



History of Fetal Tissue Research and Transplants

Human fetal tissue research has gone on for decades. However, the success of fetal tissue transplants has been meager at best, and ethically-derived alternatives exist and are coming to dominate the field.

Proponents of using fetal tissue from induced abortion point to three areas in claims of the need for harvesting tissue:

- Transplantation to treat diseases and injuries
- Vaccine development
- Basic biology research

Fetal Tissue Transplantation: The first recorded fetal tissue transplants were in 1921 in the UK, in a failed attempt to treat Addison's disease,¹ and in 1928 in Italy, in a failed attempt to treat cancer.² The first fetal tissue transplant in the U.S. was in 1939, using fetal pancreatic tissue in an attempt to treat diabetes. That attempt also failed, as did subsequent similar fetal tissue transplants in 1959. Between 1970 and 1991 approximately 1,500 people received fetal pancreatic tissue transplants in attempts to treat diabetes, mostly in the former Soviet Union and the People's Republic of China. Up to 24 fetuses were used per transplant, but less than 2% of patients responded.³ Today, patients take insulin shots and pharmaceuticals to control their diabetes, and adult stem cell transplants have shown success at ameliorating the condition.⁴

Between 1960 and 1990, numerous attempts were made to transplant fetal liver and thymus for various conditions. According to one review, "the clinical results and patient survival rates were largely dismal."⁵ Conditions such as anemias and immunodeficiencies, for which fetal tissue attempts largely failed, are now treated routinely with adult stem cells, including umbilical cord blood stem cells,⁶ even while the patient is still in the womb.⁷

¹ Hurst AF *et al.*, Addison's disease with severe anemia treated by suprarenal grafting, *Proc R Soc Med* 15, 19, 1922

² Fichera G, Impianti omoplastici feto-umani nel cancro e nel diabete, *Tumori* 14, 434, 1928

³ Federlin K *et al.*, Recent achievements in experimental and clinical islet transplantation. *Diabet Med* 8, 5, 1991

⁴ See, *e.g.*, Voltarelli JC, Couri CEB, Stem cell transplantation for type 1 diabetes mellitus, *Diabetology & Metabolic Syndrome* 1, 4, 2009; doi:10.1186/1758-5996-1-4; Couri CEB *et al.*, C-Peptide Levels and Insulin Independence Following Autologous Nonmyeloablative Hematopoietic Stem Cell Transplantation in Newly Diagnosed Type 1 Diabetes Mellitus, *JAMA* 301, 1573-1579, 2009; Voltarelli JC *et al.*, Autologous Nonmyeloablative Hematopoietic Stem Cell Transplantation in Newly Diagnosed Type 1 Diabetes Mellitus, *JAMA* 297, 1568-1576, 2007

⁵ Ishii T, Eto K, Fetal stem cell transplantation: Past, present, and future, *World J Stem Cells* 26, 404, 2014

⁶ See, *e.g.*, Bernaudin F *et al.*, Long-term results of related myeloablative stem cell transplantation to cure sickle cell disease, *Blood* 110, 2749-2756, 2007 AND de Heredia CD *et al.*, Unrelated cord blood transplantation for severe combined immunodeficiency and other primary immunodeficiencies, *Bone Marrow Transplantation* 41, 627, 2008

⁷ Loukogeorgakis SP, Flake AW. In utero stem cell and gene therapy: Current status and future perspectives, *Eur J Pediatr Surg* 24, 237, 2014

Note that fetal tissue has been taken in a number of cases from fetuses at developmental ages where fetal surgery is now used to correct problems and save lives, and at stages where science now demonstrates that the unborn fetus can feel pain.

Between 1988 and 1994, roughly 140 Parkinson's disease patients received fetal tissue (up to six fetuses per patient), with varying results.⁸ 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.⁹

In 2001, the first report of a full clinical trial¹⁰ (funded by NIH) using fetal tissue for Parkinson's patients was prominently featured in the *New York Times*,¹¹ 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.¹² 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.¹³ In contrast, adult stem cells have shown initial success in alleviating Parkinson's symptoms.¹⁴

A recent 2009 report emphasizes the instability and danger of fetal tissue transplants. A patient with Huntington's disease was recruited into a study (funded by NIH) in which she had fetal brain cells injected into her brain. She did not improve, and instead developed in her brain a growing mass of tissue, euphemistically termed "graft overgrowth" by the researchers.¹⁵

Disastrous results for patients are seen not only with fetal tissue but also with fetal stem cells. In a recent example, a young boy developed tumors on his spine, resulting from fetal stem cells injected into his body.¹⁶

