevention, pathogenesis, and treatment. *Retrovirology* 8,65 (2011).; reviewed in R. Akkina, et al. New generation humanized mice for virus research: Comparative aspects and future prospects. *Virology* 435, 14 (2013).

generate humanized mice.[191] Other humanized mouse models generated with ethical alternatives, such as peripheral blood, are also beneficial. In fact, Hu-PBMC mice are an ideal model for rapid drug discovery and were used in early testing of some therapeutics, including Enbrel for rheumatoid arthritis. Therefore, ethical alternatives obviate the need for HFT from abortions, which have been misleadingly argued as "required" to generate humanized mouse models.[192]

In regard to other animal model systems, nonhuman primates are considered one of the most relevant animal models for HIV/AIDS research and are used repeatedly for testing therapies for safety and efficacy before treating people. In addition, many pharmaceutical companies use non-fetal and non-human sources for the production of biotherapeutics. Plant cells, insect cells, bacteria, yeast, CHO cells, murine cells, and HT-1080 cells (created from a tissue biopsy of a fibrosarcoma from a 35-year-old human male) have all been used to produce therapies.[193] In fact, CHO cells are the "workhorses behind more than half of the top-selling biologics on the market today,"[194] including Humira for arthritis and Crohn's disease, Herceptin and Perjeta for breast cancer, Avastin for metastatic colorectal cancer, Rituxan for six diseases including chronic lymphocytic leukemia and Non-Hodgkin's lymphoma, Prolia for osteoporosis, and Xolair for asthma, just to name a few. This does not include insulin made in bacteria and yeast to treat diabetes, and many successful treatments developed using adult stem cell sources.[195]

Furthermore, none of the FDA-approved cellular and gene therapy products use primary HFT from elective abortions.[196] In fact, the majority of these products use cord blood-derived adult stem cells, blood stem cells from consenting adult donors, or a patient's own cells for treatment. Examples include ALLOCORD for donor cord blood transplantation, KYMARIAH using autologous (patient's own) T cells to treat B-cell lymphoma, PROVENGE using autologous peripheral blood mononuclear cells to treat prostate cancer, MACI using autologous chondrocytes on a porcine (pig) collagen membrane to treat cartilage defects of the knee, and GINTUIT using cells isolated from donated human newborn foreskin tissue to treat mucogingival conditions.

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[191] M. E. Brown, et al., A Humanized Mouse Model Generated Using Surplus Neonatal Tissue, *Stem Cell Reports*, 10(4), 1175-1183 (2018).

[192] *https://www.sciencemag.org/news/2018/12/report-nih-will-cancel-fetal-tissue-research-contract-fuels-controversy*; After reviewing the Brown et al. paper on NeoThy mice, Dr. Weissman argued that: "the technique it describes would require additional invasive procedures to withdraw bone marrow from the infant donors, in order to replicate the method used now to create humanized mice using fetal tissue."

[193] J. Dumont, D. Euwart, B. Mei, S. Estes, R. Kshirsagar, Human cell lines for biopharmaceutical manufacturing: history, status, and future perspectives. *Crit Rev Biotechnol* 36, 1110 (2015).

[194] *https://ucsdnews.ucsd.edu/pressrelease/researchers_develop_new_tools_to_optimize_cho_cell_lines_for_making_biologi.*

[195] D. A. Prentice, Adult Stem Cells: Successful Standard for Regenerative Medicine. *Circ Res.* 124, 837-839 (2019).

[196] FDA Approved Cellular and Gene Therapy Products. Available at *https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products.* [Accessed February 20, 2020].

Finally, the FDA is not charged with regulating the sourcing of donors of human tissues used in preclinical studies that support investigational new drug applications for clinical trials. The agency's primary regulatory and enforcement role is to ensure the safety and ethical treatment of human subjects in clinical trials and the subsequent safety and effectiveness of pharmaceuticals that are marketed for medical treatments. Reflecting this primary focus, FDA guidances that address the eligibility of donors as sources of human material for clinical investigation and clinical development do not address fetal sources at all.[197,198] They are primarily focused on the testing of donors and harvested human materials to prevent the exposure of clinical trial subjects and future treated patients to infectious pathogens and toxicants. The only official regulatory directive for fetal tissue by the FDA is in the case of FDA-funded research projects.[199] Even in this case, the FDA does not officiate an independent policy, but simply requires that funded investigators adhere to the governing federal and state statutes within their legal jurisdiction, in particular regarding obtaining informed consent from parents who donate fetal tissue for research.

Legislation and the Law

In 1988, President Ronald Reagan placed a moratorium on federal funding of all research using aborted HFT. That moratorium remained in place until lifted by President Bill Clinton in January 1993. Subsequently Congressman Henry Waxman led an effort that resulted in passage of legislation in 1993 allowing federal funding of HFT research. The statute [42 U.S.C. 289g-1 and g-2] particularly addressed fetal tissue research funded by the Secretary of Health and Human Services for transplant: "The Secretary may conduct or support research on the transplantation of human fetal tissue for therapeutic purposes." The statute was silent on basic research using fetal tissue; funding for basic research was allowed at the discretion of the NIH Director and the HHS Secretary. NIH is required by statute to make an annual report to Congress of all transplantation research funded.

