Chapter 1

Summary, Policy Issues, and Issues for Congressional Action

CONTENTS

Figures

Tables

Chapter 1

Summary, Policy Issues, and Options for Congressional Action

Tens of millions of Americans suffer from some form of neurological disorder. Some of these disorders are minor and are easily treated with medication or rest. Others are marked by severe, debilitating symptoms and result in pain, suffering, and sometimes death. Some neurological disorders may be treatable by neural grafting—i.e., the transplantation of tissue into the brain and spinal cord (table l-l). Although few neural grafting procedures have been carried out to date, the number could increase in the future.

Neural grafting has long been used in basic research to study the nervous system. In fact, much neural grafting continues to be used as a tool for understanding the development of the nervous system and its response to injury. In addition to its use as a research tool, however, neural grafting is being examined as a possible therapy for neurological disorders. In the clinical arena, neural grafting consists of the surgical transfer of tissue from various sources into specific areas of the nervous system that have been affected by a disease or injury. This report focuses on the field of neural grafting into the brain and spinal cord to treat neurological disease and injury.

Current treatments for neurological disorders include drugs, surgery, physical therapy, and behavioral interventions. These treatments may improve significantly as advances in the field of neuroscience provide a better understanding of the causes and mechanisms of neurological injury and disease. For most neurological disorders, current treatments do not provide a cure, but rather relief of symptoms. It is possible that neural grafting could provide a cure in some cases where current treatments cannot (e.g., injury) or could bring about sustained relief from symptoms where existing therapies either fail or lose their effectiveness (e.g., certain diseases, such as Parkinson's). Because of this potential, transplantation of tissue into the central nervous system (CNS) may become a significant therapeutic alternative in the future.

Table l-l—Prevalence of Neurological Disorders in the United States

Neurological disorder	Prevalence
Alzheimer's disease	1 to 5 million
Stroke	2.8 million
Epilepsy	1.5 million
Parkinson's disease	500,000 to 650,000
Multiple sclerosis	250,000
Spinal cord injury	180,000
Brain injury	70,000 to 90,000[a]
Huntington's disease	25,000
Amyotrophic lateral sclerosis	15,000

[a] Estimate of persons permanently disabled from head injury.

NOTE: Prevalence is defined as the total number of cases of a disease estimated to be in existence in the United States at any given time.

SOURCE: Office of Technology Assessment, 1990.

Currently, grafting of tissue into the CNS to treat neurological disorders is highly experimental. Neural grafting has advanced to clinical human research only for the treatment of Parkinson's disease; for other applications, basic research is continuing. (Federal funding of neural grafting research is presented in table 1-2.) While several strategies for the use of neural grafting have emerged, much additional basic research is needed to determine in what ways and to what extent neural grafting may be beneficial. It has the potential for treating damage to the brain and spinal cord, thereby benefiting millions of Americans with impaired neurological functions. Realizing the benefits of neural grafting will depend on a better understanding of both the potential uses of neural grafts and the mechanisms underlying neurological disorders.

This report is about the technology of neural grafting, the neurological disorders that it may be used to treat, the patient populations that might be affected, and the issues raised by the development of this technology. Two considerations related to the development of neural grafting are:

. sources of materials for transplantation, and

- protection of human subjects in research.

In particular, concerns have been raised about whether or under what circumstances to use human fetal tissue as a graft material and when to move from the laboratory to clinical research.

Table 1-2—Federal Funding of Neural Grafting Research (in millions of dollars)

Agency	1987	1988	1989	1990[a]
National institutes of Health:				
National institute of Neurological Disorders and Stroke	4.1	6.5	7.3	7.5
National Eye institute	1.2	1.4	1.6	1.6
National institute on Aging	1.1	1.1	1.6	2.1
National institute of Child Health and Human Development	—	0.2	0.4	0.4
Alcohol, Drug Abuse, and Mental Health Administration	0.3	0.3	0.5	0.4
Department of Veterans Affairs	*0.4*	*0.5*	*0.5*	*0.5*
National Science Foundation[a]	*0.2*	*0.2*	*0.2*	*0.2*

a Estimated.

SOURCE: Office of Technology Assessment, 1990.

GENERAL FEATURES OF THE NERVOUS SYSTEM AND NEURAL GRAFTING

The fundamentals of neural grafting are based on an understanding of how the nervous system grows and develops, how it responds to injury and disease, and the mechanisms underlying neurological disorders. The nervous system is divided into the CNS and the peripheral nervous system (PNS) (figure l-l). The brain and spinal cord, which make up the CNS, are complex structures that control and regulate all of the activities and functions of the body. Cells of the brain and spinal cord are much more flexible in their ability to grow and form interconnections during development than in the fully formed CNS. Also, PNS elements can regrow following an injury, even in an adult, whereas regrowth in the CNS is extremely limited. Neural grafting takes what is known about these phenomena and the mechanisms underlying neurological disorders and tries to harness them to repair the injured or diseased nervous system.

Neural grafting differs from organ transplantation, wherein an entire diseased or injured organ, such as the heart or kidney, is replaced with a healthy one. Although neural grafting may entail replacing a diseased portion of the brain, animal experiments suggest that it may also serve a number of other functions and may use tissues from a variety of sources. Thus, neural grafting is a generic term that includes many different treatment goals and materials.

Therapeutic Strategies

How a neural graft improves CNS function within the graft recipient is not completely understood. In fact, neural grafts display a wide range of potential capabilities. These diverse functions lead researchers to predict that neural grafts may be employed to accomplish different treatment goals in different neuropathological disorders. Continued research is necessary to determine precisely how neural grafts function and how those functions can benefit a graft recipient. Three possible functions of neural grafts have been identified:

- They may provide a continuous supply of chemical substances that have been depleted by injury or disease in affected regions of the brain or spinal cord.
- They may introduce new substances or cells that promote neuron survival, neuron regrowth, or both.
- They may replace nerve cells in the *CNS* that were lost to injury or disease.