⁸ Reviewed in: Fine A, Transplantation of fetal cells and tissue: an overview, *Can Med Assoc J* 151, 1261, 1994

⁹ Folkerth RD, Durso R, Survival and proliferation of nonneural tissues, with obstruction of cerebral ventricles, in a parkinsonian patient treated with fetal allografts, *Neurology* 46, 1219, 1996

¹⁰ Freed CR *et al.*, Transplantation of embryonic dopamine neurons for severe parkinson's disease, *N Engl J Med* 344, 710, 2001

¹¹ Gina 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>

¹² Olanow CW *et al.*, A Double-blind Controlled Trial of Bilateral Fetal Nigral Transplantation in Parkinson's Disease, *Ann Neurol* 54, 403, 2003

¹³ Braak H, Del Tredici K, Assessing fetal nerve cell grafts in Parkinson's disease, *Nature Medicine* 14, 483, 2008

¹⁴ See, *e.g.*, Lévesque MF *et al.*, , Therapeutic microinjection of autologous adult human neural stem cells and differentiated neurons for Parkinson's disease: Five-year post-operative outcome, *The Open Stem Cell Journal* 1, 20, 2009

¹⁵ Keene CD *et al.*, A patient with Huntington's disease and long-surviving fetal neural transplants that developed mass lesions, *Acta Neuropathol* 117, 329, 2009

¹⁶ Amariglio N *et al.*, Donor-Derived Brain Tumor Following Neural Stem Cell Transplantation in an Ataxia Telangiectasia Patient, *PLoS Med* 6(2): e1000029. doi:10.1371/journal.pmed.1000029, 2009; BBC News, "Stem cell 'cure' boy gets tumour", 18 February 2009, accessed at: <http://news.bbc.co.uk/2/hi/health/7894486.stm>

In contrast, a recent review found that as of December 2012, over one million patients had been treated with adult stem cells.¹⁷ The review only addressed hematopoietic (blood-forming) adult stem cells, not other adult stem cell types and transplants, so this is a significant underestimate of the number of patients who have benefitted from adult stem cell therapies.

Vaccine Development: The earliest attempts at growing viruses sometimes used cultures of mixed human fetal tissue, but not individual cultured cells. For example, the proof of principle experiment showing that polio virus could be grown in non-nervous tissue culture in 1949, used human fetal tissue.¹⁸ But it is not the case that the 1954 Nobel Prize given to Enders *et al.* was for production of polio vaccine, nor even for growth of enough virus used to produce the polio vaccine.

Instead, the original Salk and Sabin polio vaccines were both produced using laboratory-cultured monkey tissue.¹⁹ Later, poliovirus was produced in human fetal cell lines (WI-38, 1961,²⁰ fetal female lung; MRC-5, 1966,²¹ fetal male lung), but also in HeLa cells,²² a human cancer cell line that is not made from fetal tissue. Most modern manufacturers of polio vaccine now use other specific cell types including monkey cells; most do not use any human fetal cells, and none use freshly aborted fetal tissue. No current vaccines are made using fresh aborted fetal tissue.

The first individual human cell (not tissue) grown in the lab was a tumor cell in 1951,²³ because the growth character of cancerous cells made them easiest to grow. In the 1960's and 1970's, cell culture work operated under an assumption that younger cells were better, grew faster, lived longer, so fetal cells obtained from abortion were used. These cells adapted to lab culture and continued to grow, becoming known as a "cell line" because they developed as a lineage from different, specific cells grown in the lab. A few human fetal cell lines (WI-38, MRC-5) are still in use for some vaccine production.²⁴ However, few vaccines are now produced using fetal cell lines, and none using fetal tissue. Newer cell lines, e.g., A549 cells (adult human),²⁵ Sf9 cells

¹⁷ Gratwohl A *et al.*, One million haemopoietic stem-cell transplants: a retrospective observational study, *Lancet Haematology* 2, e91, 2015

¹⁸ Enders JF *et al.*, Cultivation of the Lansing strain of poliomyelitis virus in cultures of various human embryonic tissues, *Science* 109, 85, 1949

¹⁹ Salk JE, Recent Studies on Immunization against Poliomyelitis, *Pediatrics* 12, 471, 1953; and Salk JE *et al.*, Formaldehyde Treatment and Safety Testing of Experimental Poliomyelitis Vaccines, *Am. J. Public Health* 44, 563, 1954; and Salk JE *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 Sabin AB, Present status of attenuated live-virus poliomyelitis vaccine, *JAMA* 162, 1589, 1956

²⁰ Original fetal cell cultivations 1961, original poliovirus growth 1962 in WI-1, standardized in WI-38; Hayflick L, Moorhead PS, The serial cultivation of human diploid cell strains, *Experimental Cell Research* 25, 585, 1961; Hayflick L *et al.*, Preparation of poliovirus vaccines in a human fetal diploid cell strain, *Am. J. Hyg.* 75, 240, 1962; Hayflick L, The limited in vitro lifetime of human diploid cell strains, *Exp. Cell Res.* 37, 614, 1965.