Two large controlled clinical trials were finally funded to transplant aborted fetal brain tissue into Parkinson's patients. Those results, which came out in 2001[200] and 2003,[201] showed that fetal tissue transplants did not help patients and actually made many patients worse. The *New York Times* front-page story contained the doctors' de-

[197] Guidance for Industry—Eligibility determination for donors of human cells, tissues, and cellular and tissue-based products (HCT/Ps), August 2007.

[198] Guidance for Industry and FDA Staff—Regulatory considerations for human cell, tissues, and cellular and tissue based products: minimal manipulation and homologous use, November 2017.

[199] FDA Staff Manual Guide 9001.3, Vol. IV, Agency Program Directives, General or multidiscipline research involving human fetal tissue, February 11, 2016.

[200] C. R. Freed, et al., Transplantation of embryonic dopamine neurons for severe parkinson's disease, *N Engl J Med* 344, 710 (2001).

[201] C. W. Olanow, et al., A Double-blind Controlled Trial of Bilateral Fetal Nigral Transplantation in Parkinson's Disease, *Ann Neurol* 54, 403 (2003).

scriptions of patients writhing, twisting, and jerking with uncontrollable movements; the researchers called the results "absolutely devastating," "tragic, catastrophic," and labeled the results "a real nightmare."[202] Subsequently, in its required annual reports to Congress, the NIH notes that it has not provided any financial support for research on HFT transplantation, other than for data analysis of previously funded projects, since FY2003.

The 1993 federal statute has remained relatively unchanged since its initial passage, and various reviews and reports for Congress have not added substantively to the debate in a way that has resulted in modifications.[203] The undercover videos released by the Center for Medical Progress in 2015, exposing problems in enforcement of the statute as well as ethical violations, resulted in investigations by both the U.S. House and Senate in 2016, and referrals to the Department of Justice. The revelations in the undercover investigative videos and Congressional hearings led to several proposals for changes in the fetal tissue statute,[204] but none of the proposed legislation passed both chambers or was signed into law.

While there were no legislative changes in fetal tissue research policy or funding, Executive actions have made changes in federal policy. After revelations about multi-million dollar federal fetal tissue research contracts and NIH intramural research, the Department of Health and Human Services (HHS) issued a decision on June 5, 2019 to stop funding intramural fetal tissue research as well as a large research contract, and to invoke a statutory ethics review of extramural proposals for new or renewal of research.[205] HHS also renewed its commitment to fund alternative models and techniques that do not use fetal tissue. NIH and HHS subsequently issued notices implementing these changes in expectations for grant and contract proposals[206] and clarifying grant application instructions,[207] effective with any applications on or after September 25,

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[202] G. Kolata, "Parkinson's Research Is Set Back by Failure of Fetal Cell Implants," *New York Times* March 8, 2001; accessed at: *http ://www.nytimes.com/2001/03/08/health/08PARK.html*.

[203] See, e.g., Human Fetal Tissue: Acquisition for Federally Funded Biomedical Research, GAO-01-65R; Oct 4, 2000; accessed at: *https://www.gao.gov/products/164170*; Federal and State Regulation of Research Involving Human Fetal Tissue, *CRS Report* RL31147, Oct 9, 2001; Finklea K et al., Fetal Tissue Research: Frequently Asked Questions, *CRS Report* R44129, July 31, 2015.

[204] e.g., Rep. Sensenbrenner, F. James, Jr. [R-WI-5] (Introduced 02/17/2017), H.R.1203—Safe RESEARCH Act; Rep. Luetkemeyer, Blaine [R-MO-3] (Introduced 04/04/2017), H.R.1895—Protecting Life and Integrity in Research Act of 2017; and see Meredith Wadman, Senate panel seeks middle ground on human fetal tissue research and abortion, Sep. 8, 2017, *https://www.sciencemag.org/news/2017/09/senate-panel-seeks-middle-ground-human-fetal-tissue-research-and-abortion*.

[205] Statement from the Department of Health and Human Services, June 5, 2019, accessed at: *https://www.hhs.gov/about/news/2019/06/05/statement-from-the-department-of-health-and-human-services.html*.

[206] Changes to NIH Requirements Regarding Proposed Human Fetal Tissue Research, Notice Number: NOT-OD-19-128, July 26, 2019.

[207] Clarifying Competing Application Instructions and Notice of Publication of Frequently Asked Questions (FAQs) Regarding Proposed Human Fetal Tissue Research, Notice Number: NOT-OD-19-137, August 23, 2019.

2019. The new policy put in place gives ethics primacy in funding decisions. HHS has continued to move ahead with the new policy, announcing on December 23, 2019 that nominations for the ethics review board would be requested in 2020.[208] HHS announced the commencement of a 30-day period for nominations for the board on February 20, 2020.[209]

NIH funding of fetal tissue had increased over the last few years, even though all of the work was basic research and none was for transplant research (see **Table** below).