Materials for Neural Grafting

Several types of biological materials maybe used for neural grafting, each of which raises unique technical issues. The most important determinant of a particular material's usefulness is its ability to improve CNS function with minimal risk to the recipient.

Tissue from the fetal CNS, because of its ability to develop and integrate readily within a host organism, has been extensively studied. Many scientists consider fetal CNS tissue to be the most effective material currently available for neural grafting. However, ethical, social, and political

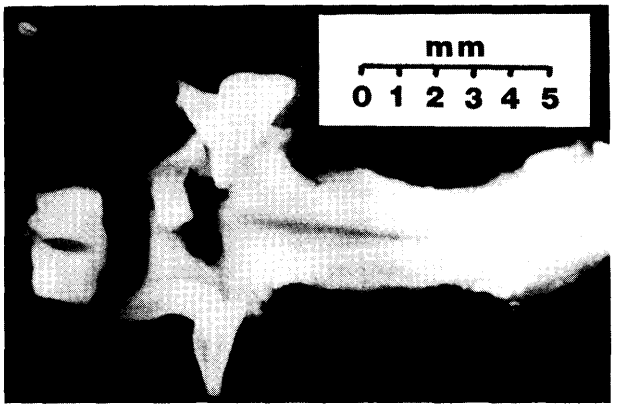


Photo credit: C. Freed, Department of Medicine and Pharmacology, University of Colorado

A portion of the dissected human fetal central nervous system.

issues surrounding its use have been raised in the United States and propel the search for alternative materials. Other materials that are being examined include PNS tissue; peripheral autonomic neurons; tissue from outside the nervous system; and isolated, cultured, or genetically engineered cells (figure 1-2).

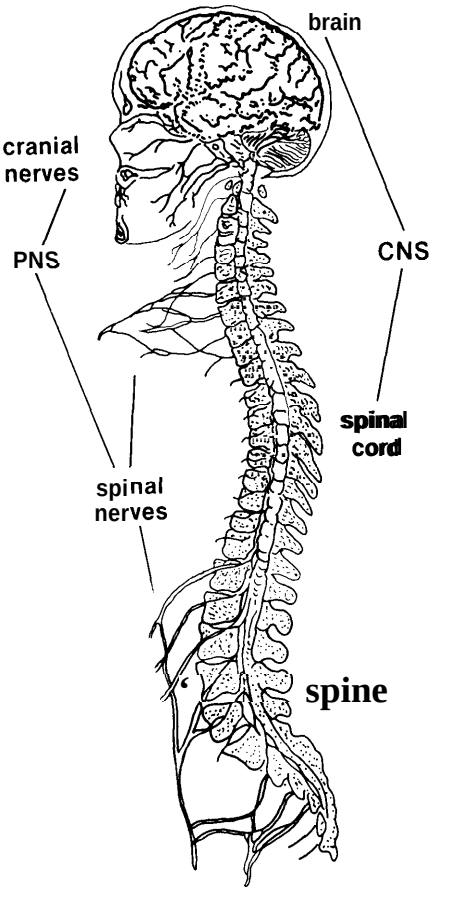
Determinants of Successful Neural Grafting

To survive grafting, cells must endure mechanical and metabolic disruption during preparation for grafting, and they must incorporate into the foreign, and potentially hostile, environment of the host. The surgical technique and specific material used for neural grafting are important determinants of success. Immature tissue can survive grafting more readily than its mature counterpart. The ability of grafted materials to avoid immunological rejection by the host and to obtain ready access to nutritional support and a supply of oxygen by becoming incorporated with the host blood supply are major determinants of graft survival.

Potential Risks

As with any surgical intervention, neural grafting presents risks to the recipient. Unfortunately, many of the risks attributed to neural grafting are either poorly understood or simply speculative. Before neural grafting can become routine in humans, the risks must be carefully delineated, minimized, and measured against expected benefits. Problems may result from complications associated with the neurosurgery itself or immunological rejection of the graft. Concerns that grafts could induce unwanted psychological effects, be a means for transmitting bacterial and viral infections, or grow excessively once implanted have also been raised.

Figure I-l-Components of the Nervous System



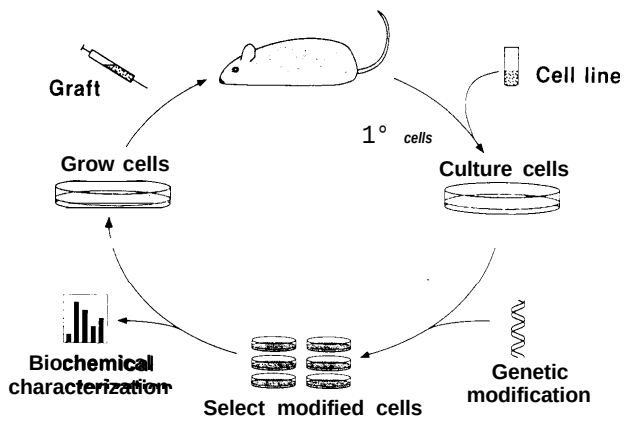
The nervous system is composed of the central (CNS) and peripheral nervous systems (PNS).

SOURCE: C. Romero-Sierra, *Neuroanatomy, A Conceptual Approach (New York, NY:* Churchill Livingstone, 1986).

APPLICATIONS OF NEURAL GRAFTING INTO THE BRAIN AND SPINAL CORD

The technology of grafting into the brain and spinal cord to restore functions lost through disease or injury is still very much in the initial stages of development. Research in animals has indicated that neural grafting may provide beneficial therapeutic effects in some neurological conditions, notably Parkinson's disease. But in every case, including Parkinson's disease, there is still much information that needs to be collected before neural grafting can be adapted for general use in humans. Research currently being conducted in this field is

Figure 1-2—Methods Used To Graft Genetically Modified Cells



SOURCE: F. Gage, Department of Neuroscience, School of Medicine, University of California, San Diego.

aimed at learning more about basic mechanisms involved in grafting tissues into the CNS and the actions and effects neural grafts can exert there.

