

A Search for the Right Answer: Fetal Tissue Research and Parkinson's Disease

by

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Gretchen was 62 years old when she first noticed the weakness in her right hand. She was enjoying a winter sunset from her terrace overlooking Teague Bay on the island of St. Croix. Her neighbors had joined her, bringing snacks on a fine Wedgwood plate. As the appetizers were passed, she dropped the plate, spreading fragments and food on the tile floor. She felt terrible and embarrassed. The small group of friends put the event aside as fatigue. Gretchen's husband had recently died after a five-year battle with bone cancer.

Gretchen was vigorous, independent, and refined. She walked two to three miles every day. She was an avid golfer. She was adjusting to her husband's absence and did not depend on her three adult sons for support or advice. However, after she returned to Boston for the summer months she noticed a tremor in her right hand. She was soon diagnosed with early-stage Parkinson's disease. Gretchen was frightened. Her brother-in-law had died of pneumonia brought on by the effects of Parkinson's. At the end stage of his Parkinson's, he had developed contractures on his right side (arm and wrist). His right arm would push his hand into his throat, causing him to have trouble breathing. He received physical therapy to help prevent the contractures, but breathing became more difficult and his body was not able to successfully fight the effects of pneumonia.

Gretchen consulted several physicians and then her sons. Her oldest son, Duffy, a financial planner with Anderson Associates, advised his mother to sell the villa in St. Croix as well as the town house in Boston, and purchase an apartment in a long-term-care senior citizen complex. Her youngest son, Geoff, an insurance salesman with Lincoln Life, was in denial. He did not want anything to change. He insisted that the diagnosis was wrong and that she was fine and simply suffered from a nervous tremor, as other aging people did. Her middle son, Frank, a computer analyst with Computer Associates, was always curious and inquisitive. Once his mother was diagnosed, he searched the medical school library at the University of Massachusetts (via the Internet), beginning his research with the *Merck Manual of Diagnosis and Therapy*, which is somewhat technical for a lay-person. However, after becoming familiar with the language and the physiological effects of the disease, Frank was able to seek out and understand some of the latest results in ongoing research. He then used the *Directory of Medical Specialists* to find a doctor that he felt was "on the cutting edge" in regard to diagnosis and therapy. Frank encouraged Gretchen to use the Internet, which they found to be a mixed bag of information but an excellent resource for advocacy and support.

Description of the Disease

Parkinson's disease is a common and severe neurodegenerative disorder brought on by a progressive loss of dopamine neurons in the nigro-striatal system of the brain. (A neurodegenerative disorder results in the death of cells deep within the brain.) Symptoms vary in each patient and may include akinesia (inability to

move), tremor, weakness, poor balance, loss of dexterity, reduced sense of smell, depression, swallowing and speech problems, and double vision. Current treatment, which is based on drugs increasing dopamine in the affected areas, is effective in the early stages of the disease. However, after four to 10 years, as the disease progresses, the capacity to produce the desired result is reduced due to severe side-effects caused by the drug treatment. Consequently, after 10 years of drug treatment, the majority of Parkinson's patients are not able to maintain any sort of quality of life and eventually die of complications. This factor has led to a search for alternative treatments that can halt the disease progression and/or restore clinical function.

The Science

Most human neural tissue will not regenerate if damaged. Therefore, researchers began looking into the possibility of transplanting neural tissue. The first scientific report on neural grafting trials in human patients was published in 1905 (Shirres, D.A., "Regeneration of axons of the spinal neurons in man." *Montreal Medical Journal*, 34, 239–49). It was 80 years before another report on clinical intracerebral transplantation appeared in the scientific literature (Backlund, E.O. et al., 1985 "Transplantation of adrenal medullary tissue to striatum in parkinsonism." *Journal of Neurosurgery*, 62, 169–73). Since the middle 1980s techniques for dopamine replacement by intracerebral transplants into the striatum have been worked out in animal models of Parkinson's disease. This was done first in rodents and later in primates. The results of this research showed that transplanting fetal neurons induced long-term recovery of motor impairment. Clinical trials were subsequently initiated in several research centers in Europe, Central and North America, and China. By the end of 1990, over 100 Parkinson's patients had received grafts of fetal dopaminergic neurons. By 1994 studies had shown that "patients experienced more-prominent clinical benefits beginning 6–12 weeks after the transplant procedure with continued improvement over the three-year observation period" (Lindvall, O., et al. 1994 "Evidence of long-term survival and function of dopaminergic grafts in progressive Parkinson's Disease." *Ann. Neurol.* 35, 172–180).