NIH Funding of Fetal Tissue Research

Research/Disease Areas (Dollars in millions, rounded)	FY 2014 Actual	FY 2015 Actual	FY 2016 Actual	FY 2017 Actual	FY 2018 Actual	FY 2019 Actual	FY 2020 Estimated
Human Fetal Tissue	$76	$80	$103	$98	$115	$109	$116

Estimates of Funding for Various Research, Condition, and Disease Categories (RCDC)
Table published: February 24, 2020
Accessed 20 April 2020, via search on "fetal tissue" at: *http://report.nih.gov/categorical_spending.aspx*

However, the change in policy with its emphasis on ethics, as well as the shift toward funding newer techniques that do not use fetal tissue, would be expected to result in a reduced level of extramural grant funding. While this is not reflected in the NIH estimate for FY 2020, news stories with interviews of scientists who had previously used aborted fetal tissue in their research as well as personal communications with scientists and journalists indicate that many researchers are removing fetal tissue from their grant proposals and switching research techniques. Even so, the research continues.

States are free to ban the practice of selling or donating aborted fetuses, as well as subsequent use of the fetuses, their organs, or parts, because federal statute does not preempt such state policies. In particular, the relevant federal statute, 42 U.S.C. 289g-1(e), allows for the conduct of fetal tissue transplantation only in accordance with applicable state and local law. A number of states have enacted policies that limit research and experimentation on aborted fetal tissue, or that restrict any monetary transactions regarding any fetal tissue use or transfer. Following is a current list of states' statutes restricting research, experimentation, sale or transfer of aborted fetal tissue.

[208] Notification of HHS Plan to Publish a Statement Announcing the Intention to Convene an NIH Human Fetal Tissue Research Ethics Advisory Board for Fiscal Year 2020 and Soliciting Nominations, Notice Number: NOT-OD-20-053, December 23, 2019.

[209] HHS Notice of Committee Establishment, Notice of Intent To Convene, and Call for Nominations for the NIH Human Fetal Tissue Research Ethics Advisory Board for Fiscal Year 2020, 85 FR 9785 (February 20, 2020). *Federal Register: The Daily Journal of the United States*. Web. 20 February 2020.

State	Year	Statute
North Dakota	1975 and 1989	Illegal to sell, transfer, or for research or experimentation
Oklahoma	1978	Illegal to sell or experiment upon
South Dakota	1993	Illegal for research
Kansas	2000	Illegal to solicit, knowingly acquire or transfer for consideration
	2013	Illegal to use fetal tissue in Midwest Stem Cell Therapy Center
	2018	Illegal for any state agency to expend money for fetal tissue research
North Carolina	2015	Illegal to sell or donate fetal tissue
Michigan	2016	Illegal to receive any compensation for transfer after elective abortion
Tennessee	2016	Illegal to buy, sell, or offer or accept money for transfer, shipping, handling
Idaho	2016	Illegal to buy, sell, transfer, or for research or experimentation
Louisiana	2016	Illegal to buy, sell, donate, transfer or use for any purpose
Alabama	2016	Illegal to buy, sell, transfer, or experiment upon
Arizona	2016	Illegal to use for research or experimentation
Indiana	2016	Illegal to acquire, receive, sell or transfer
Wyoming	2017	Illegal to sell, transfer, distribute or give away, for any form of experimentation
Texas	2017	Illegal to donate tissue obtained from elective abortion
Pennsylvania	2018	Illegal to donate tissue from induced abortion
Arkansas	2018	Illegal to buy, sell, give, exchange, barter or offer to do so if tissue is from abortion
Iowa	2018	Illegal to acquire, provide, receive, or otherwise transfer

The Complex Bioethics of Human Fetal Tissue Research

Because of an atypical aspect, the bioethics debate on the permissibility of HFT research has been particularly complicated. Not surprisingly, its atypical character is highly reminiscent of the still-unsettled public debate over the permissibility of hESC research, which has in common several fundamental elements of ethics contention.

Generally, bioethics is concerned with two main categories of potential ethical trespasses in biological and biomedical scientific research. The first category of ethical trespass is breach of scientific integrity. This includes violations such as scientific fraud, plagiarism, and other forms of dishonesty or misconduct that are widely regarded as unallowable individual moral missteps. These are missteps that directly injure victimized individual scientists, as well as greater scientific communities and human society on the whole, by undermining the quality and progress of scientific research.

The second category of ethics trespass, which is a large and significant focus of bioethics, encompasses acts that cause undue injury to research subjects used in biological and biomedical research, including bodily harm, intolerable pain, extreme stress and emotional anguish, and death. This important role of bioethics regulations in ensuring the safe and humane treatment of human research subjects also extends to animals used for scientific research.