Scientists use many different kinds of experiments with animals to obtain this information. The need for animal models that mimic a given neurological disorder in humans is as important in the field of neural grafting as it is in most other areas of clinical research. The closer an animal model is to the human condition of interest (in terms of the neurological damage induced and the behavioral effects that damage produces), the easier it is to extend observations from the model to a human disorder. Virtually all scientists in the field of neural grafting believe it is essential to develop good animal models for use in neural grafting experiments.

Neural grafting has been used to treat some patients with Parkinson's disease; however, this clinical use of neural grafting, begun in the early 1980s, has generated controversy in the scientific and medical communities. The tissue used has come from two sources: the recipient's adrenal gland and the fetal *CNS. In* both cases, there is some concern that the treatment has been used prematurely. In the case of adrenal grafting, many observers believe that there has been a rush to proceed with human trials without having first collected adequate data from animal experiments. In the case of fetal tissue grafts, while there is a larger base of animal data to draw on, there is still concern that widespread implementation of human fetal tissue grafting could proceed before adequate information has been derived from experimental studies.

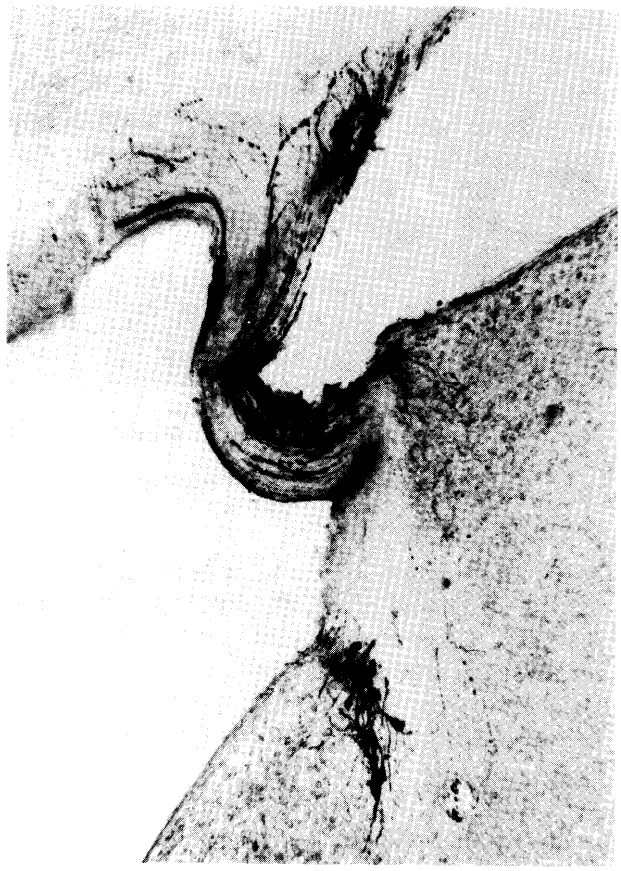


Photo credit: J.R. Sladek, Jr.

A picture of a graft of monkey fetal tissue implanted into the brain of an adult monkey.

As of 1990, between 300 and 400 persons with Parkinson's disease had received neural grafts worldwide, with about 100 of them having received fetal tissue grafts. In the United States, approximately 130 patients have been treated with adrenal tissue, while fewer than 10 have had fetal tissue implants. The use of fetal tissue for implantation is limited in the United States to privately funded ventures because the Secretary of Health and Human Services has imposed a moratorium on Federal funding of research involving the transplantation of human fetal tissue obtained from induced abortions into human subjects.

The question of whether clinical experiments using grafting procedures to treat Parkinson's disease patients should continue before additional data are gathered from animal experiments is unan-

swered. In the case of adrenal grafts, many persons in the medical and scientific communities have retreated from the rush of enthusiasm that accompanied their initial use. In the case of fetal tissue grafts, many believe that questions can best be answered with additional animal research, coupled with limited human experimentation.

The use of neural grafts for other neurological disorders is still at the stage of animal experimentation. Much basic research is being conducted to examine what role grafts might play in a variety of neurological conditions. For neurodegenerative diseases (e.g., Huntington's disease, Alzheimer's disease, and motor neuron disease), the ability of grafts to provide lost neurotransmitters, replace lost cells, and stimulate growth in the diseased brain is being studied. Neural grafts are being used in animal models of brain and spinal cord injury in hopes of reversing functional deficits by inducing regrowth or replacing damaged areas. In conditions such as epilepsy, neuroendocrine defects, and demyelinating diseases (i.e., multiple sclerosis), the ability of grafts to supply specific chemicals to control or reverse the effects of these disorders is being examined.

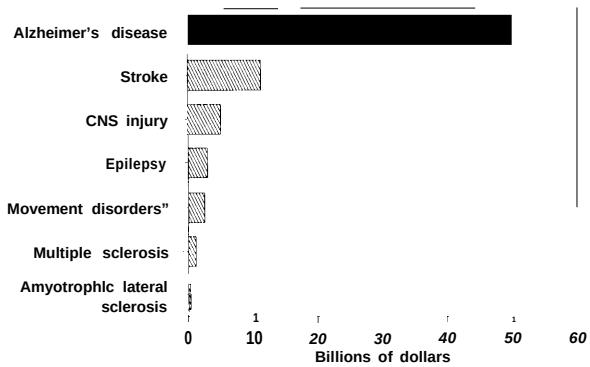
Neural grafting holds the promise of new treatments for neurological disorders, but a final determination of its usefulness must await more information about the mechanisms underlying neurological disorders, graft functions, and how those functions relate to various neurological disorders.

