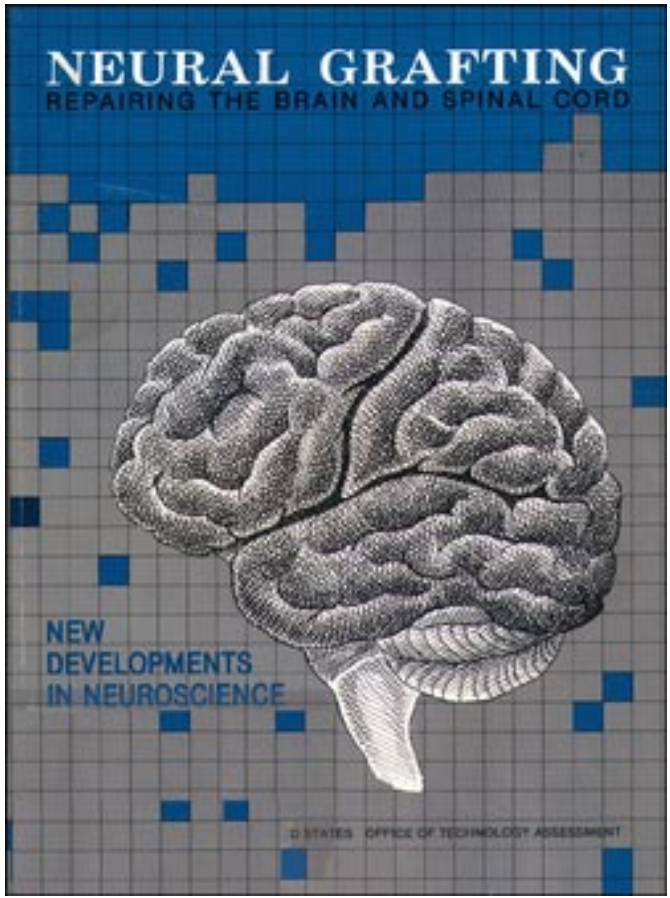
Neural Grafting: Repairing the Brain and Spinal Cord

October 1990

OTA-BA-462
NTIS order #PB91-114249



Recommended Citation:

U.S. Congress, Office of Technology Assessment, *Neural Grafting: Repairing the Brain and Spinal Cord, OTA-BA-462* (Washington, DC: U.S. Government Printing Office, September 1990.

For sale by the Superintendent of Documents
U.S. Government Printing Office, Washington, DC 20402-9325
(order form can be found in the back of this report)

Foreword

Extraordinary developments in the neuroscience in recent years have shown promise of new advances for treating diseases of the nervous system and for increased general understanding of the human mind. Paralleling these developments has been a growing congressional interest in their policy implications. The designation of the 1990s by the101st Congress as the "Decade of the Brain" is one indication of this interest, as was the request for OTA to undertake a series of reports under an assessment of "New Developments in Neuroscience." Requesting committees are the House Committees on Energy and Commerce; Science, Space, and Technology; Appropriations; Veterans Affairs; and the Senate Subcommittee on Science, Technology, and Space of the Committee on Commerce, Science, and Transportation.

This special report, the second of our neuroscience series, discusses the field of neural grafting into the brain and spinal cord to treat neurological disorders. It describes the technology of neural grafting, the neurological conditions that it may be used to treat, and the patient populations that are affected. Also, the legal and ethical issues raised by the development of neural grafting techniques are discussed. The report includes a range of options for congressional action related to the Federal funding of transplantation research using human fetal tissue, 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.

The first publication in OTA's assessment of "New Developments in Neuroscience" was *Neurotoxicity: Identifying and Controlling Poisons of the Nervous System,* published in April 1990. OTA was assisted in preparing the present study by a panel of advisers, a workshop group, and reviewers selected for their expertise and diverse points of view on the issues covered by the assessment. OTA gratefully acknowledges the contribution of each of these individuals. As with all OTA reports, responsibility for the content of the report is OTA'S alone.