²¹ Jacobs JP *et al.*, Characteristics of a Human Diploid Cell Designated MRC-5, *Nature* 227, 168, 1970

²² Scherer WF *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

²³ Gey GO *et al.*, Tissue culture studies of the proliferative capacity of cervical carcinoma and normal epithelium, *Cancer Res.* 12, 264, 1952

²⁴ 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>

²⁵ See e.g., Shabram P and Kolman JL, Evaluation of A549 as a New Vaccine Cell Substrate: Digging Deeper with Massively Parallel Sequencing, *PDA J Pharm Sci Technol* 68, 639, 2014

(insect),²⁶ EB66 (duck),²⁷ and better culture techniques make reliance on fetal cells an antiquated science. In addition, the CDC and other leading medical authorities have noted since 2001 that “No new fetal tissue is needed to produce cell lines to make these vaccines, now or in the future.”²⁸

A clear example of the lack of necessity for further fetal tissue is development of the new vaccine -- rVSV-ZEBOV -- against Ebola virus. The successful results of the field trial, published July 31, 2015, were very welcome in the fight against this deadly disease.²⁹ This successful Ebola vaccine was not developed using fetal tissue or fetal cell lines, but rather with Vero, a monkey cell line, demonstrating again that medical science has moved beyond any need for fetal tissue in useful medical research.³⁰

Another clear example of the lack of need for freshly aborted fetal tissue in virus and vaccine studies are the recent reports on the susceptibility of developing human brain cells to Zika virus. Scientists from Florida State, Emory, and Johns Hopkins developed a successful model system to show that the Zika virus can infect and damage some developing brain cells.³¹ The established experimental model, which the authors of the paper note can now be used for further investigations of developing brain as well as screening therapeutic compounds, was not developed using fetal tissue. The successful system uses human induced pluripotent stem cells (iPS cells), which are ethically created from skin or other normal cell types, earning the 2012 Nobel Prize for Dr. Shinya Yamanaka, their originator.

Another recent study by a Brazilian group confirms the susceptibility of developing human brain cells to Zika virus infection, with potential damage to infected brain cells. Again, the successful study did not use human fetal tissue, but rather human iPS cells.³²

Modern vaccine development does not rely on fetal tissue or human fetal cell lines. Another example of this is the recent success of a field test of a **vaccine against Dengue virus**, a close

²⁶ See e.g., Glenn GM et al., Safety and immunogenicity of a Sf9 insect cell-derived respiratory syncytial virus fusion protein nanoparticle vaccine, *Vaccine* 31, 524, 2013; AND Khan AS, FDA Memo: Cell Substrate Review for STN 125285, January 14, 2013; accessed at:

<http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM339125.pdf>

²⁷ See e.g., Brown SW, Mehtali M, The Avian EB66(R) Cell Line, Application to Vaccines, and Therapeutic Protein Production, *PDA J Pharm Sci Technol.* 64, 419, 2010

²⁸ See, e.g., “Vaccine Ingredients – Fetal Tissues,” The Children’s Hospital of Philadelphia, 2014; accessed July 21, 2015 at www.chop.edu/centers-programs/vaccine-education-center/vaccine-ingredients/fetal-tissues; CDC quote accessed at: <http://www.ascb.org/newsfiles/fetaltissue.pdf>

²⁹ Butler D et al., Ebola on trial, *Nature* 524, 13, 6 August 2015; Henao-Restrepo AM et al., Efficacy and effectiveness of an rVSV-vectored vaccine expressing Ebola surface glycoprotein: interim results from the Guinea ring vaccination cluster-randomised trial, *Lancet* published online July 31, 2015; doi: 10.1016/S0140-6736(15)61117-5

³⁰ Agnandji ST 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>

³¹ Tang H et al., Zika Virus Infects Human Cortical Neural Progenitors and Attenuates Their Growth, *Cell Stem Cell* 18, 2016; *in press*, doi: 10.1016/j.stem.2016.02.016

³² Garcez PP et al., Zika virus impairs growth in human neurospheres and brain organoids, *PeerJ Preprints* 4:e1817v3; doi: 10.7287/peerj.preprints.1817v3

relative of Zika.³³ The vaccine provided 100% protection,³⁴ but was developed using monkey cells and a mosquito cell line.³⁵