Currently the Food and Drug Administration is considering another tremor control therapy. With the "Activa system," doctors drill through the skull and implant an electrode into the thalamus, the message relay center in the brain. A wire runs just under the scalp down to the collarbone, where a pacemaker-sized "pulse generator" is implanted. It sends electrical waves, custom set for each patient, to the electrode which blocks tremors by emitting constant, small electrical shocks. Activa is already sold in Europe with over 2,000 patients wearing implants since 1995. Another procedure being refined for Parkinson's patients is called postero-ventral pallidotomy (PVP), where a small metal probe is inserted into the skull, deep into the globus pallidus of the brain to surgically deaden a few of the cells in the critically overstimulated pathways. Dr. Lauri Laitinen and Dr. Iacono, Swedish researchers who have been on the forefront of fetal tissue transplant as well as PVP research, report that the prospects of relieving more symptoms using PVP may be greater than fetal grafting.

The technique of transplanting nerve tissue is still in an exploratory phase. Different procedures have been used at the various research centers. Researchers have learned from the results of the clinical studies that several important factors influence the likelihood of success. The most important are donor age, method of tissue storage, type of graft (suspension or solid), number of donors, distribution of transplanted tissue, site of implantation, use of immunosuppression, source of tissue, and patient selection. Some of the details follow but it is important to note that transplantation of fetal tissue has been used in other disease conditions. Experimental evidence is strong that fetal islet cell transplants will restore normal insulin function in diabetics (Kevin Lafferty, statement to Fetal Tissue Transplantation Research Panel, National Institutes of Health, September 15, 1988). Fetal thymus and liver transplants may be useful for blood and

immune system disorders. Also, possibilities for transplant therapy may be found for spinal cord injuries, cortical blindness, bone marrow diseases, Alzheimer's, and Huntington disease.

- For Parkinson patients, the optimal donor age for graft survival following transplantation is thought to be from the time dopamine-containing cells first appear in the mesencephalic subventricular layer until they differentiate and extend neuritic processes (Bjorklund, A. et al., 1983 "Intracerebral grafting of neuronal cell suspensions. I. Introduction and general methods of preparation." *Acta Physiol. Scand. Suppl.* 522, 1–7). This study suggests that the optimal fetal age should be between 5.5 weeks and 9 weeks post-conception. During this time the tissue is rapidly growing. It is not fully differentiated and will adapt fairly well to the signals received from surrounding tissue in the host.
- With regard to tissue storage, human embryonic tissue can be stored for up to two days in chemically defined "hibernation medium" without decrease in either the viability or number of transplanted neurons and with robust graft survival in Parkinson's disease patients. (Freeman, T.B. and Kordower, J.H., (1991) *Intracerebral Transplantation in Movement Disorders*, pp. 163–184, Elsevier).
- As to the type of graft, solid grafts extend the donor age for transplantation up to the nine-week limit. They are easier to prepare and facilitate multiple donor acquisition because of the time frame.
- The optimal number of cells required to provide a functional benefit to patients is not precise. However, clinical studies suggest that using cells from more than one donor generally produce a greater degree of improvement by the patient.
- The success of transplantation for benefits for Parkinson's disease patients is dependent on the location of the graft. The best results from substantial nigral grafting appear to be achieved with implantation into both the putamen and the caudatum. Bilateral grafts are recommended.
- Immunosuppression is still being studied. The central nervous system is a relatively immunologically privileged site. However, surgical trauma or the graft itself could disrupt tissue and permit the immune system access to graft antigens.
- Regarding donor source, fetal tissue from elective abortions is preferred. Fetal tissue from spontaneous abortions (miscarriage) is often likely to contain genetic defects, be infected or disrupted, and often nonviable due to earlier death of the fetus.
- It has not yet been determined which Parkinson's patients are the best candidates for transplantation. Patients with early development of the disease are preferred because their overall health is better due to less deterioration and fewer drug-related side effects.

New Ethical Questions

An important aspect in neural transplantation in humans is the fact that it raises ethical questions in bio-medical research concerning the retrieval and use of human embryonic and fetal material. *Embryonic state* is defined by scientists as between 15 days and 8 weeks post-conception. The *fetal stage* is taken to be the subsequent period between 8 weeks and birth. *Conception* is thought to have taken place two weeks after the beginning of the woman's last menstrual period. By 8 weeks of age the rudiments of nearly all the principal structures of the fetus have been organized when four limbs and a head are visible.

Conflict of opinion with regard to bio-medical ethical issues revolves around many facets of fetal tissue transplant research. One source of conflict lies in the collection of fetal tissue from planned abortions rather than spontaneous abortions. Nearly 80 percent of induced abortions are performed between the sixth and

eleventh weeks of gestation. Should women who abort to end unwanted pregnancies be allowed to donate the fetus for use in medical research or for therapy? Those struggling with the bio-medical issues have insisted that the abortion and subsequent transplant use remain clearly separated in all respects (reason, timing, method, result). Should fees be paid for procurement, transportation, or storage? Most guidelines established have forbidden profit or remuneration. Should a fetus be kept alive for future use as tissue transplant? Guidelines unanimously prohibit this; however, tissue can be stored in a “hibernation medium.” Death of an intact fetus is defined as absence of respiration and heart beat.