JOHN H. GIBBONS
Director

New Developments in Neuroscience Advisory Panel

Peter S. Spencer, ***Chair***
Center for Research, Occupational, and Environmental Toxicology
Oregon Health Sciences University
Portland, OR

Robert H. Blank
Social Science Research Institute
Northern Illinois University
DeKalb, IL

James F. Childress
Department of Religious Studies
University of Virginia
Charlottesville, VA

Fred H. Gage
Department of Neuroscience
University of California-San Diego
La Jolla, CA

Bernice Grafstein
Department of Physiology
Cornell University
New York, NY

Ronald Kartzinel
Vice President for CNS Development
CIBA-GEIGY Corporation
Summit, NJ

Alan Kraut
Executive Director
American Psychological Society
Washington, DC

Laurane G. Mendelssohn
Manager of Personnel Research
Lilly Research Laboratories
Indianapolis, IN

Franklin E. Mirer
Director, Health and Safety Department
United Auto Workers
Detroit, MI

Albert S. Moraczewski
Regional Director
Pope John XXIII Medical, Moral, Research, and Education Center
Houston, TX

Herbert Paroles
Department of Psychiatry
Columbia University
New York NY

Richard M. Restak
Physician
Neurological Associates, P.C.
Washington, DC

Neural Grafts Study Panel

Roy A. E. Bakay
Section of Neurosurgery
The Emory Clinic
Atlanta, GA

Nancy Buc (ad hoc)
Partner
Weil, Gotshal & Manges
Washington, DC

Robert P. Gale
Division of Hematology and Oncology
University of California-Los Angeles
Los Angeles, CA

Patricia King (ad hoc)
Georgetown University
Law Center
Washington, DC

Mary B. Mahowald
Center for Clinical Medical Ethics
University of Chicago
Chicago, 11

Jerry Silver
Department of Developmental Genetics
Case Western Reserve Univ.
Cleveland, OH

John R. Sladek, Jr.
Department of Neurobiology and Anatomy
University of Rochester
Rochester, NY

H.Fred Voss
Program Director
Biotrack, Inc.
Mountain View, CA

NOTE: OTA appreciates and is grateful for the valuable assistance and thoughtful critiques provided by the advisory and study panel members. The panels do not, however, necessarily approve, disapprove, or endorse this report. OTA assumes full responsibility for the report and the accuracy of its contents.

OTA Project Staff-Neural Grafting: Repairing the Brain and Spinal Cord

Roger C. Herdman, Assistant Director, OTA, Health and Life Sciences Division

Gretchen S. Kolsrud, *Biological Applications Program Manager*[1]

OTA Project Staff

David R. Liskowsky, *Project Director*

Timothy P. Condon, *Project Director*[2]

Monica Bhattacharyya, *Research Assistant*

Joyce Anne Brentley, ***Legal*** *Analyst*

Laura Lee Hall, *Analyst*

Wendy S. Pachter, *Legal Analyst*

Claire L. Pouncey, *Research Assistant*

E. Blair Wardenburg, *Research Analyst*[3]

Gladys B. White, *Analyst*[4]

Patricia Anderson, *NIH Detailee*[5]

Support Staff

Cecile Parker, Office *Administrator*

Linda Rayford-Journiette, *Administrative Secretary*

Jene Lewis, *Secretary*

Sharon Oatman, *Administrative Assistant*[6]

Contractors

Blair Burns Potter (editor), Bethesda, MD
Julie Phillips (indexer), Oakton, VA
Lori Andrews, American Bar Foundation
Alan Fine, Dalhousie University
Thomas B. Freeman, University of South Florida
Karen Gervais, University of Minnesota Center for Biomedical Ethics
William F. Hickey, Washington University
Ronald D. McKay, Massachusetts Institute of Technology
Rosa Lynn Pinkus, University of Pittsburgh
Ali H. Rajput, University of Saskatchewan

---

[1] Through September 1989
[2] Through August 1989.
[3] Through August 1989.
4 Through June 1989.
5 Through October 1989.
6 Through February 1989.

