



## 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,<sup>1</sup> and in 1928 in Italy, in a failed attempt to treat cancer.<sup>2</sup> 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.<sup>3</sup> Today, patients take insulin shots and pharmaceuticals to control their diabetes, and adult stem cell transplants have shown success at ameliorating the condition.<sup>4</sup>

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."<sup>5</sup> 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,<sup>6</sup> even while the patient is still in the womb.<sup>7</sup>

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.

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

<sup>2</sup> Fichera G, Impianti omoplastici fetto-umani nel cancro e nel diabete, *Tumori* 14, 434, 1928

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

<sup>4</sup> 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

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

<sup>6</sup> 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

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

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

In 2001, the first report of a full clinical trial<sup>10</sup> (funded by NIH) using fetal tissue for Parkinson's patients was prominently featured in the *New York Times*,<sup>11</sup> 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.<sup>12</sup> 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.<sup>13</sup> In contrast, adult stem cells have shown initial success in alleviating Parkinson's symptoms.<sup>14</sup>

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.<sup>15</sup>

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.<sup>16</sup>

In contrast, a recent review found that as of December 2012, over one million patients had been treated with adult stem cells.<sup>17</sup> 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.

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

<sup>9</sup> 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

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

<sup>11</sup> 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>

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

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

<sup>14</sup> 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

<sup>15</sup> 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

<sup>16</sup> 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>

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

Vaccine development: Early attempts at growing viruses used cultures of mixed human fetal tissue, not individual cells, *e.g.*, for growth of poliovirus, 1949.<sup>18</sup> Later, poliovirus was produced in human fetal cell lines (WI-38, 1961,<sup>19</sup> fetal female lung; MRC-5, 1966,<sup>20</sup> fetal male lung). Now most manufacturers of polio vaccine use other cell types including monkey cells, and most do not use fetal cells.

The first individual human cell (not tissue) grown in the lab was a tumor cell in 1951,<sup>21</sup> 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.<sup>22</sup> However, newer cell lines and better culture techniques make this reliance on fetal cells an antiquated science. In addition, the CDC and other leading medical authorities have noted that "No new fetal tissue is needed to produce cell lines to make these vaccines, now or in the future."<sup>23</sup>

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.<sup>24</sup> 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.<sup>25</sup>

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,

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

<sup>19</sup> 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.

<sup>20</sup> Jacobs JP *et al.*, Characteristics of a Human Diploid Cell Designated MRC-5, *Nature* 227, 168, 1970

<sup>21</sup> Gey GO *et al.*, Tissue culture studies of the proliferative capacity of cervical carcinoma and normal epithelium, *Cancer Res.* 12, 264, 1952

<sup>22</sup> 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>

<sup>23</sup> 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](http://www.chop.edu/centers-programs/vaccine-education-center/vaccine-ingredients/fetal-tissues); CDC quote accessed at: <http://www.ascb.org/newsfiles/fetaltissue.pdf>

<sup>24</sup> 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

<sup>25</sup> 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/NEJMoal1502924; originally developed by the Public Health Agency of Canada, which patented it in 2003, <http://www.google.com/patents/WO2004011488A2?cl=en>

and with the ability to form virtually any cell type for study and modeling,<sup>26</sup> or potential clinical application.<sup>27</sup> 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.<sup>28</sup>

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<sup>26</sup> 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

<sup>27</sup> 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

<sup>28</sup> 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