Fetal Tissue Transplantation in Parkinson's Disease: A Literature Review

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FETAL TISSUE TRANSPLANTATION IN PARKINSON’S DISEASE: A Literature Review

by

Kathleen Thompson
Bachelor of Science in Physical Therapy
University of North Dakota, 1993

An Independent Study
Submitted to the Graduate Faculty of the
Department of Physical Therapy
School of Medicine
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in partial fulfillment of the requirements
for the degree of
Master of Physical Therapy

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1994
This Independent Study, submitted by Kathleen Thompson in partial fulfillment of the requirements for the Degree of Master of Physical Therapy from the University of North Dakota, has been read by the Faculty Preceptor, Advisor, and Chairperson of Physical Therapy under whom the work has been done and is hereby approved.

[Signatures]

(Faculty Preceptor)

(Graduate School Advisor)

(Chairperson, Physical Therapy)
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Title                Fetal Tissue Transplantation in Parkinson's Disease: A Literature Review

Department          Physical Therapy

Degree              Masters of Physical Therapy

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ABSTRACT

Parkinson's disease (PD) is a common progressive neurological disorder. It affects the central nervous system by depleting the basal ganglia of dopamine. To date, the standard treatment is drug therapy to replace the lacking dopamine. However, this treatment is problematic as there are many side effects to the drugs. Also, this treatment does not effect the progression of this disease. Therefore, drug therapy becomes continuously less effective in treating PD. For this reason, new forms of therapy are being researched for the treatment of advanced PD. One of the most recent therapeutic interventions is fetal tissue transplantation.

The purpose of the independent study is to review literature regarding fetal tissue transplantation in PD. This study will include a brief overview of the pathophysiology and current treatment methods for PD. Also, an overview of the history of neural transplantation for PD will be presented. In addition, the paper will include a discussion of the ethical and legal issues surrounding fetal tissue transplantation.

Physical therapists (PT) treat many patients with PD. In the future, PT's maybe responsible for rehabilitating PD patients following fetal tissue transplantation surgery. This paper may be used as a tool by PT's to gain a greater understanding of a very innovative research technique.
CHAPTER 1

PD PATHOLOGY AND TREATMENT

In 1917, James Parkinson published an essay about the shaking palsy.\textsuperscript{1,2} This disorder was subsequently named Parkinson's disease (PD). PD is a debilitating neuro-muscular disease which presents with numerous pathological movement symptoms. The disease affects the motor planning areas of the brain. The primary manifestations are rigidity, bradykinesia, and tremor.\textsuperscript{2,3} PD causes an inability to initiate movements as well as a characteristic "pill-roll" involuntarily tremor.\textsuperscript{2-4} PD also presents with flexed posture, festinating gait and "cog-wheel" or "lead-pipe" rigidity.\textsuperscript{3,4} The rigidity is different than that displayed in spasticity because there is an increase in antagonist as well as agonist neuromuscular output.\textsuperscript{3} PD also decreases associated movements such as: normal arm swing during gait, facial expressions, and gestures during conversation.\textsuperscript{2,3}

The anatomical structures involved in PD include the basal ganglia and the substantia nigra. The term basal ganglia is used to designate several structures including the caudate nucleus, putamen, and globus pallidus.\textsuperscript{3,4} These structures are intimately related to the cerebral cortex, thalamus, and substantia nigra through networks of neurons.\textsuperscript{4} The structures of the basal ganglia are thought to be involved in the planning and programming of voluntary movements.\textsuperscript{3}

PD is referred to as the most common type of basal ganglia disease.\textsuperscript{2,4} Patho-physiology of the disease is characterized by massive degeneration of
the substantia nigra. There is also a depletion of dopamine, an inhibitory neurotransmitter of the caudate nucleus and putamen. This is caused by a degeneration of the neurons of the basal ganglia. This is a process of normal aging, however in PD, this steady loss of dopamine is accelerated. Dopamine levels in persons with PD may be as low as 50% of normal. With the degeneration of the basal ganglia and subsequent loss of dopaminergic cells, the usual balance between excitatory acetylocholine and inhibitory dopamine is disrupted. This imbalance leads to an impairment of the control of smooth, voluntary movement.