Contents

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

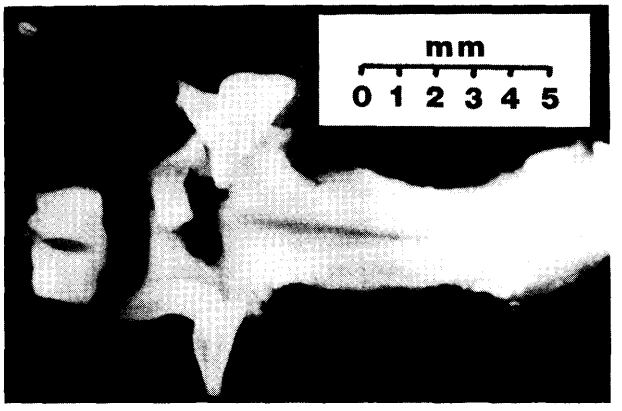


Photo credit: C. Freed, Department of Medicine and Pharmacology, University of Colorado

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).

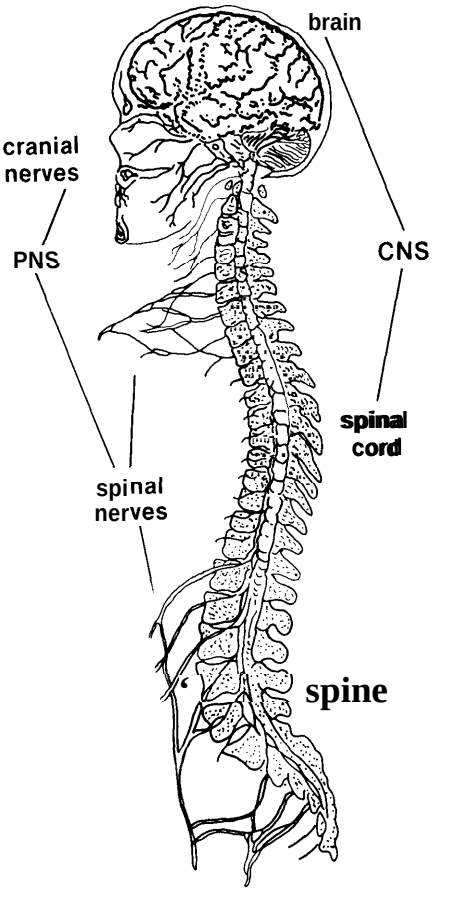
Determinants of Successful Neural Grafting

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



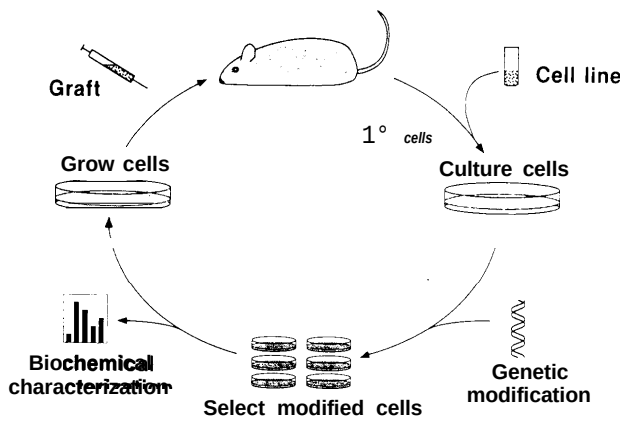
The nervous system is composed of the central (CNS) and peripheral nervous systems (PNS).

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.