RELEVANT NEUROLOGICAL DISORDERS

Since neural grafting is in the very early stages of development, predicting its ultimate utility is speculative at best. However, since current animal research intimates that neural grafting may be applied to the study and treatment of diverse neurological disorders, this technology may have a significant impact on medicine and society.

Neurological disorders are a significant cause of illness, disability, and death in the United States. They cost, by conservative estimates from the National Institutes of Health, more than $100 billion per year in medical expenses and lost income (figure 1-3). Not all neurological disorders are amenable to treatment by neural grafting. The Office of Technology Assessment identifies those disorders that may one day be treatable with grafting technology. A disorder was considered treatable if current understanding of its nature and cause suggests that neural grafting may be a beneficial treatment approach or if results from animal experiments offer support for this possibility.

Figure 1-3-National Institutes of Health 1989 Estimates of Costs of Neurological Disorders



● Parkinson's and Huntington's diseases.
NOTE: Costs are per year, including medical care, lost income, etc.
SOURCE: National institutes of Health.

These neurological disorders afflict persons of all ages. Adolescents and young adults are most likely to suffer from epilepsy, head or spinal cord injury, or multiple sclerosis; Huntington's disease and amyotrophic lateral sclerosis first appear in middle age; stroke, Alzheimer's disease, and Parkinson's disease afflict primarily the elderly.

Preventive measures can reduce the incidence of CNS injury, but the causes of the other diseases are unknown. While in every case the pathological hallmarks of the disorder can be described, there is no cure for the nerve cell death and abnormal functioning that cause mortality and morbidity. Research involving genetic analysis, molecular biology, and new drug development, as well as neural grafting, continues to advance our understanding of the various disorders and possible treatments for them.

LEGAL AND REGULATORY ISSUES

To the extent that Federal funds are used to support research involving neural grafts or to pay for

the clinical use of such procedures, Federal regulations govern the conduct of that research. Even if Federal funds are not used, the Federal Government has powers under the interstate commerce clause to regulate neural grafting research. This power is the basis for the establishment of the Food and Drug Administration (FDA), the prohibition on payment to organ donors for transplantation, and the regulation of medical laboratories engaged in interstate commerce. The Federal Government may, under the Public Health Service Act, regulate intrastate activities as necessary to prevent transmission or spread of communicable diseases. However, questions have been raised about the extent to which these mechanisms address neural grafting procedures. Some existing Federal policies governing experimentation and organ transplantation could affect tissue transplants, but they were developed before the recent extensive debate on fetal tissue transplantation.

Protection of Neural Graft Recipients

Department of Health and Human Services (DHHS) regulations apply to all research with human subjects that is conducted or funded by DHHS [45 CFR 46.101]; in addition, DHHS regulations are used widely as guidelines by other institutions, regardless of whether they receive Federal funding. These regulations specific that research protocols be reviewed and approved by an Institutional Review Board (IRB), that selection of subjects be equitable, and that informed consent be obtained from each subject. IRB review is also necessary for any product for which marketing approval is sought from the FDA. Informed consent is defined by Federal regulations which specify what information must be provided to the research subject. Other Federal regulations pertain to research on particularly vulnerable groups, including the mentally disabled, and provide guidelines for IRB approval and informed consent related to research involving these subjects. Such regulations may also pertain to those experimental neural transplant subjects who are mentally impaired. In research programs where there is no Federal involvement or influence, government oversight will depend on whether there are State statutes, although few States have statutes that address human experimentation in any detail.

Decisions regarding the safety and efficacy of neural grafting materials are likely to come within FDA jurisdiction. However, FDA's role in regulating neural grafting materials is complicated by the fact that there are several different types of materials, each of which raises slightly different questions. In addition, neural grafting materials represent developing technologies that have not yet been directly addressed by the FDA. The FDA has jurisdiction over the manufacture and distribution of materials that meet statutory definitions of drugs, devices, or biologics. Safety considerations and the FDA's current regulation of similar products make it likely that the agency will seek to regulate most neural grafting materials. Questionable jurisdiction under the Public Health Service Act could limit FDA's ability to regulate these materials, since it is unclear whether neural tissue grafts, cell lines, and products of biotechnology to be used as neural grafts are analogous to the articles listed as biologics in the statute. Other legal issues include questions of FDA jurisdiction when a neural graft is produced and performed intrastate and jurisdiction in relation to the practice of medicine.

Unlike the intricate system of regulation to ensure the safety and efficacy of articles intended for use in the diagnosis, treatment, or prevention of disease in humans, there is no direct Federal regulation of new surgical procedures developed for the same purposes. New surgical procedures are usually subject to IRB review and are regulated indirectly by third-party payers, including Federal insurers such as the Health Care Financing Administration, the Department of Veterans Affairs, and the Department of Defense, which decide whether or not to reimburse. Other forms of indirect regulation include hospital standards set by the Joint Commission on Accreditation of Healthcare Organizations, professional standards of practice, State licensing laws, and medical malpractice cases. This system of indirect regulation will preside over the development and introduction of neural grafting procedures using materials that fall outside the jurisdiction of the other Federal regulatory mechanisms.

Protection of Donors of Fetal Tissue

Since fetal tissue is one of the possible sources of neural grafts, Federal regulations and State laws governing the donation and use of embryos and fetal tissue in research may apply. Federal regulations [45 CFR 46.201-211] lay out specific guidelines for research conducted on living fetuses. Under these regulations, certain types of fetal research are

allowed, with constraints based on obtaining parental consent and minimizing risk to the pregnant woman and the fetus. They defer to State laws on the subject of research on fetal cadavers.