To date, the principle treatment for PD has been drug therapy to replace the lacking dopamine. However, this has been problematic as dopamine cannot cross the blood brain barrier (BBB). Dopamine is therefore prescribed in the form of levadopa (L-dopa), which will penetrate the BBB. L-dopa is the metabolic precursor of dopamine. L-dopa is combined with a dopa-inhibitor (Sinamet or Madopar) to prevent it from being converted to dopamine in the periphery.

Treatment of PD with drug therapy has many undesirable side-effects. These include nausea, vomiting, hallucinations, dizziness, and painful spasms or cramps. There is also the development of the "on-off" phenomenon or end-of-dose deterioration. This is a fluctuation in performance and drug response. Fletcher describes the on-off phenomenon as periods of abnormal mobility, alternating with periods of complete immobility. According to O'Sullivan, 50% of patients taking L-dopa for more than two years experience the on-off phenomenon.

L-dopa therapy does not influence disease progression. With the advancement of the disease, drug therapy is less effective as the number of dopamine producing cell decreases. To continue to get the therapeutic
effects of L-dopa, increasingly larger doses are required. In time, patients develop adverse side effects or become tolerant of the drug. Patients with decreased responsiveness to L-dopa may be put on "drug holiday". This is a period of 7-10 days of transient withdrawal from the drug. This may enhance motor response to L-dopa and decrease the negative effects of the drug.

Because the treatment of severe PD is so problematic, new forms of therapy are being researched. One of the most innovative and often controversial is neural transplantation, which will be discussed in chapter 2.
CHAPTER 2
HISTORY OF NEURAL TRANSPLANTATION

Neural transplantation, first performed in 1890, was initially perceived as an experimental tool for the systematic study of neural development and regeneration. In contemporary science, neural transplantation is rapidly becoming a potential treatment for some previously difficult diseases, namely PD. Research on neural transplantation with respect to PD began with extensive work utilizing animal models. This approach was then adopted in human patients in 1985. According to Rosenfeld et al, "Since that time several hundred human transplants have been carried out for PD with only limited success".

Two very different basic procedures have been done with neural transplantation for severe PD. One method is to take dopamine manufacturing cells from the adrenal medulla and place them directly into the substantia nigra of that same individual. Bakay and Barrow reviewed eleven reports and found that this procedure has been performed 84 times since 1985 with a 33% incidence of major complications. This may be due to the fact that three major procedures must be performed consecutively, with as little time lapse as 10-12 hours. First, the tissue must be excised from the adrenal medulla of the patient. Secondly, that tissue must be made into a suspension. Finally, the tissue is then implanted into the substantia nigra of the patient. Regarding adrenal medulla transplant, according to Rosenfeld et al, it has been found that "some patients have apparently
improved significantly in the short term but this has not been sustained”. Further discussion of adrenal medullary grafts is beyond the focus of this paper.

"Following the overall failure of adrenal medullary grafts, attention swung toward the use of fetal tissue to replace damaged or lost neurons in PD". With fetal tissue transplant, tissue from the mesencephalon of aborted fetuses is made into a suspension and injected, through a frontal burr hole, into the basal ganglia of a PD patient. The origin of the fetal tissue (from voluntary abortions) is the cause of much ethical debate.

Collectively, the findings of the literature reviewed are contradictory. Both inter and intra study results are inconsistent. Most patients showed improvements which were of scientific relevance, however, because their quality of life was not noticeably changed, these patients did not view the procedure as a success. The procedures and results of seven studies of experimental fetal neural transplantation surgeries for PD will be reviewed and discussed in the following chapter.
A Czechoslovakian experiment by Subrt et al\textsuperscript{8} was published in 1991. In this study, three patients with PD who received neural transplantation were followed for one year. The patients were closely monitored for two months prior to surgery. The surgery technique included transplantation of mesencephalic tissue from 7-8 week old fetuses into three advanced PD patients. A frontal burr hole was used to implant the tissue stereographically into the head of the caudate nucleus of the three patients. A longer outer cannula was used to prepare the bed for the transplant. Then fetal tissue was placed with a small inner cannula.

The three patients had immediate prolongation of On phase.\textsuperscript{8} Other improvements became apparent at approximately three months. Patients became relieved of L-dopa side effects and doses were reduced. One patient showed remarkable results. Before the procedure, she was bed-ridden and symptoms could only be alleviated by intravenous anticholinergic drugs. After surgery, she could eat alone and ambulate with a cane. The other two patients L-dopa levels were reduced to 60\% the pre-surgery dosage. However, these two patients did not value their improvements as their lifestyles did not change.