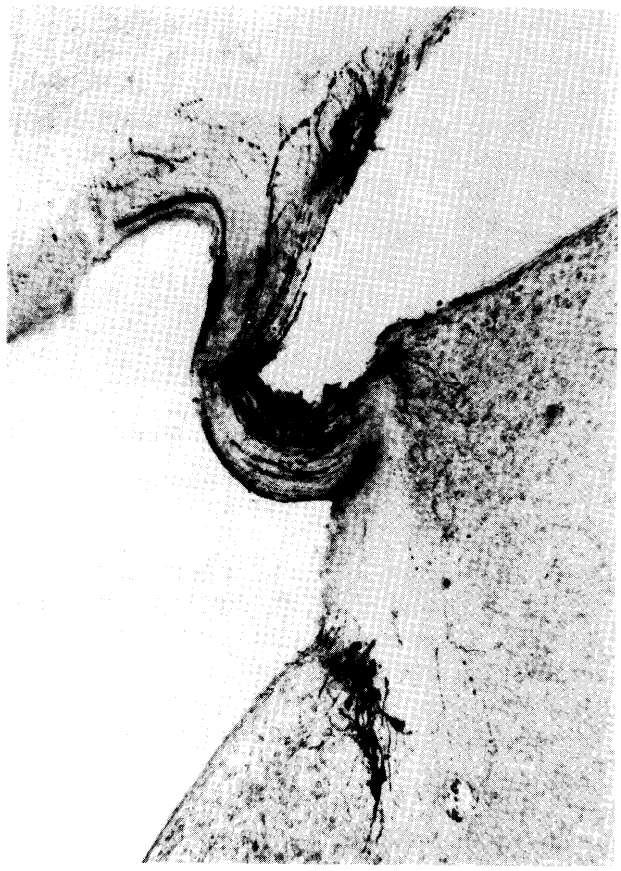


Photo credit: J.R. Sladek, Jr.

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.

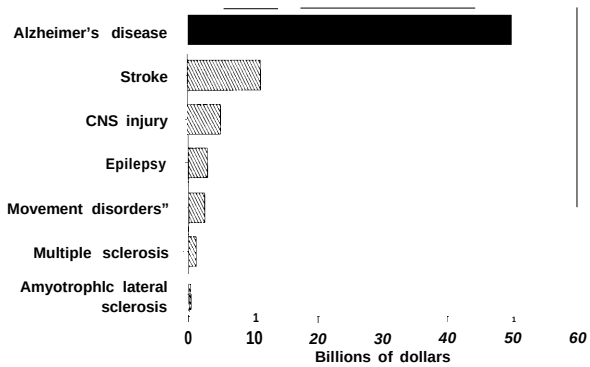
Neural grafting holds the promise of new treatments for neurological disorders, but a final determination of its usefulness must await more information about the mechanisms underlying neurological disorders, graft functions, and how those functions relate to various neurological disorders.

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.

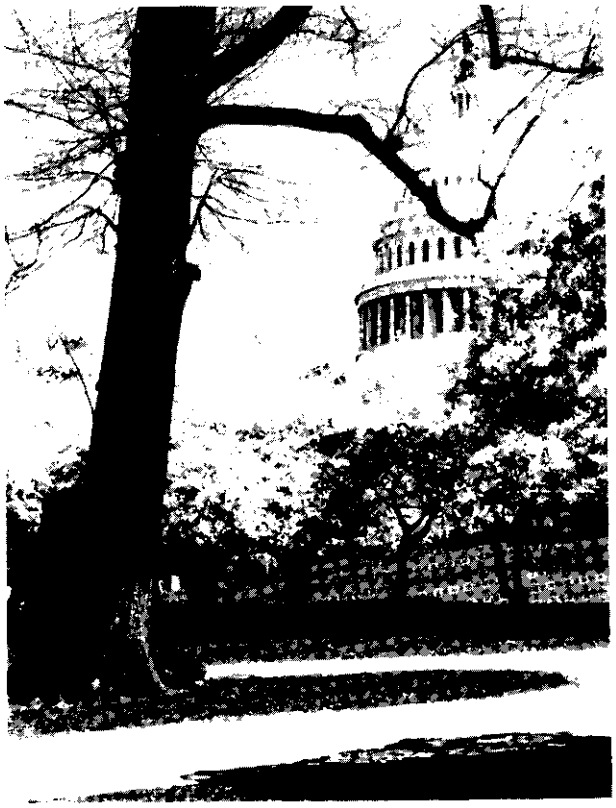


Photo credit: Robyn Nishimi

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.