Bioethical discourse on the permissibility of HFT research has proven to be more challenging because this type of human-subjects research does not fit nicely into either of the two well-developed areas of general bioethics practice and thought, as described above. Examination of the practice of animal-based research illustrates the basis for the poor fit. Scientific research with living creatures has two primary and interrelated forms of conduct: research can occur with live creatures or with their bodies after humane sacrifice. In the latter case, the bioethics distinction between human and non-human animals arises. Whereas there are well-developed ethical guidelines for how living research animals should be treated and humanely sacrificed, no guidelines have been developed for deciding whether the organs and tissues derived from sacrificed animals should be used for research. Organs and tissues from ethically sacrificed research animals are freely available for biological and biomedical research without pause regarding ethics.

In marked contrast to animal tissues, human organs and tissues evoke complex and deep emotional responses regarding what is proper and expected for their treatment, use, and disposal. This difference in attitudes and regard owes in large part to a rich diversity of human cultural and religious practices regarding death and respect for dead human bodies. It also manifests the greater value of human organs and tissues for medical applications like organ transplantation. These attitudes and values are highly evident in professional medical practice. For example, in current medical schools, students are taught respect and reverence for cadavers, who, when alive, consented for the use of their bodies for training new doctors in human anatomy and surgical technique. A motivating element for this important professional respect is its expression of gratitude for the free, willing, consented altruism of human donors, whether enabling research when living or after death. Unlike animal research, consent is obligatory for human donor research. Only organs and tissues of properly consented persons can be lawfully harvested for any purpose, medical or research. This difference in practice and attitudes for deceased humans transfers directly into bioethics considerations of HFT research.

Another significant distinction responsible for increasing the complexity of bioethics deliberations on HFT research, in particular, is that HFT specimens used for research exist in displacement from their source. Generally in animal research, the scientist who sacrifices an animal is the same scientist who performs research with the derived tissues. There are, of course, also many examples of animal tissues being supplied to secondary, and even tertiary, sites of use; but the synonymous identity of the producer and the user is widespread in biological and biomedical research. Currently, in HFT research, such an identity rarely, if ever, occurs. This displacement of the user from the

producer acts to displace and confuse responsibility for evaluating whether the use of HFT for research is ethical or unethical scientific conduct. The same relationship is also responsible for complicating the current bioethics debate of this issue.

The displacement of responsibility that complicates the bioethics discussion on HFT research is not a new bioethics problem. The same problem existed and continues to exist for hESC research. However, an important distinction is that, although HFT research began in this state, hESC research did not. In the early days of hESC research, the producer and user were the same scientist. In later years, as a basis for permitting continued public funding of hESC research in the U.S., the NIH issued guidelines that permitted funding of research projects, if they had a displaced source of hESCs, which were not expressly derived for the instant research. A similar tactic was used to achieve a court judgment against a public complaint that hESC research was in violation of existing law.[210] The court ruled that an ambiguity in the language of the law regarding the nature of impermissible relationships between the producers of hESCs, which required the death of human embryos, and the subsequent users of them for research made the intent of the law's congressional authors uncertain. Based on this uncertainty, the court ruled that the law (the Dickey-Wicker Amendment) was ambiguous on the permissibility of research with hESCs that were not destroyed in the funded research, *per se*. This ruling allowed research with displaced hESCs to continue, legally if not ethically.

The legal precedent of hESC research significantly motivates a very prevalent proponent bioethics view for HFT research. In both cases, a highly pragmatic ethic operates as the justification argued by scientists who wish to engage in the research. The common argument is that the potential for good in the form of biomedical advances outweighs troubling concerns over ethical and moral trespasses. Here, the producer-user displacement relationship is deployed in a twist of ethics logic. Since the using scientists view themselves as not responsible for the deaths that yield human tissues for their research, they often suggest that their activity turns a bad thing, the death of innocent human beings, into a good thing, potentially life-saving research. This ethics legerdemain is further enabled by the common fatalistic suggestion that the sourcing human deaths will occur whether or not the research occurs. Thereby, proponents of the research conclude that since the deaths were inevitable, attempting to derive some benefit from them for the public good is ethically permissible and even desirable (See for example McCune and Weissman, 2019).[211]

Users of HFT for research leverage the producer-user displacement to argue that the research is not an economic driver for the deaths that support it. Even proponent scientists and others who advocate for HFT research acknowledge that the commodification of human beings, whether embryos or fetuses, is ethically unacceptable and morally reprehensible. To maintain their position that HFT research does not engender

[210] *Sherley v. Sebelius*, 2010, 2011, 2012.

[211] J. M. McCune and I. L. Weissman, The ban on U.S. government funding research using human fetal tissues: How does this fit with the NIH mission to advance medical science for the benefit of the citizenry? *Stem Cell Reports* 13, 777-786 (2019).

economic incentives for elective abortions (and embryo destruction for hESC production), as described earlier herein, advocates for the research ignored the emergence of a complex human organs and tissues supply economy based on both procurement and distribution by nonprofit and for-profit agents. The well-reported undercover video surveillance of the CMP[212] demonstrated how financial incentives for HFT from elective abortions extended from research scientists, to for-profit suppliers, to abortion providers. As a result of the CMP investigations, sanctions by both state and federal regulators have, for the time being, disrupted—but not totally blocked—this pipeline by closing the operations of several for-profit suppliers.