The research team has already begun to modify its procedure as other studies are done. They anticipate that transplantation will be a viable alternative to drug therapy.
In a study by Henderson et al,10 12 patients received Fetal Transplant Tissue for advanced PD. Of the 12, nine patients were consistently followed for 12 months post-operatively. All patients were at Hoehn-Yahr 11 stage 4/5 (Table 1.) before surgery. The procedure was an injection of Fetal Tissue through a right frontal burr hole into the caudate nucleus of each patient.

Twelve patients had surgery, three of which did not comply with the follow-up schedule. Of the nine monitored for 12 months post-operative, four "experienced immediate subjective post-operative improvements".10 Five patients had a mean decrease in levadopa dosage of 60% of their previous levels at 12 months. One patient did not need levadopa treatment at 12 months and another individual required only 10% of presurgery dosage. At one year, three patients deteriorated compared to pre-operative assessment. Maximal changes were seen at six months after surgery. These researchers concluded that there are many operations being done world-wide and research will continue at the same rate as the "increasing understanding of human fetal development and the pathogenesis of PD".10

In a study by Freed et al,6 seven patients who had advanced PD for 7-20 years received FTT. Patients ranged in age from 39-66 years old. Preoperatively, five patients were rated a stage IV on the Hoehn-Yahr scale and two patients were rated stage III. For all patients selected, drug therapy had failed and most were experiencing significant on-off phenomenon. This included periods of complete immobility, falling and dyskinesia. Patients were evaluated daily for four months to one year pre-surgery and 12-46 months post-surgery.

Fetal tissue, six to eight weeks old, was injected stereotaxically into as many as nine needle tracts.6 This study focused on the putamen as the transplant site. Patient one and two received grafts to the caudate and
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<td>I</td>
<td>Minimal unilateral disability</td>
</tr>
<tr>
<td>II</td>
<td>Minimal disability either bilateral or midline</td>
</tr>
<tr>
<td>III</td>
<td>Righting reflexes are impaired, patient lives independently with some restrictions in activities</td>
</tr>
<tr>
<td>IV</td>
<td>Parkinson's manifestations are present and severe</td>
</tr>
<tr>
<td>V</td>
<td>Patient is either bed or wheelchair bound</td>
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Table 1. Hoehn and Yahr PD Rating Scale\textsuperscript{11}
putamen unilaterally. Patients three through seven had bilateral grafts to the putamen only.

Overall, the group dropped an average of 1.2 stages on the Hoehn-Yahr scale with the greatest difference from a stage IV to a stage II post-operative. The level of dopamine dosage dropped an average of 39% for the seven patients. The largest decrease in dosage was 58%. Patient one, at 46 months, showed the greatest improvements in the contralateral hand. His time spent in "on" phase went from 70 to 85 % of his day. Patient two showed no clinical improvement over a 33 month examination period. Patient three, at 21 months, had a reduction in periods of dyskinesia, as well as, time spent in the "off" phase. This patient appeared normal at times and had resumed social activities. Patient four had been followed for 13 months. She regained control of her gait and did not fall as she had pre-operatively. She was in the "on" phase 100% of the day, as compared to 65% of the day before surgery. Patient five had, before surgery, experienced extreme on-off phenomenon. At 12 months, the patient had a considerable reduction in duration and severity of "off" phase and dyskinesia following surgery. This patient was able to regain his driver's license. Patient six, at 12 months after surgery, returned to his pre-operative level of function with improved postural control and a marked decrease in bradykinesia. At 11 months following surgery, patient seven had normal movement for as much as 30% of the day. Prior to surgery, he had no movement classified as normal. This patient went from sleeping only three hours per night before FTT to eight hours after.

These authors stated that all patients in this study, made improvements in the "On" phase. Four of the patients, and their physicians, felt the gains significantly changed their daily lives. These researchers contended that a
placebo effect may be ruled out on the grounds that adrenal medullary graft patients did not sustain their improvements. The authors concluded that FTT may add a new dimension to the treatment of severe PD.

In a study by Spencer et al, four patients received FTT. The implants were injected stereotaxically into the right caudate nucleus. The patients needed three or four of the cardinal signs of PD to be included in the study. These signs were resting tremor, rigidity, bradykinesia and postural instability. Also, the individual had to be at a Hoehn-Yahr stage IV.