Chapter 2

Introduction

CONTENTS

Figure

Tables

Chapter 2
Introduction

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. These conditions include dementias, such as Alzheimer's disease; movement disorders, such as Parkinson's disease; damage caused by stroke or injuries to the brain or spinal cord; and epilepsy. Some of these neurological disorders may be treatable by neural grafting—i.e., the transplantation of tissue into the brain and spinal cord.

In 1989, over ***500,000*** Americans received tissue or organ transplants. The vast majority of these operations involved transplantation of bone, cornea, kidney, liver, heart, pancreas, lung, and bone marrow (table 2-l). A small number of procedures, however, involved neural grafts. Although few neural grafting procedures have been carried out to date, the number could increase in the future.

The use of neural grafting in the laboratory is not new. It 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 disease or injury. The ability of neural grafts to repair injured nerves in the peripheral nervous system has been studied fairly extensively. Examination of the potential therapeutic effects of neural grafts within the central nervous system (CNS) (i.e., the brain and spinal cord) is a more recent field of study. This report focuses on the field of neural grafting into the brain and spinal cord to treat neurological disorders. It is about the technology of neural grafting, the neurological disorders that neural grafts may be used to treat, the patient populations that might be affected, and the legal and ethical issues raised by the development of this technology.

Table 2-l—Tissue and Organ Transplants in the United States, 1989

Material transplanted	Number
Bone or bone fragment	450,000 (approximate)[a]
Cornea	36,900'
Kidney	8,886
Bone marrow	2,500 (approximate)
Liver	2,160
Heart	1,673
Pancreas	412
Lung	89
Heart and lung	70
Neural	<30

a 1998~

SOURCE: United Network for Organ Sharing; American Association of Tissue Banks; Eye Bank Association of America; North American Autologous Transplant Registry; International Bone Marrow Transplant Registry; Office of Technology Assessment, 1990.

Although therapeutic neural grafting into the CNS of humans is relatively new, several strategies for its use have emerged. These strategies can be grouped as follows:

- grafts to replace lost chemicals of the nervous system;
- grafts to stimulate growth and promote survival of cells in the nervous system; and
- grafts to replace lost structures in the nervous system.

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.

NATURE OF NEUROLOGICAL DISORDERS

Injury

Injury to the CNS can result from mechanical damage to the brain or spinal cord (e.g., skull fracture, concussion, wounds from projectiles, broken backs) or a disruption in the normal flow of blood to the brain (e.g., stroke). It can result in short- or long-term impairment. Blunt injury to the head, for example, can result in immediate but short-term unconsciousness that has no lasting effect. Blunt injury to the head can also cause severe trauma to the brain (swelling, decreased blood flow, lack of oxygen, and massive cell death), resulting in permanent paralysis, loss of the sense of touch or ability to feel pain, loss of cognitive function, or death. Severe trauma, such as that which can occur in automobile collisions or sports injuries, can cause profound and often permanent damage to the spinal cord. Such damage usually results in paralysis and severe physical disability. The ability of grafted material to replace tissue lost through injury and to promote recovery following an injury is a major area of investigation.

Disease

The brain and spinal cord are complex and fragile organs susceptible to a number of diseases. Among them are neurodegenerative disorders, demyelinating disorders, and epilepsy.