Guidelines

Concerns with regard to tissue procurement procedures have been addressed with some success. These procedures involve the timing, substance, and process of consent. In the guidelines of all research centers internationally, the reader will find that the decision to terminate a pregnancy must not be influenced by the possible use of the fetal tissue. Thus, neither the fetal age, nor the subsequent use of the fetus, should ever be a factor with regard to the procedure of abortion. Consent is always required and, whenever possible, before the abortion (NECTAR Guidelines, see Appendix).

Pros / Cons

Is it possible that the need for fetal transplant tissue may lead to planned pregnancies and abortions to produce fetal tissue? Two possible scenarios may lead to such a decision. One possibility may arise if fetal tissue transplant proves to be a successful therapy for diseases. Another may occur if the demand becomes greater than the supply available from abortion clinics.

Advocates for fetal tissue transplant research are driven by their search for ways to alleviate the pain and suffering of the disease victims and the possibilities of relief for future generations. Opponents of fetal tissue research are motivated by their concern over the exploitation of women and pressure for increased numbers of abortions. They are troubled by the prospects of doctors benefiting financially for their surgical service in abortion and the fact that they see the fetus as a living human being who is being sacrificed for another person’s welfare.

Directions for the Case

In the next class period we will have an extensive discussion of Parkinson’s disease and the particular case of Gretchen and her three sons. Each team of students in the class will be asked to consider the problem from the viewpoint of one of the sons. Their profiles are below. You and your team mates will be assigned one of these roles to research and discuss. Be prepared to “solve” the family dilemma next time.

Duffy

Duffy has accepted his mother’s fate and is concerned that she be as comfortable as possible with caregivers who can see to her physical needs. He has little respect for the medical community, believing that their primary concern is treatment of the disease, prolongation of life at all costs, and financial security. Duffy has read extensively on the utility of group homes and is searching for one such home dedicated to individuals suffering from Parkinson’s.

Frank

Frank has thoroughly investigated the medical and scientific nature of the disease and is convinced that the cure for Parkinson’s is “just around the corner.” He is convinced that the new procedures using fetal tissue

transplants and the newer ideas of cell farming, in which specific lines of cells are grown in large numbers, will give Gretchen the needed neurons to cure the disease or at least alleviate most of her symptoms.

Geoff

Geoff and his wife Marcia are extremely religious and, although not confirmed Christian Scientists, believe that good living and the grace of God will see a person through most of life's misfortunes. They know that Gretchen is aging and that children must care for their parents. Geoff does not understand the abandonment of parents proposed by Duffy. Furthermore he doesn't accept scientific explanations of disease and treatment, which so fascinate Frank.

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Internet Sites

- American Parkinson Disease Association
<http://www.apdaparkinson.org/>
- National Parkinson Foundation
<http://www.parkinson.org/>
- GateWay to Neurology at Massachusetts General Hospital
<http://neurosurgery.mgh.harvard.edu/>
- Parkinson's Disease Research Web
<http://www.ninds.nih.gov/research/parkinsonsweb/index.htm>
- NYU Hospital for Joint Diseases
<http://www.med.nyu.edu/hjd/>
- Northwestern University's Parkinson's Disease and Movement Disorders Center
<http://www.parkinsons.northwestern.edu/>
- Functional and Stereotactic Neurosurgery Staging of Parkinson's Disease
<http://neurosurgery.mgh.harvard.edu/functional/pdstages.htm>

Appendix

“Ethical Guidelines for the Use of Human Embryonic or Fetal Tissue for Experimental and Clinical Neurotransplantation and Research,” Network of European CNS Transplantation and Restoration (NECTAR).

1. Tissue for transplantation or research may be obtained from dead embryos or fetuses, their death resulting from legally induced or spontaneous abortion. Death of an intact embryo or fetus is defined as absence of respiration and heart beats.
2. It is allowed to keep intact embryos or fetuses alive artificially for the purpose of removing usable material.
3. The decision to terminate pregnancy must under no circumstances be influenced by the possible or desired subsequent use of the embryo or fetus and must, therefore, precede any introduction of the possible use of the embryonic or fetal tissue. There should be no link between the donor and the recipient, nor designation of the recipient by the donor.
4. The procedure of abortion, or the timing, must not be influenced by the requirements of the transplantation activity when this would be in conflict with the woman’s interests or would increase embryonic or fetal distress.
5. No material can be used without informed consent of the woman involved. This informed consent should, whenever possible, be obtained prior to abortion.
6. Screening of the woman for transmissible diseases requires informed consent.
7. Nervous tissue may be used for transplantation as suspended cell preparations or tissue fragments.
8. All members of the hospital or research staff directly involved in any of the procedures must be fully informed.
9. The procurement of embryos, fetuses or their tissue must not involve profit or remuneration.
10. Every transplantation or research project involving the use of embryonic or fetal tissue must be approved by the local ethical committee.

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