The results of the study are discussed in the following paragraphs. Patient one, pre-operatively, was house bound and unable to perform activities of daily living. After surgery, she had gradual reduction in bradykinesia, and rigidity, and improvements in gait ability. She also had improvements in visual searching, visual memory, and cognitive testing. However, after six months, all measures returned to pre-operative baselines with the exception of visual searching. Patient two was very involved pre-operatively. Following surgery, he showed minimal gains in autonomic functions. This patient died four months after receiving FTT. Post-mortem examination documented that the FTT grafts showed a viable blood supply and the formation of synapting neurons. Patient three presented with resting tremor, rigidity, gait disorder and dysphasia before surgery. Following FTT, this patient developed motor seizures, transient panic disorder, agoraphobia, and major depression. These were all controlled with medications. The patient had an increase in IQ test score of 14 points. Patient four was significantly debilitated by the on-off phenomenon before receiving FTT. He was unable to perform activities of daily living. Post-surgery, his trend towards worsening rigidity and tremor stabilized. A one year follow-up study showed an increase of nine points in his IQ.
Overall, the most significant result was that patients' levadopa levels decreased by 60%. The grafts were placed unilaterally in all patients, however, there was no change in function between the two sides of the body. The authors concluded that moderate bilaterally improvements were made in specific motor tasks. However, the patients still remained markedly affected by their disease according to the Hoehn-Yahr scale. These authors concluded that it is difficult to compare FTT studies as research teams use different procedures and evaluation methods. In addition, the procedure of FTT "remains highly investigational and should not yet be considered a clinical treatment for PD."  

In an on-going study by Lindvall et al., a total of four patients have received FTT for PD. A recently published article described the results of one-year clinical observations of two of those patients (patients three and four). The patients entered the study one year before surgery and were followed for one year post-operatively. Patients self-monitored their motor symptoms in a daily log every 30 minutes. The patients were also evaluated every two weeks by the researchers for an eight hour period.

The procedure was stereotaxic implantation of ventral mesencephalic tissue in the anterior, mid and post putamen on the side contralateral to the most involved limb. Patient three was a 50 year old male with stage III Hoehn-Yahr PD pre-operative. During off periods he had severe rigidity, moderate tremor, and hypokinesia immediately following FTT. Patient three had an increase in PD symptoms followed by a significant decrease in time spent in off phase. According to the patient, there was a decrease in rigidity. However, the patient had a slight increase in muscle tone.

Patient four was a 60 year old male with stage III Hoehn-Yahr PD previously. This patient had moderate resting tremor and severe rigidity.
He also had marked hypokinetic movements. This patient spent 60% of his day in the off phase. Following FTT, the patient had a "marked reduction of both the number and duration of daily off periods." He spent only 30% of his day in the off phase. There were no significant improvements in rigidity or tremor. Some gains were made in arm and hand functions up to the seventh month but these improvements were not sustained through the 12th month.

Following surgery, these researchers kept the patients' L-dopa dosages at pre-operative levels to decrease the risk of improvements being credited to changes in medication. The conclusion of this research team was that neural grafting has potential as a treatment for PD. However, the results do not merit large clinical trials.

In an ongoing study by Madrazo et al., seven patients with PD received FTT. Madrazo stated that follow up of these patients is very important. The ultimate goal of FTT is to produce long lasting benefits. In a recently published article, Madrazo described the status of two FTT PD patients, two years post-surgery.

One patient was a 50 year old male diagnosed with PD nine years previously. He had been receiving levadopa therapy at 1,000 mg/day. This patient suffered from drug induced dystonia and dyskinesia. The second patient was a 35 year old female who had PD for five years.

These patients received FTT two years previously. The progress of the patients regarding L-dopa dosages was as follows; patient one went from taking 1000 mg/day pre-operative to 500 mg/day at 24 months; patient two had been taking 750 mg/day of L-dopa and at six months, her dosage was 250 mg/day, while at 24 months after surgery, it was 500 mg/day. This implied a significant decrease in the patients daily L-dopa requirements.
Time spent in the off phase decreased by 60% in patient one and by 50% in patient two over the two year period. Functionally, patient one had "significant amelioration of rigidity, bradykinesia, postural imbalance and gait disturbances." His tremor was also decreased. This patient was said to be leading a normal life, following surgery, including going back to work.