Neurodegenerative Disorders

Neurodegenerative disorders are a class of neurological diseases marked by the loss of specific nerve cell population(s) in the brain or spinal cord. In most cases, the cell loss is a gradual progression that continues indefinitely. Neurodegenerative disorders include Parkinson's disease, Huntington's disease, Alzheimer's disease, and amyotrophic lateral sclerosis (Lou Gehrig's disease). The nature of the functional loss or impairment associated with a neurodegenerative disorder is directly related to the population of neurons affected. In Parkinson's disease, for example, the loss of dopamine-producing cells in the substantial nigra results in such motor symptoms as tremors and rigidity, while in Alzheimer's disease loss of acetylcholine-producing cells in the forebrain results in cognitive deficits such as memory loss and confusion. Although the cause of the selective loss of cell populations in neurodegenerative disorders remains unknown, it is possible that multiple factors are responsible. It is also possible that the ultimate mechanism of cell death in these disorders may be similar, although the stimuli that trigger the mechanism could be quite different in each.

Neural grafting might play a number of roles in treating neurodegenerative disorders or their symptoms. Neural grafts could replenish chemicals that have been depleted by cell loss, replace the lost cells with new ones that could reestablish contacts with other brain cells, or furnish growth factors that could protect threatened cells or stimulate new growth from other cells. All of these potential applications are being studied in animal models and other experimental paradigms to determine their feasibility.

Photo credit: National Institutes of Health

A patient undergoing a brain scan.

Demyelinating Disorders

Demyelinating disorders are marked by loss of the fatty material (myelin) that surrounds many axons in the brain and spinal cord. When a cell loses this myelin sheath, its ability to send messages is impaired. Myelin loss can be caused by certain types of injuries and by disease. One of the most common demyelinating diseases is multiple sclerosis. The ability of grafted myelin-producing cells to replace myelin lost as a result of disease or injury is currently being explored.

Epilepsy

Epilepsy is a disruption of the normal electrical activity of the brain. It can occur in a specific, confined area of the brain, or it can involve the entire brain. The seizures normally associated with epilepsy result from an episode of abnormal electrical activity in the brain. Epilepsy can occur spontaneously or as a result of disease or injury to the brain. Neural grafts are being examined in animal research for their ability to curtail the number and severity of epileptic seizures.

APPROACHES TO TREATMENT

Current treatments for neurological disorders include drugs, surgery, physical therapy, and behavioral interventions. For most disorders, current treatments do not provide a cure, but rather relief of symptoms. Nevertheless, treatments are likely to improve significantly as advances in the field of neuroscience provide a better understanding of the causes and mechanisms of neurological injury and disease. 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 disease).

Currently, grafting of tissue into the nervous system to treat neurological disorders is highly experimental. It is just beginning to emerge into the clinical arena, and there is a great need for basic research to determine the scope of its effectiveness in a variety of disorders. To date, neural grafting has only been used to treat a relatively small number of patients. However, because of its potential to replace damaged nerve cells, restore chemicals lost through injury to nerve cells, and stimulate nerve cell growth and regeneration, grafting of tissue into the CNS may become a significant therapeutic alternative in the future.