The overwhelming majority of State legislatures have yet to address the issues associated with experimental neural grafting using fetal tissue. Only Missouri and Pennsylvania have enacted legislation directed specifically toward fetal tissue transplants. Although other States have not specifically addressed the question of neural tissue grafts from fetuses, the general fetal research laws pertaining to research on living fetuses, in effect in 25 States, may come to bear on it. Of these 25 States, 14 have provisions regulating research with fetal cadavers. In addition, 16 of the State fetal research statutes prohibit the sale of fetal tissue, 7 of them for any purpose and 9 for research purposes. The most significant factor in regulating research on dead or live fetuses and in determiningg the extent of restriction imposed appears to be whether the research concerns a fetus that has been or is to be intentionally aborted. Most of the State fetal research statutes were passed as part of abortion legislation.

Government Oversight

Issues and questions raised by the introduction and development of neural grafting procedures could make other government regulatory mechanisms relevant. For example, issues and legal questions regarding restrictions imposed on research could be raised. Not all regulations on research are constitutional. Laws restricting research may be struck down as too vague or as violating the equal protection clause of the Constitution. Laws applying to experimentation on fetuses or in the context of abortion may violate the constitutional right to privacy. Some legal commentators posit that there is a constitutional right to undertake or participate in research; however, even if undertaking and participating in research were constitutionally protected, certain restrictions to further health and safety could be permissible.

Regulations regarding the disposition of cadavers, particular fetal remains, may be of relevance. Most State statutes specify when fetal deaths must be registered and how fetal remains are to be disposed of. These statutes are important not only because they provide penalties for unauthorized uses of dead bodies, but also because they determine what must be done with fetal remains once their research or clinical value has been exhausted and what reports must be filed.

The Uniform Anatomical Gift Act (UAGA) is of special significance because it is the only uniform body of law that might be used to regulate fetal tissue implants. Adopted in all 50 States, the UAGA regulates the donation and distribution of cadaveric organs. While it includes fetuses and their tissues, some States exclude these provisions from their version of the UAGA. Because this Act was drafted before neural grafting technology became known, it was not designed to address the specific and unique problems that fetal grafts raise, and some of its provisions may not be appropriate for this use.

The possibility that women might be paid for fetal tissue for transplants has raised particular concern within some groups. The National Organ Transplant Act (NOTA) bans the sale of certain listed organs (including certain fetal organs and their subparts) [42 U.S.C. 274(e)] and provides that the Secretary of Health and Human Services may list additional organs. Since the brain, spinal cord, and other components of the nervous system are not listed as organs, payment for use of fetal nervous system tissue for transplantation will not be banned until the Secretary so designates. Apart from NOTA, the procurement of fetal tissue is regulated by State statutes.

ETHICAL ISSUES

Neural grafting technology is a complex subject for ethical discussion because of the scope of the issues it raises. Some ethical issues raised by neural grafting are not unique to this technology, as they concern the allocation of limited resources and the tension between the Federal Government's commitment to promote the public health by funding biomedical research and its responsibility to respond to public concern about certain research and its possible applications.

Public funding of biomedical technology involves broad analyses of economic benefits and costs, as well as possible social benefits and ethical consequences of the new technology. Knowledge of economic consequences is necessary for financial planning, but it is also integral to ethical decisionmaking, since the allocation of public funds raises

questions about justice and equity. Some people believe that justice requires the expenditure of funds in areas where they can benefit the greatest number of persons. To resolve some of these questions, it might be helpful to evaluate neural grafting in relation to treatments for other diseases, keeping in mind the priorities set and the amount of research funded. In order to make decisions about funding neural grafting research, it will be necessary to estimate the efficacy of the technology, the number of people now affected by the neurological disorder, and the number likely to be affected in the future.

The use of various grafting materials and the risks of surgery to recipients of grafts also raise ethical issues. The most ethically problematic issue is the use of fetal tissue. Fetal tissue from spontaneous abortion or ectopic pregnancy has been suggested as an acceptable source of graft material since this tissue is free of association with elective abortion. There is some question as to whether the physiological anomaly that caused the pregnancy to end would also cause increased risk to the graft recipient after implantation. While using fetal tissue from therapeutic or spontaneous abortions may avoid association of neural grafting with elective abortion, it may not be a practical source of graft material.

Tissue obtained from electively aborted fetuses is currently believed to be the most promising neural graft material, but it is also the most controversial. The primary impediment to resolving this ethical issue has been the lack of consensus about the moral relevance of elective abortion to any subsequent use of the tissue. The positions taken on the morality of fetal tissue grafting, however, do not necessarily reflect a person's beliefs about the morality of abortion. Both supporters and opponents of abortion rights have articulated reasons for supporting fetal tissue grafting research, and both have identified reasons for not doing so. Although personal opinions on fetal tissue transplantation tend to be consistent with personal opinions on elective abortion.

Arguments for and against the use of electively aborted fetal tissue for neural grafting stem from issues raised by current research and issues that may be raised if neural grafting is accepted as standard medical practice in the future. These include questions of whether the grafting procedure denies respect for fetal life by using the fetus as a means to an end. There has also been discussion of whether groups besides fetuses, such as women and society at large, maybe adversely affected by a policy that endorses fetal tissue grafting. Some claims have been made about the consequences of neural grafting in the future, such as the effect this research may have on the number of elective abortions performed in the United States. Currently, there is no evidence to support or refute the contention that fetal tissue grafting research would cause an increase in the number of abortions performed.

The use of small amounts of fetal tissue to start cell lines that can be propagated in a laboratory may allay some concerns about the consequences of using electively aborted fetal tissue for neural grafting. Such use complicates the issue of consent, however, because questions are raised about whether the tissue donor has property rights. For example, although it maybe deemed appropriate for a woman who aborts to consent to the use of fetal tissue in a cell line, it may not be considered appropriate for her to profit financially from it. While questions regarding the ownership of tissues used for commercially profitable cell lines are being addressed by the courts, discussion has been limited to the ownership of adult tissues. Questions pertaining to ownership of fetal tissue remain unanswered.