Though the displacement factor is a major complication in the HFT research bioethics debate, it pales in comparison to the challenge caused by the more long-standing issue of the personhood status of prenatal human beings. In the bioethics of equal treatment, the absence of standing as a human being is a significant disadvantage. It is also a disadvantage in law, where legal standing is required to be acknowledged for rights to and in court proceedings. Enacted in 1986, only one state in the U.S., Louisiana, has a law that affirms and protects the rights of human embryos as juridical persons, meaning that they cannot be owned as property or destroyed intentionally.[213] In all other states, the biological status of human embryos as living human beings does not translate into legal status and legal standing in the courts. The same paradoxical breach between certain biological human status and legal person status occurs for human fetuses as well.

There is no shortage of examples in modern human history of immoral, unjust, and unethical laws. Noted examples are the now overturned anti-miscegenation laws that barred interracial marriage in some southern U.S. states and the many racially discriminatory "Jim Crow" laws that defined American society from the late 19th century until well into the second half of the 20th century. In retrospect, their trespasses and errors and the social and political forces that enabled them are generally acknowledged. HFT research, which is enabled by the effect of court decisions like *Roe v. Wade,* exists at such a moment now. The essential bioethics dilemma is not the research itself, but instead the legal elective abortions that present it as an option for consideration by scientists and the society they serve.

In *Roe v. Wade*, the Supreme Court did not acknowledge or respect the fetus as a legal person. In fact, the justices set the precedent for ignoring the biological status of human embryos and fetuses as human beings in order to justify denying them their social status as human persons. By this strategy, the Court was able to conform an unprecedented three-person court case into the traditional case form of *plaintiff v. defendant*.[214] Dismissing and ignoring the fetus, the Court enabled one of the greatest human tragedies of our time, the legalized, and in many cases government-funded, deaths of an estimated 60 million or more prenatal babies.[215]

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[212] https://www.centerformedicalprogress.org/cmp/investigative-footage/.

[213] LA-RS 9 §129.

[214] J. L. Sherley, Presumptions of scientific knowledge in the evolution of ethical policies for nascent individuals. *Ethics in Biol. Engineer. Med.—An Internat. J.* 3, 195-208 (2012).

[215] National Right to Life, https://nrlc.org/uploads/factsheets/FS01AbortionintheUS.pdf (2019).

The bioethics discussion of the permissibility of HFT research is really only a complex extension of the more foreboding moral, ethical, and social debate on the permissibility of legalized abortion. In the early days of the related hESC research debate, poor education on the biology of human life—caused by obfuscating unscientific ideas promulgated in the *Roe v. Wade* decision—was a major impediment to informed exchanges. But in the case of human fetuses, the living human status of the victims is not in question. The bioethics debate is, however, fettered by the legal controversy over whether human fetuses merit full rights as human persons under the law. The reasoned overturning of *Roe v. Wade* will be essential for achieving a historical correction of this misguided thinking in our own time. In the meantime, the moral debate will remain settled with the resolution that it reached from its start. The beginning of human life makes new human beings persons who merit all the rights and protections permitted to other human persons, to be free from harm and death caused by others.

Research Practice Implications

In the previous pages, an overwhelming amount of evidence has been presented to convince the reader that use of fetal tissue from abortions is neither ethical nor necessary to propel scientific discovery forward. Yet, if this is true, why do so many scientists continue to propagate its use? We contend that the explanation is partly historical with insufficient decades-old guidelines further fueled by faulty reasoning and a profound lack of transparency regarding the presence of HFT in the scientific community, as discussed in more detail in previous sections describing the widespread use of continuous fetal cell lines and early vaccine studies.

In 1988, the NIH convened a panel of non-government experts, which included ethicists, lawyers, theologians, physicians and biomedical researchers, to evaluate the ethical, legal and social implications of fetal tissue transplantation from elective abortions. The conclusion of the majority of panel members was that though "it is of moral relevance that HFT has been obtained from induced abortion," fetal tissue transplantation research is "acceptable public policy" provided that certain safeguards are in place. Specifically, they recommended that there be anonymity between the donor and recipient and that special consent procedures be used to separate the decision to abort from the decision to donate the tissue.[216] Panel members opposed to this decision maintained that it is impossible to isolate the abortion from use of fetal tissue[217] and, therefore, those involved with procuring and using this tissue remain complicit with abortion. Now, 32 years and 60+ million abortions later (in the U.S. alone), who was right? Have the guidelines been successful in isolating the act of abortion from use of aborted body parts? Have the guidelines been effective in exempting those procuring or using these tissues from any ethical responsibility for the abortion procedures? To assist with this question, the general process by which fetal tissue from an abortion is

[216] M. C. Coutts, *Fetal Tissue Research*, Scope Notes 21, National Reference Center for Bioethics Literature, The Joseph and Rose Kennedy Institute of Ethics (1993).