HISTORICAL PERSPECTIVE

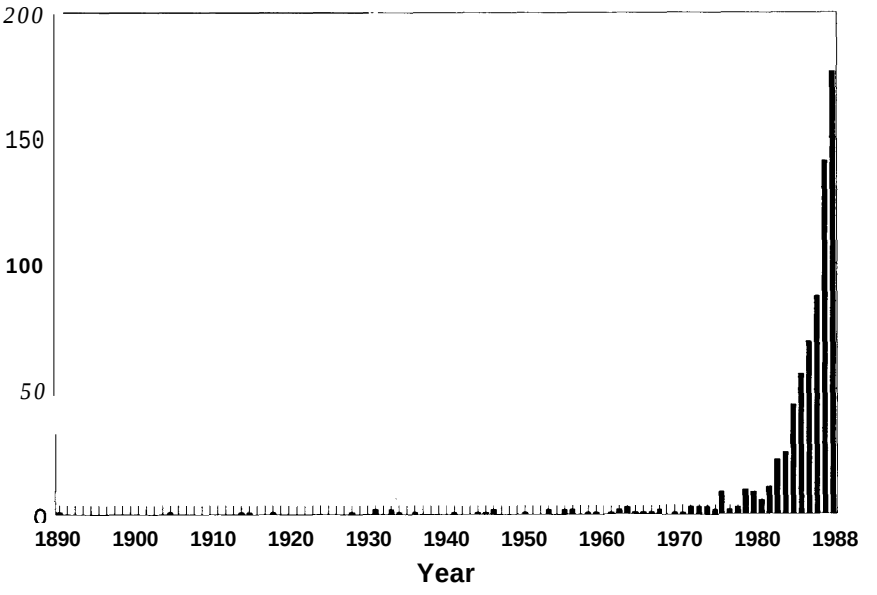
The first report of attempted tissue transplantation into the brain is attributed to W.G. Thompson, an American scientist. Thompson published a brief account of his animal experiments in 1890 (3). A number of reports followed over the next 20 years, but it was not until 1917 that E. Dunn frost demonstrated that CNS tissue transplanted from newborn rodents into adult rodents could survive over an extended period of time, provided the transplanted tissue was in an immature, developing state. During the following 50 years, only occasional reports on transplantation into the CNS appeared. In the last 20 years, however, there has been an explosion of experimental work in this area (figure 2-l). Some historical landmarks in neural grafting into the mammalian CNS are presented in table 2-2.

The vast majority of neural grafting experiments to date have been conducted on animal models (e.g., rodents and nonhuman primates). The first grafting experiments on humans were undertaken in 1982 in Sweden in an attempt to treat Parkinson's disease (2). The Swedish group implanted dopamine-producing cells into the brains of Parkinson's disease patients whose medication was no longer effective. The cells came from each patient's own adrenal gland in order to minimize the chances of rejection by the body's immune system. It was theorized that replacing the lost dopamine in the brain would ameliorate some of the characteristic symptoms of Parkinson's disease. From 1982 to 1984, neural transplants were performed on four patients. The patients, however, did not show any significant, long-term improvement (7).

In 1986, a neurosurgical team from Mexico City announced substantial amelioration of most of the clinical signs of Parkinson's disease after transplanting adrenal tissue to the patient's brain (10). Based on the success reported by this group, many other groups attempted the procedure, and by mid-1989 over 300 patients in at least six countries (Sweden, Mexico, United States, Cuba, Spain, and China) had received adrenal cell transplants, with mixed results.

Since many researchers failed to achieve the level of success reported by the Mexican group, a number

Figure 2-l—Annual Publications on Grafting Into the Nervous System



SOURCE: Adapted from J.R. Sladek, Jr., and D.M. Gash (eds.), *Neural Transplants: Development and Function* (New York, NY: Plenum Press, 1984).

of the transplant groups in the United States suspended neural grafting with adrenal cells. Some groups raised questions about the efficacy of this approach in humans, the amount of animal experimentation done prior to use of the procedure on Parkinson's patients, and the magnitude of effect seen in these animal studies (12). However, reports of limited success in treating Parkinson's patients with neural grafting of adrenal cells continue to appear in the scientific literature (1,5,6).

In 1988, grafting of human fetal CNS tissue into the brain was announced by the same Mexican and Swedish research groups that had previously performed adrenal cell transplants in Parkinson's patients (9,11). Subsequently, several centers around the world—in the People's Republic of China, Cuba, Spain, Great Britain, and the United States-began performing these procedures. Fetal CNS tissue was chosen for grafting because developing tissue is more likely to become integrated in the brain and restore lost or damaged nervous system functions than mature CNS tissue. Despite the more extensive animal research preceding this move to human experiments, concerns were still raised about the efficacy and experimental nature of this treatment for Parkinson's disease. The use of human fetal tissue from elective abortions has also raised ethical questions. Recently, some beneficial effects from human fetal tissue grafts have been reported in a limited number of Parkinson's disease patients (4,8).