At two years post FTT, patient two had shown some improvements. She had significant amelioration of only rigidity and bradykinesia, without important changes in other signs. She is said to be able to perform household tasks and to be of moderate clinical status.

In conclusion, Madrazo et al stated that, regardless of the mechanism of action, brain transplantation is affecting PD signs to a greater extent than previous methods. The authors concluded that the usefulness of tissue grafting for neurological diseases cannot be overlooked.

Additional research by Widner et al reported the technique utilized and progress of FTT in two patients with drug induced Parkinsonism. The major difference between this study and the others reviewed was that in the drug induced PD, there was no continuation of the disease process. The causative agent was no longer present. For this reason, Widner et al may be doing a more objective investigation of the viability of FTT.

Patient one was a 43 year old male who developed severe Parkinsonism following self-injection of the synthesized street drug MPTP in 1982. L-dopa therapy was causing increasingly severe side effects. This patient needed extensive help with eating, dressing and personal hygiene. He had at least six off periods each day with as little as 25% of his day in on periods. This patient had pronounced hypokinesia, rigidity, and postural abnormalities. Patient one was rated a stage IV and occasionally stage V on
the Hoehn-Yahr PD scale. During defined "Off" periods he was unable to open his eye-lids without help.

Patient two was a 30 year old female who also developed severe Parkinsonism because of an MPTP drug injection. She was becoming increasingly intolerant of L-dopa therapy. This patient suffered from continuous dyskinesia which rendered her almost completely incapacitated. She had five or six off periods each day with 50 to 75% of the day in the on phase. This patient required extensive help completing activities of daily living. She was rated as a Hoehn-Yahr stage IV.

Six to eight week old fetal mesencephalic tissue from fetuses was injected through a frontal burr hole. There were three placements in the putamen and one in the caudate nucleus, bilaterally. At 24 months after surgery, patient one had much more independence. He was able to dress and feed himself, and go to the bathroom independently. He also made trips out of the home. His "On" time increased to 50-75% of his day and his Hoehn-Yahr rating went to a stage three. By 24 months, his rigidity was virtually eliminated. His gait became smooth, with a return of natural arm swing.

Patient two had her L-dopa level reduced by 70% after 18 months. At 22 months after surgery, her dyskinesia was greatly reduced. Also, she had "On" phase 50% of the day. She was then rated at a stage II to III on the Hoehn-Yahr scale. She was able to feed herself without difficulty. Muscle rigidity was ameliorated and she was able to ambulate with spontaneous arm swing.

The authors concluded that their two patients had made more extensive gains than most patients to date. They attributed their success to the fact that the patients received a larger amount of tissue bilaterally, and also
that the patients had MPTP induced Parkinsonism as opposed to idiopathic PD. This meant that their brain lesions were not progressive and only the substantia nigra was affected. However, the researchers admitted that these patients improvements were incomplete. Therefore, they felt further research was needed before the treatment is adopted clinically.
CHAPTER 4
DISCUSSION AND DEBATE OF FTT

Research is being done all over the world to determine the efficacy of neural transplantation.\textsuperscript{10} At this point, FTT cannot be disregarded as a useful treatment for progressive neurological diseases, namely PD. However, neural transplantation for PD is still at an experimental stage and should not be used clinically until more research is done.\textsuperscript{10,12} This research is likely to continue at the same pace as the increasing understanding of the pathology of PD.\textsuperscript{10} Also, with increasing understanding of fetal development, researchers will be able to distinguish the best donors.\textsuperscript{10} In theory, multi-site implantations or perhaps a more precise placement of the graft may influence further studies. Also a better understanding of graft survival may produce a greater therapeutic response. There is the possibility of grafting dopaminergic cells in combination with growth factors, to assure the grafts integration into the existing tissue.

To date, much of the improvement seen in patients receiving FTT has been antidotal. Subjective measures, whether on the part of the researcher or the patient, were often the primary measure of success. A more rigid, standard testing battery should be designed and followed closely both pre and post operatively by all research teams.\textsuperscript{6,14} Also, a more systematic selection of the: 1) patients to receive the transplants 2) amount of FT to be used, and 3) FTT placement sites would make research more thorough.\textsuperscript{13,14} At present, there are far too many variables in these studies. It is difficult to
credit improvements solely to the procedure.\textsuperscript{6} It may also be appropriate to do the surgery on less involved patients.\textsuperscript{8} Then perhaps, more functional gains could be made.