Controversy also exists about whether the woman who elects to have the abortion is the appropriate person to give consent for fetal tissue donation and, if so, when consent should be solicited. Both the regulations for the protection of research subjects and those for the donation of body parts have been suggested as models for fetal tissue donation, but these regulations do not explicitly cover the donation of fetal tissue for transplantation research.

The ethical issues related to neural graft recipients rekindle discussions about the treatment of research subjects and the meaning of informed consent. While these issues are not unique to neural grafting, they may warrant special attention for this technology. Existing regulations may not adequately protect recipients from the risks unique to this surgery. The possibility of doing a sufficient risk-benefit analysis has been challenged on the grounds that not enough research has been done to know what the benefits of neural grafting are likely to be. Obtaining informed consent may be difficult, both because the risks and benefits cannot be realistically estimated at this time and because persons with neurological disorders may also have cognitive limitations.

POLICY ISSUES AND OPTIONS FOR CONGRESSIONAL ACTION

Three policy issues related to neural grafting were identified during the course of this assessment:

- Federal funding of human fetal tissue transplantation research,
- the adequacy of existing Federal laws and regulations regarding the use of human fetal tissue, and
- the role of the Federal Government in guiding the development and promoting the safety and efficacy of neural grafting procedures.

Associated with each policy issue are several options for congressional action, ranging from taking no action to making substantial changes. Some of the options involve direct legislative action. Others involve the executive branch, but with congressional oversight or direction. The order in which the options are presented do not imply any priority. Moreover, the options are not, for the most part, mutually exclusive; adopting one does not necessarily disqualify others within the same category or in any other category. A careful combination of options might produce the most desirable effects. It is also important to keep in mind that changes in one area may have repercussions in other areas.

ISSUE 1: Should the Federal Government fund human fetal tissue transplantation research?

A number of grafting materials are being studied for their usefulness in ameliorating the symptoms of neurological disorders. Neural tissue from human fetuses is a promising source of neural grafting material; however, the Department of Health and Human Services (DHHS) has imposed a moratorium on the use of Federal funds to support research involving the implantation of human fetal tissue from induced abortions into human patients. First imposed in March 1988, the moratorium was extended indefinitely in November 1989.

Option 1: Take no action.

If Congress takes no action, it appears that the moratorium will stand indefinitely, resulting in a lack of Federal funds for both neural grafting and other areas of research using human fetal tissue and a consequent lack of Federal involvement in the conduct of such research.

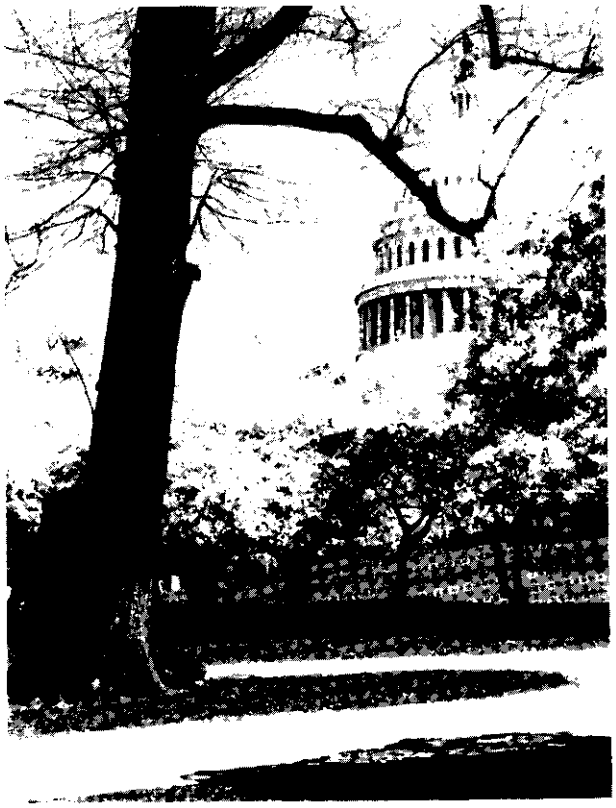


Photo credit: Robyn Nishimi

As a result of the moratorium, research involving the implantation of human fetal tissue from induced abortions into human patients can only be funded by private sources. Since the inception of the moratorium, a few privately funded efforts to examine fetal neural grafts for the treatment of Parkinson's disease have been undertaken in the United States. The lack of Federal support for these neural grafting studies has limited the scope of Parkinson's disease research in the United States.

As basic research continues, neural grafting techniques using human fetal tissue may be developed to treat other neurological disorders. The transition from animal to human studies may be difficult without Federal funding. Lack of Federal funds for clinical studies could retard the development of these techniques in the United States, leaving progress to be made by other countries, where this research is continuing. Some observers suggest that the moratorium has had the secondary effect of discouraging basic research in neural grafting, resulting in the channeling of investigators into other areas of biomedical research.

Privately funded clinical research is regulated under applicable State laws. Although Federal regulations, including review of research protocols by a local Institutional Review Board (IRB), are often voluntarily used to guide privately funded research, there is no requirement that they be used. Thus, in the absence of Federal funding, fetal tissue transplantation research can proceed without the oversight required for federally funded biomedical research. This oversight includes the peer review process established by funding agencies such as the National Institutes of Health (NIH) or the Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA), and without the steering function of these agencies to ensure efficient, standardized collection of data.

Option 2: Commission a study to assess the impact on society of the lack of Federal funding for human fetal tissue transplantation research.