[217] J. Bopp Jr., "Fetal Tissue Transplantation and Moral Complicity with Induced Abortion," Chapter 4 in *The Fetal Tissue Issue: Medical and Ethical Aspects*, ed. by Peter Cataldo and Albert Moraczewski, 1994.

used for research or medicine is schematized in **Figure 4**. As illustrated, the abortion takes place and organs are harvested from the fetus (Step 1) often with the assistance of a tissue procurement organization (TPO). The fetal organs may be delivered directly to a researcher (Step 2a), sent to a commercial entity for further processing (Step 2b), or delivered directly to medical personnel for direct transplantation (Step 2c). The fetal tissue products are sold by the commercial entity, often in another form (*i.e.*, cells) rather than recognizable organs (Step 3). The researcher will purchase the tissue or cells for their experiments (Step 4) and publish the results of their studies (Step 5a) with the goal that the findings may eventually lead to a better understanding of human health and disease, which may in turn result in new drugs or strategies administered by medical personnel (Step 5b) to the public (Step 5c). Funding and/or other means of support for one or more steps of this process is or has been provided by various organizations such as abortion clinics (i.e., Planned Parenthood), the National Institutes of Health (NIH), the Food and Drug Administration (FDA), and both public and private companies.

Based on the recommended guidelines, a clear separation between the act of the abortion (step 1) and all ensuing steps (2-5) should be in place. Yet, is this actually true or even possible? There are several reports of researchers being physically present at the time of the abortion to assess the quality or type of organs obtained.[218] While some claim that this direct interaction rarely occurs, the requirement that the fetal tissue have a minimal postmortem period before use, contain living cells, and be of a certain quality to meet the specific needs of the researcher will never change. In order to sustain 95% of the cells, the live tissue would need to be preserved within five minutes of the abortion. Within an hour, the cells deteriorate, rendering the specimens useless.[219] These requirements are standard and thus common to all agents procuring, processing or using this tissue. Therefore, whether the agent makes this demand directly to the abortion provider, to a commercial entity or by simply purchasing such "products," the end result is effectively the same. The researchers' requirements influence the abortion process. Additional requirements for a certain type and age of tissue have also been shown to dictate the timing of the abortion, as well as certain aspects of the procedure itself, which can also increase the risk to the mother. For example in order to harvest brain tissue from fetuses of 9-11 weeks gestational age, the mother underwent general rather than safer local anesthesia.[220] While still in the womb and alive, the fetus succumbed to the performance of a vacuum aspiration. Clearly, even if the end-user is not physically present at the time of the abortion, some degree of cooperation between the end-user and the abortion provider remains.

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[218] B. Gridelli, et al., Efficient Human Fetal Liver Cell Isolation Protocol Based on Vascular Perfusion for Liver Cell–Based Therapy and Case Report on Cell Transplantation. *Liver Transplantation* 18, 226-237 (2012); G. Pietrosi, C. Chinnici, "Report on Liver Cell Transplantation Using Human fetal Liver Cells" in Methods in Molecular Biology. (Humana Press Inc, 2017) Chapter 20, pp. 283-294.

[219] Ibid.

[220] I. Madrzao et al. *Fetal Homotransplants (Ventral Mesencephalon and Adrenal Tissue) to the Striatum of Parkinsonian Subjects*, *Archives of Neurology*, 47, 1281-2 (1990).