The use of FTT for PD has become a highly debated topic. There are those who feel the procedure is unethical and ineffective,\textsuperscript{7} while others contend FTT has potential as a viable treatment for PD.\textsuperscript{16,17} In the following paragraphs, some of the discussions and debates surrounding the use of fetal tissue transplants in Parkinson's Disease (PD) is presented.

According to Rosenfeld et al,\textsuperscript{7} fetal tissue transplant studies lacked vigorous assessment and long-term follow-up. He believed that the clinical applications of neurotransplantation for PD was premature. Rosenfeld stated that, late in the course of the disease, symptoms cannot be controlled and complications arise because of long-term Leva-Dopa therapy. For these reasons, other types of therapy for PD need to be explored. According to Rosenfeld, there have been eight studies of human fetal grafting in PD, with a total of 50 cases. He contended that it would be difficult to interpret the results of the studies to date because of the lack of uniformity in assessment of responses and the often inadequate follow-up.

Rosenfeld's theories as to why many of the grafts were failing included: (a) insufficient quantities of tissue transplanted, (b) the fact that the disease process of PD attacks the newly grafted cells, (c) the possibility that the graft site was not optimal, and (d) the initial insult to the tissue may cause immediate but short term improvements. Rosenfeld concluded that neural transplantation for PD is still in the experimental stages and should not be used while many of the major questions remain unanswered.

Larry Thompson\textsuperscript{15} highlighted recent advances in fetal tissue transplantation at the July 1992 4th International Symposium on Neural
Transplantation. It was proposed that, currently, research of fetal tissue transplants of PD was being done in a haphazard way. Right now, there are 15 research centers in 11 countries. The consensus was that research would be more effective if there were only a few centers to undertake larger clinical trials. This would promote more uniform, systematic assessment of the patients and procedures from before surgery through the long-term. Overall, the consensus at the symposium was one of optimism regarding the potential of fetal tissue transplantation as a viable treatment for PD.

Fahn stated that there has been at least some benefit in humans given fetal ventral mesencephalic implants, and in some patients there was substantial benefit. Fahn stated that the most impressive results were those of Widner et al, who studied patients with non-progressive MPTP-induced PD. Fahn concluded that this study was important due to the fact that patients maintained their improvements, indicating the grafts were surviving and growing.

However, Fahn noted that PD is a progressive disease and the fate of the implanted tissue may be the same as that of the original dopamine producing cells. This author stated that the most dramatic functional benefit of the three studies he critiqued was a statistically significant decrease in off time and an increase in on time. Also, the reduction of L-dopa dosage was noteworthy. Fahn disputed the notion that the insult to the tissue and subsequent healing was the basis for improvement. He contended that adrenal medullary grafts caused similar damage with no clear equivalent benefit. Fahn concluded that this surgical procedure remained investigational but showed optimistic promise for future use. However, reports with longer follow-up are essential.
According to Christopher Goetz et al,17 humans with PD who have received fetal nigral transplants to the striatum, have improved clinically. He contended the attraction of surgery is its highly focused targeting, ideally suited to a disease like PD in which neurodegeneration is also largely circumscribed.

Sue Fletcher 1 stated that early results of fetal tissue transplantation are encouraging. She contended it is unclear, however, if the benefits are the result of a placebo effect or another non-specific action of the graft.
CHAPTER 5
POLITICAL AND ETHICAL ISSUES

This paper would not be complete without addressing the political and ethical issues surrounding FTT. The political influence has been a withholding of public funds for research. From 1988 through 1993, there was a ban on funding of fetal tissue research in the U.S.\textsuperscript{18} Consequently, fetal tissue research done in the U.S. has been privately funded.\textsuperscript{19} The ban was originally placed by the Reagan administration to avoid any indication that they encouraged abortion.\textsuperscript{19} After the moratorium was in effect, a Human Fetal Tissue Transplantation Research (HFTTR) Panel was appointed to study the matter.\textsuperscript{7} Experts in medicine, law and ethics made up the 21 member team. In late 1988, the panel "found it acceptable public policy to fund the research."\textsuperscript{19} However, the recommendation was not implemented by the Bush administration, and the moratorium was continued indefinitely.\textsuperscript{20} As recently as February, 1993, the Clinton administration lifted the ban on public funding of FTT research.\textsuperscript{18}