Congress could commission a study by a governmental or nongovernmental agency, such as the National Academy of Sciences, to assess the implications for society of the lack of support by the Federal Government of fetal tissue transplantation research. Public debate has highlighted a number of areas that could be affected by Federal support of this research, including the manner and timing of the procurement of fetal tissue; the possible commercialization of fetal tissue; the conditions for informed consent for donation of the tissue; the effect that the use of fetal tissue could have on the incidence of abortion; and the implications that the lack of Federal funding could have for the acquisition of new biomedical information and the development of new treatments for some neurological disorders. To date, there has been no comprehensive study of what effects Federal funding might have on these areas. The results of such a study could be used to guide policy decisions and develop guidelines for Federal funding of fetal tissue transplantation research.

Option 3: Enact legislation to permit Federal funding of human fetal tissue transplantation research.

Congress could reinstate Federal funding of human fetal tissue transplantation research and introduce guidelines for its implementation through direct legislative mandate. Guidelines could be based on the recommendations of the NIH's Human Fetal Tissue Transplantation Research Panel, which was convened under the direction of the Assistant Secretary for Health in 1988. The DHHS Ethics Advisory Board, which was disbanded in 1980, could also be reconvened to propose guidelines.

Such legislation would most likely result in increased research in neural grafting in the United States. Increased research could clarify the role that neural grafts might play in some neurological disorders and could result in the development of new therapies for those disorders.

On the other hand, some observers have expressed the concern that if Congress takes this action and research in this area were to increase, a number of detrimental effects could ensue. Arguments made by supporters of the moratorium include concerns that Federal funding of human fetal tissue transplantation research might encourage induced abortion; that the number of induced abortions in the United States might increase; and that, in the absence of carefully crafted guidelines, negative effects related to the donation, procurement, distribution, and transplantation of fetal tissue could occur.

ISSUE 2: Do existing Federal laws and regulations governing organ transplantation adequately address concerns raised by human fetal tissue transplantation?

Concerns over the possible commercialization of fetal tissue and the lack of regulation of its use have been raised in public debates about human fetal tissue transplantation. Neither DHHS regulations for the protection of human subjects [45 CFR 46] nor the National Organ Transplant Act (NOTA) explicitly addresses the use of cadaveric fetal tissue in neural grafting, although either could be amended to do SO.

The DHHS regulations for the protection of human subjects apply to research supported or conducted by DHHS, although they are often voluntarily followed for privately funded research. These regulations impose specific conditions on research involving living fetuses or their tissues. With respect to research involving fetal cadavers or the use of cadaveric fetal tissue, the regulations state that research must be conducted according to State and local laws. The extent to which other provisions of the DHHS regulations apply to research using tissue obtained from a fetal cadaver is unclear. NOTA bans the sale of certain organs (including fetal organs and their subparts) and provides that the

Secretary of Health and Human Services may list other organs. The brain, spinal cord, and other components of the nervous system are not listed as organs covered by NOTA.

The Uniform Anatomical Gift Act (UAGA), which was drafted by the Commissioners on Uniform State Laws and adopted in all 50 States, is the only other body of law that might be used to regulate the use of cadaveric fetal tissue for neural grafts. It provides guidelines for the donation and receipt of cadavers for research, education, therapy, and transplantation. The UAGA specifically includes stillborn infants and fetal cadavers, although some States have excluded fetuses from their provisions of the law. However, some observers feel that there are provisions of the UAGA that do not take into account concerns raised by fetal tissue donation. The UAGA allows the next of kin, starting with either parent and following a fixed order of priority, to donate fetal tissue and allows the donor of the tissue to designate a recipient. It also allows consent for donation to be sought immediately before death. If this last provision were applied in the case of fetal tissue, it might allow consent to be obtained from a pregnant woman before an abortion. The ethics of designating a recipient and obtaining consent for donation before an abortion are controversial. The question of who has the right to donate tissue from an elective abortion has also been raised. Thus the appropriateness of some of the provisions of the UAGA for the regulation of the donation of fetal tissue for transplantation is in question.

Option 1: Take no action.

In the absence of congressional action, no direct Federal regulatory framework pertaining to the use of cadaveric fetal tissue for transplantation would exist. While some aspects of fetal tissue transplantation would continue to be covered under the UAGA and other State laws, such regulations differ from State to State. No specific regulations would pertain to the use of cadaveric fetal tissue for transplantation research supported by DHHS, and payment for fetal brain, spinal cord, or other components of the nervous system will not be banned by Federal law, although it might be banned by State laws.

Option 2: Establish a congressional commission to recommend ***Federal policy on human fetal tissue transplants.***

Congress could establish a commission to examine the comprehensiveness of existing legislation and regulations surrounding the use of human fetal tissue for transplantation. Such a commission could suggest guidelines for regulating the donation, procurement, distribution, and use of fetal tissue for transplantation. Findings could be used to direct further Federal regulatory and legislative action or to amend the UAGA.

Option 3: Encourage the National Conference of Commissioners on Uniform State Laws to amend the Uniform Anatomical Gift Act.

Congress could encourage the Conference, through a letter of request by a Committee or through legislation, to amend the UAGA to take into account the issues raised by the donation of cadaveric fetal tissue. While the Conference is under no obligation to respond to congressional initiatives, taking this action would indicate Congress' concern about the appropriateness of some of the provisions of the UAGA for dealing with fetal tissue donation.

Option 4: Direct the Secretary of Health and Human Services to amend the current Department of Health and Human Services regulations regarding the protection of human subjects.

Congress could direct the Secretary of Health and Human Services to amend existing regulations to address specifically the use of cadaveric human fetal tissue for transplantation research. Such regulations could guide the procurement, distribution, and use of fetal tissue. If Congress takes this action, it would result in the establishment of uniform, specific regulations for the use of tissue from fetal cadavers in federally funded research.

Option 5: Mandate that the brain and nervous system tissue be added to the list of organs covered by the National Organ Transplant Act.