Figure 4

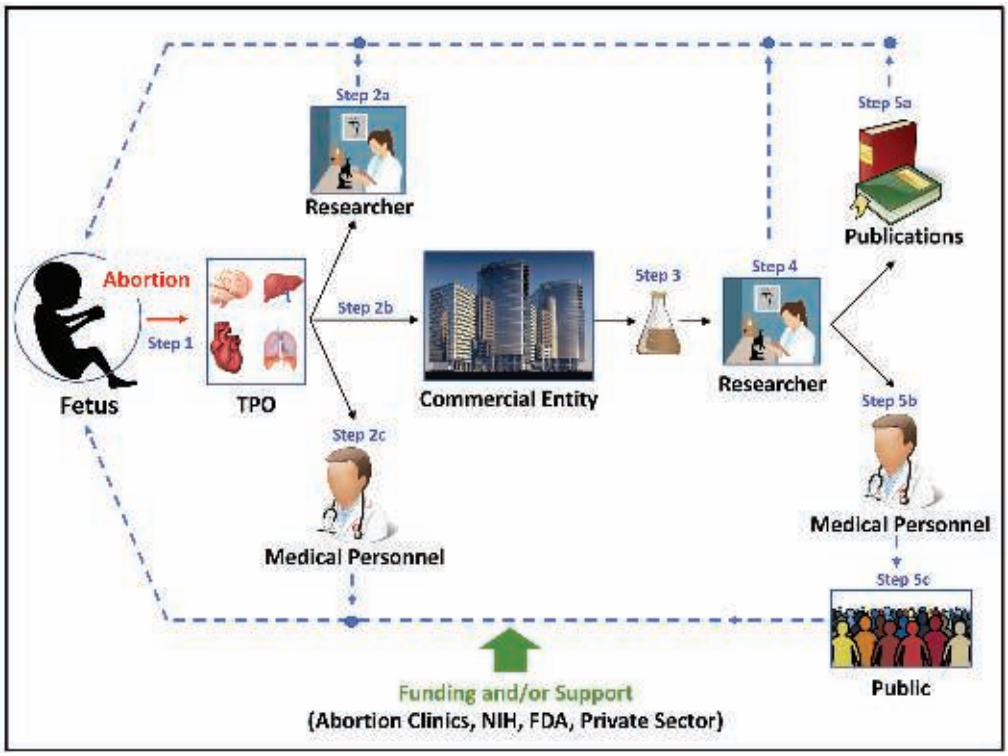

Figure 4. Fetal tissue supply chain. Shown are the steps to obtain and use fetal tissue in research and medicine. Organs are harvested from the aborted fetus (Step 1), often with the assistance of a tissue procurement organization (TPO). Fetal organs may be delivered directly to a researcher (Step 2a), sent to a commercial entity for further processing (Step 2b), or delivered directly to medical personnel for direct transplantation (Step 2c). Fetal tissue products are sold by the commercial entity, often in another form (i.e., cells) rather than recognizable organs (Step 3). The researcher will purchase the tissue or cells for their experiments (Step 4) and publish the results of their studies (Step 5a). Biomedical research leads to new drugs or strategies administered by medical personnel (Step 5b) and available to the public (Step 5c). As indicated, the use of this tissue continues to fuel the abortion—industry—researcher pipeline, which is funded and/or supported in direct or indirect ways by several different entities.

Despite the many interdependencies between the act of abortion and the use of fetal tissue, many argue that they are still not morally complicit because they did not "intend" that the abortion occur. Those using this argument are particularly satisfied with this explanation when tissue from an abortion that occurred decades earlier (*e.g.* HEK293[221]) is used. It is argued that the abortion has already been performed. Their action now has nothing to do with a decision made in the past. As Wong *et al*. describe, it is not difficult to imagine a scenario where the researcher may have to meet certain research deadlines, or may have tried unsuccessfully for the past several months to

[221] A. Wong, *The Ethics of HEK 293*, National Catholic Bioethics Quarterly, 473-795 (2006).

generate a cell line with certain characteristics and now needs more fetal tissue. The researcher may therefore begin to hope that more abortions take place so that there is a greater chance of obtaining the tissue needed by a certain date to continue the work. This scenario, described almost 14 years ago, is no longer simple conjecture. Laboratory documents subpoenaed by the U.S. House Select Panel on Infant Lives show comments in the notebook of a lab assistant that included "stomach broken, no pancreas"—with a frowning face emoji next to it. Another entry declared "entire pancreas—whoo hoo!!" Still another entry regarding brain tissue stated, "she plated it Monday they grew wonderfully!!" Clearly the claim that the end-user does not intend the abortion since he has no control over the decision or procedures to abort is therefore untenable in this context. It is ethically discordant to say, "I had no control over the abortion" and then eagerly wait for it to take place.

Still the rationalization continues. A common analogy used to justify use of aborted tissue is that it is analogous to the situation of using the heart of a murder victim to save the life of a person dying of heart disease. It is argued that it would be wrong *not* to use an available heart despite the sordid circumstances that made it available. However, there is a very important difference between homicide, which is against the law, and abortion, which is legal. It is highly unlikely that homicide will become legal to provide organs for transplants. In striking contrast, abortion is presently legal. There is nothing to stop abortion from occurring simply for reasons of obtaining tissue for sale or research or even "summer camps," like the case of aborted fetal tissue being used to supply human brain dissections for summer students.[222] In a recent article published in the *Nature* magazine,[223] researcher Lishan Su said that his research, working with humanized mice, requires one fetal liver per month, between 14 and 19 week gestation; and this demand for fetal tissue is continuous as is true for other labs doing similar research. Plainly, without the existence of a market created by the end-user there would be no need to obtain, process and sell fetal tissue. There would be no scientifically motivated "need" for abortion. Therefore, all those knowingly and freely involved with fostering and funding the continuation and growth of this abortion-industry-researcher complex are cooperating with the moral and ethical trespass of abortion.

Emphasized above are the words "knowingly and freely," which allude to the ultimate responsibility of the researcher using this tissue or products derived from it. Many researchers who use these abortion-derived materials and seeking a certain type of cell line or tissue for purchase (Fig 4, Step 4) obtain them by contacting a commercial entity that sells research products. The company representative may recommend a "standard" kit that might include materials originally sourced from abortions. As a result, the researcher may unknowingly become involved in this abortion-industry-complex. By the time a researcher becomes aware of the origins of the tissue from elective abortions,

[222] R. Nathanson, UNMHSC lab assistant's notebook details use, condition of fetal tissue, *Albuquerque Journal*, Jul 31, 2016.