Basic Biology Research: Broad, undefined claims continue to be made that fetal tissue and fetal cells are needed to study basic biology, development, disease production, or other broad study areas. However, this still relies on antiquated science and cell cultures. Current, progressive alternatives such as **induced pluripotent stem (iPS) cells** provide an unlimited source of cells, which can be produced from tissue of any human being, without harm to the individual donor, and with the ability to form virtually any cell type for study and modeling,³⁶ or potential clinical application.³⁷ A November 2015 published report convincingly documents that iPS cells are molecularly and functionally equivalent.³⁸

Stem cells from **umbilical cord blood** also show significant potential not only as laboratory models, but also have unique advantages for clinical applications and are already treating patients for numerous conditions.³⁹

Further, in terms of modeling human tissues and cells, including during development, scientists have now developed methods to form 3-dimensional cellular structures that faithfully form tissue structure and function as that from normal organs. Termed “**organoids**”, the constructs provide superior models to study tissue organization and disease, as well as starting points for potential transplantation. One 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 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.⁴⁰

Several recent studies have used **organoids to observe normal brain development as well as model aspects of abnormal development**. The organoids have also provided excellent models

³³ Kirkpatrick BD *et al.*, The live attenuated dengue vaccine TV003 elicits complete protection against dengue in a human challenge model, *Sci. Transl. Med.* 8, 330ra36, 2016.

³⁴ Check Hayden E, Dengue vaccine aces trailblazing trial, *Nature*, 16 March 2016, doi: 10.1038/nature.2016.19576

³⁵ Men R *et al.*, Dengue Type 4 Virus Mutants Containing Deletions in the 3' 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 Medina F *et al.*, Dengue Virus: Isolation, Propagation, Quantification, and Storage, *Current Protocols in Microbiology* 15D.2.1-15D.2.24, November 2012

³⁶ See, *e.g.*, Marchetto MC *et al.*, Induced pluripotent stem cells (iPSCs) and neurological disease modeling: progress and promises, *Human Molecular Genetics* 20, R109, 2011

³⁷ See *e.g.*, Li HL *et al.*, Precise Correction of the Dystrophin Gene in Duchenne Muscular Dystrophy Patient Induced Pluripotent Stem Cells by TALEN and CRISPR-Cas9, *Stem Cell Reports* 4, 143, 2015

³⁸ Choi J *et al.*, A comparison of genetically matched cell lines reveals the equivalence of human iPSCs and ESCs, *Nature Biotechnology* 33, 1173, November 2015

³⁹ See, *e.g.*, Ballen KK *et al.*, Umbilical cord blood transplantation: the first 25 years and beyond, *Blood* 122, 491, 2013; AND, Roura S *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

⁴⁰ 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

to investigate Zika virus infection⁴¹ of the developing human brain, all without resorting to destruction of human life to obtain cells or samples of fetal brain tissue.

Lack of need for fetal tissue to study Zika virus was also shown by Shan et al., who developed an infectious cDNA clone of the Zika virus.⁴² The virus was originally isolated from a patient and cultured in monkey (Vero) cells. After sequencing the DNA, a template was created and cDNA produced, which could be transferred and grown in Vero cells as well as mosquito cell line C6/36.

⁴¹See e.g. Nathalie Broutet *et al.*, “Zika Virus as a Cause of Neurologic Disorders,” *New England Journal of Medicine* 374.16 (April 21, 2016): 1506–1509, doi: 10.1056/NEJMp1602708; Patricia P. Garcez *et al.*, “Zika Virus Impairs Growth in Human Neurospheres and Brain Organoids,” *Science* 352.6287 (May 13, 2016): 816–818, 10.1126/science.aaf6116; Hengli Tang *et al.*, “Zika Virus Infects Human Cortical Neural Progenitors and Attenuates Their Growth,” *Cell Stem Cell* 18.5 (May 5, 2016): 587–590, doi: 10.1016/j.stem.2016.02.016; Xuyu Qian *et al.*, “Brain-Region-Specific Organoids Using Mini-bioreactors for Modeling ZIKV Exposure,” *Cell*, e-pub April 21, 2016, doi: 10.1016/j.cell.2016.04.032.

⁴²Chao Shan *et al.*, “An infectious cDNA clone of Zika virus to study viral virulence, mosquito transmission, and antiviral inhibitors,” *Cell Host & Microbe* 19 (June 8, 2016): 1-10, doi: 10.1016/j.chom.2016.05.004