NOTA lists certain organs (including those from a fetus) that cannot be bought or sold and provides that the Secretary of Health and Human Services may add other organs to the list. The brain, spinal cord, and other components of the nervous system are not now on that list. Congress could add them, either by amending NOTA directly or by directing the Secretary of Health and Human Services to do so. Taking this action would result in a Federal injunction against the buying or selling of tissue from the fetal nervous system and would thus ban

the commercialization of fetal nervous tissue for use in neural grafting procedures.

ISSUE 3: Should the Federal Government take further action to guide the development and promote the safety and efficacy of neural grafting procedures?

The development of new medical and surgical procedures, such as neural grafting, generally proceeds through a series of stages. First, basic research is conducted using animal models and other experimental designs. Based on the results of these studies, researchers may proceed to clinical research, prior to introduction of the procedure as standard therapy. However, unlike the elaborate Federal regulatory framework that guides the development and introduction of new drugs and medical devices to ensure their safety and efficacy, there is little direct Federal oversight of the development and introduction of new medical and surgical procedures.

Because of the diverse nature of neural grafting materials, it is unclear where in the Federal regulatory framework neural grafting procedures will fall. In addition, concerns have been raised about the criteria that have been used to move neural grafting from the laboratory to clinical research.

Option I: Take no action.

If Congress takes no action, the Food and Drug Administration (FDA) could seek to regulate the development of those neural grafting procedures that use materials which fall under its jurisdiction. There will be little or no Federal regulation of neural grafting materials that do not come under FDA oversight. In such cases, and in the absence of congressional action, decisions concerning when the transition from animal to human studies should occur, how human research should be carried out, and when a neural grafting procedure ceases to be experimental will be made through traditional mechanisms for the development of new surgical procedures.

The decision to move from animal to human studies, as was made for the use of neural grafts for the treatment of Parkinson's disease, is generally made by individual researchers or institutions. For federally supported studies, research protocols are subject to the peer review process conducted by Federal funding agencies and to DHHS regulations for the protection of human subjects. These regulations require that research proposals be approved by the local IRB; however, IRBs have no specific criteria for moving from animal studies to human trials. While nonfederally funded studies may be submitted to local IRB scrutiny and may undergo a peer review process, there is no requirement that they do so. If Congress takes no action, the decision of when a neural grafting procedure is ready to proceed from animal to human experimentation will be made in this way. Some observers believe that this framework did not provide adequate guidance in the case of neural grafting for the treatment of Parkinson's disease, resulting in a premature move to clinical trials. Others believe that additional oversight would be unduly burdensome and could stifle scientific progress.

In clinical research, the designs of the studies and the protocols followed are determined by the researchers involved. Coordination of efforts, to enhance the efficient collection and analysis of data (as has been attempted in some trials of neural grafting for the treatment of Parkinson's disease), is sometimes undertaken voluntarily by professional societies, private organizations, or agreements between research groups. Federal funding agencies can impose criteria for the conduct of research and thus ensure more efficient data collection and analysis. In the absence of congressional action, the development of neural grafting procedures in humans may proceed in a fashion that does not optimize the coordination of research efforts, which could result in an inefficient collection of the data necessary to make a determination about the safety and efficacy of procedures.

Data collected during clinical trials guide the transition from research to standard therapy. Neural grafting procedures have not yet reached this stage, but it is possible that they may. Clinical use and availability of a procedure are indirectly regulated by third-party payers, professional societies, State licensing laws, and medical malpractice claims. There is no direct Federal oversight of this process; however, the Federal Government regulates it indirectly in its role as an insurer of medical care. The Health Care Financing Administration (HCFA) determines when sufficient information is available to warrant Medicare or Medicaid coverage; HCFA may also establish criteria that must be met by facilities providing the procedure. The Department of Defense, through the CHAMPUS insurance program, and the Department of Veterans Affairs are

also third-party payers. The decisions of these Federal agencies often influence private third-party payers' decisions to reimburse for a new medical or surgical procedure and the medical community's decision to provide it.

The Agency for Health Care Policy and Research (AHCPR), established within DHHS to promote research on selected surgical and medical procedures in order to assess their appropriateness, necessity, and effectiveness, could also play a role in this process. If directed to do so, the AHCPR could serve as a Federal mechanism for assessing neural grafting procedures. In the absence of congressional action, AHCPR may or may not choose to study neural grafting procedures.

Option 2: Direct that the National Institutes of Health establish guidelines for neural grafting research protocols with humans.

Congress could direct the Secretary of Health and Human Services, through NIH, to provide IRBs and peer review boards with guidelines concerning proposed grafting research projects using human subjects. Such guidelines could provide information about the status of the procedure, what animal research has been conducted, and whether sufficient data have been collected to warrant the transition from animal to human studies. These guidelines could be used to direct decisions regarding federally funded research proposals and provide guidance for decisions about nonfederally funded studies.

Option 3: Direct the Secretary of Health and Human Services to coordinate federally funded human neural grafting trials in order to optimize the collection of data.

Congress could direct the Secretary of Health and Human Services, through NIH and ADAMHA, to coordinate federally funded human neural grafting trials. Such coordination could take a number of forms, such as designating specific centers to carry out experimental trials using uniform protocols and procedures or requiring federally funded studies to follow specified guidelines concerning experimental design and the collection of data. By taking this action, Congress could ensure that federally funded experimental trials to determine the safety and efficacy of neural grafting procedures would proceed in the most efficient manner.

Option 4: Mandate that the Agency for Health Care Policy and Research monitor the development of neural grafting procedures.

The AHCPR, through the Medical Treatment Effectiveness Program, assesses the medical effectiveness and patient outcomes associated with selected medical and surgical procedures. Congress could direct AHCPR to assess the development of neural grafting procedures and develop guidelines for the use of these procedures.