[223] M. Wadman, The Truth About Fetal Tissue Research, *Nature* 528(7581), 178-181 (2015).

they may have already performed numerous experiments, published data and applied for grant funding, making it increasingly difficult to switch to a non-abortion alternative without concerns about losing their funding or job. In essence, the researcher has become unknowingly "addicted" to an abortion-derived cell source and a victim of an undisclosed commercial product. It gets worse. As the studies continue, the researcher publishes his results, fostering more interest by other scientists, who in turn perform similar studies, using the same cell source, publish their results and further foster use and dissemination of these abortion-derived cell sources (Fig.4, Step 5a). If the studies result in a treatment for human disease, the medical profession now becomes involved (Fig. 4, Step 5b). Eventually, the public (Fig. 4, Step 5c) becomes the recipient of treatments developed or produced using abortion-derived material, further fueling rationalization to justify their source from elective abortions.

Certainly, we are fast approaching a time when the abortion industry is so enshrined in our "free-market" society that decreased options for ethically-derived medical treatments limit our "free choice." Clearly, there is an urgent need to bring to science a greater awareness and responsibility regarding the ethical implications of our choices. Yet there is also an important need to improve transparency regarding the use and propagation of abortion-derived fetal tissue for the scientist, the company employee, medical personnel, and the public. This, in turn, should lead to a mobilization of conscience in favor of ethically and morally responsible treatment of human beings at all stages of their life, not only by scientists, but by everyone else as well.

Conclusion

This in-depth analysis surrounding the conduct and practice of using HFT from elective abortions in research has uncovered the depth of injustice being done to the preborn in our society. Facts expose how the remains of aborted fetuses, obtainable only by the deliberate induction of their death, have been exploited and treated as commodities for over a century. And this practice continues today, perpetuated by a small proportion of scientists who want to keep this practice ongoing. Financial incentives also exist for various individuals and entities, and the market dynamics of supply and demand place vulnerable populations at risk for abuse, specifically women seeking abortions and their preborn children.

Many false and misleading claims continue to be used to justify these requests for HFT, despite an abundance of ethical alternatives that have proven success and have been used to achieve many scientific advancements, including adult stem cells, cord blood, hiPSCs, organoids, and humanized mice generated with ethical sources.

Many states have recognized the importance of instituting restrictions and bans on the use of HFT from abortions for research. In addition, federal agencies are taking steps to ensure that federal funding is not used indiscriminately to support research using HFT from abortions by 1) allocating money to advance ethical alternatives that do not rely on tissue from abortions, 2) establishing an ethics panel to review the justification

for every extramural grant that proposes to use HFT from abortions, and 3) prohibiting intramural spending on abortion-derived HFT specimens.

The complex bioethics and serious societal implications of continuing the use of HFT from abortions in research cannot be overstated. The use of all HFT from abortions—and all products derived from it—in research must come to an end, so that only the best and most ethical scientific advancements are made moving forward. The path chosen by a certain number of scientists in the past need not determine the future path for the rest of us. One can never know the breakthroughs that would have come if a different path had been chosen, a path free from the controversy of abortion. Ample scientific evidence points to several valuable ethical alternatives that have always been available. There was, and will never be a "need" for HFT from abortions to make scientific advancements in research and medicine.

By adhering to the highest ethical standards, the best science and most honorable endeavors of scientific discovery will move forward. These practices will service all humanity, because they will value the sanctity of *every* human life and respect the consciences of *all* scientists, physicians, and patients, without exclusion or exploitation of any group within our society.

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Abbreviations

ABR	Advanced Bioscience Resources
ATCC	American Type Culture Collection
BLT	bone marrow, liver, thymus (humanized mouse model)
CDC	Centers for Disease Control and Prevention
CHO	Chinese hamster ovary
CMP	The Center for Medical Progress
DNA	Deoxyribonucleic acid
FDA	Food and Drug Administration
HEK293	Human embryonic kidney
hESC	human embryonic stem cell
HFT	human fetal tissue
HHS	Health and Human Services
HIPAA	Health Insurance Portability and Accountability Act of 1996
hiPSC	human induced pluripotent stem cell
HIV	human immunodeficiency virus
HSC	hematopoietic stem cell
hu-HSC	humanized mouse model produced with hematopoietic stem cells
hu-PBL	humanized mouse model produced with peripheral blood mononuclear cells

hu-PBMC	humanized mouse model produced with peripheral blood mononuclear cells
HUVEC	human umbilical vein endothelial cell
JP2MRI	John Paul II Medical Research Institute
NeoThy	humanized mouse model produced with neonatal thymus
NIH	National Institutes of Health
PBMC	peripheral blood mononuclear cell
PP	Planned Parenthood
RNA	ribonucleic acid
TPO	tissue procurement organization