For FTT experiments to take place, an abortion must have occurred. This is the cause of much ethical debate. Anti-abortion proponents contend that this research will encourage ambivalent pregnant women to choose abortion.\textsuperscript{19} If these women think that having an abortion would benefit someone else, their decision may be swayed. Perhaps a woman would be pressured to conceive in order to supply fetal tissue for a family member who has PD.\textsuperscript{1}
Most supporters of the research believe that "absolute separation of the tissue harvesting from the donation procedure is an essential requirement." Kassirer et al argued that FTT research does not show "support of abortion, any more than transplanting organs from murder or accident victims constitutes support for murder or accidents." A woman's decision to have an abortion involves a great deal of personal consideration. According to Kassirer et al, it is not the place of the government to scrutinize the motives of a woman contemplating abortion.

Nevertheless, the HFTTR panel developed safeguards to prevent a pregnant woman's decision, to have an abortion, from being influenced by the possibility of helping another. The guidelines are as follows: 1) A woman should not be approached about the issue of FTT until she has made her decision to have an abortion; 2) The donor and recipient must not know one another; 3) Fetal tissue should not be donated for a specific patient; 4) There should be no financial incentive either for the woman or for the facility. It is imperative that the decision to have an abortion and the decision to donate tissue are two separate entities.

There is also the concern about supply and demand. With the continued research on fetal implantation in neurological diseases such as PD and Alzheimer's, will there be enough tissue to go around? According to Fletcher et al, "in the United States, it is estimated that 1.6 million pregnancies are voluntarily terminated each year, and approximately 78% of these occur between the 6th and 11th weeks of pregnancy, which would provide adequate supplies of fetal tissue for the present demand."
CHAPTER 6
CLINICAL APPLICATIONS AND CONCLUSIONS

PD is a progressive, neuromuscular disease that effects the motor planning areas of the brain, namely the substantia nigra and basal ganglia. PD presents with slowed movement, muscle rigidity, resting tremor and postural abnormality. To date there is no cure for PD, however, it is controlled primarily through drug therapy.21

Physical therapy (PT) can be instrumental in helping PD patients improve functional ability and combat subsequent deformities.22 According to O'Sullivan et al,2 physical therapy treatment of PD usually consists of: (1) relaxation exercises to reduce muscle tone, (2) range of motion exercises to maintain functional mobility, (3) gait training to increase arm swing and step length, (4) strengthening exercises to prevent muscle atrophy, and (5) respiratory exercises to maintain the plyability of chest wall musculature.

In a study by Formisano et al,23 it was found that, for PD patients, PT treatment along with drug therapy was effective in improving functional performance. The study compared motor performance test results of 16 test patients and 17 control patients over a four month period. The test patients received physical therapy together with drug therapy, while the control groups receive only drug therapy. After four months, the patients receiving physical therapy rated higher on the motor performance tests. There was also a statistically significant difference in the daily activity scale and walking tests.
FTT could have a great influence on physical therapy treatment of patients with PD. Early intervention is the key to the efficacy of physical therapy in PD.\textsuperscript{23} Those receiving FTT surgery may then enter a rehabilitation facility to maximize potential gains. These patients could be intensively trained in gait, postural mobility and other functional activities immediately following surgery. Also, in many of the studies outlined, patients have continued to make gains over as long a period as 24 months.\textsuperscript{5,6} Continued PT has been found to be beneficial in helping PD patients maintain a high degree of independence as long as possible.\textsuperscript{23} This suggests that these patients would continue to benefit from further physical therapy as the FTT grafts integrate into the surrounding tissue.

There is no literature to date on the physical therapy treatment of PD patients receiving FTT. This is perhaps due to the fact that there have been only 50 patients in the world who have received FTT.\textsuperscript{7} However, it is noted that in the follow-up of these patients, there has been no mention of rehabilitation.\textsuperscript{5–14} Even with this small number of subjects, individual case studies could be done to illustrate the efficacy of PT for these patients.

With continued research in the area of FTT surgery, more emphasis could be placed on translating the neurological improvement into function. Perhaps these patients would make even greater functional gains with the incorporation of a comprehensive rehabilitation program following FTT surgery.
REFERENCES