In a few instances, neural grafting has been attempted inpatients suffering from other neurological disorders. (See ch. 5 for a complete description of the history of neural grafting in Parkinson's disease and its use to date in other disorders.)

FEDERAL INTERESTS

As is often the case in the biomedical sciences, the development of neural grafting has raised scientific, legal, and ethical issues, including:

- protection of human subjects in research, and
- sources of tissue for transplantation.

The role of the Federal Government in the research, development, and regulation of neural grafting is questioned by some parties.

A continuing question in biomedical research is when to move from the laboratory to the clinical arena. How much animal experimentation should be conducted before performing new or innovative procedures on humans? What kind of animal experimentation should be conducted? How should the results be assessed? What mechanisms and safeguards exist to guide the development of

Table 2-2—Landmarks for Neural Grafting in Mammalian Central Nervous Systems

Year	Researcher	Accomplishment
1890	W.G. Thompson (U. S.A.)	Attempt to graft adult CNS tissue into brain
1898	J. Forssman (Sweden)	Neurotrophic effects of grafted CNS tissue
1907	G. Del Conte (Italy)	Attempt to graft embryonic tissues into brain
1909	W. Ranson (U. S.A.)	Successful grafting of spinal ganglia into brain
1911	F. Tello (Spain)	Successful grafting of peripheral nerve into brain
1917	E. Dunn (U.S.A.)	Successful grafting of neonatal CNS tissue into adult brain
1921	Y. Shirai (Japan)	Demonstration of brain as an immunologically privileged site
1924	G. Faldino (Italy)	Successful grafting of fetal CNS tissue into anterior eye chamber
1940	W.E. LeGros Clark (U.K.)	Successful grafting of fetal CNS tissue into neonatal brain
1957	B. Flerko and J. Szentagothai (Hungary)	Successful intraventricular grafting of endocrine tissue
1979	A. Bjorklund and U. Stenevi (Sweden) M.J. Perlow et al. (U.S.A.)	Functional recovery after grafting dopamine-producing cells into the brain
1982	E.O. Backlund et al. (Sweden)	Human neural graft with adrenal chromaffin cells (autograft)
1985, 1986	R.A.E. Bakay et al. (U.S.A.) D.E. Redmond et aL (U.S.A.)	Reversal of experimentally induced Parkinson's disease in nonhuman primates
1987	O. Lindvall et al. (Sweden) I. Madrazo et al. (Mexico);	Human fetal tissue graft (allograft)

NOTE: All experimental work performed in animals unless otherwise indicated.

SOURCE: Adapted from A. Björklund and U. Stenevi (eds.), "Intracerebral Grafting: A Historical Perspective," Neural *Grafting in the Mammalian CNS* (Amsterdam: Elsevier Science Publishers, 1985).'

new treatments from conception and evolution in the clinical research environment to accepted medical practice?

In its efforts to protect the public health, the Federal Government regulates one important aspect of medical care, namely, the development, testing, and marketing of drugs, biologics, and medical devices. Are similar regulatory schemes necessary or desirable to protect patients' welfare in clinical trials of medical and surgical procedures? Is the present system of Institutional Review Boards, under the auspices of the Department of Health and Human Services, adequate to safeguard patients in cases of experimental surgical procedures? When does an experimental surgical or medical procedure, such as neural grafting, become standard therapy?

Related to these questions is the issue of the type and function of the material to be grafted. There are many possible sources of material for neural grafts. One is cultured and genetically manipulated cells. Because of the nature and possible functions of these materials (e.g., as drug delivery systems), regulation would probably fall under the jurisdiction of the Food and Drug Administration (FDA). Another possible source of material is unmanipulated tissue from other organs or fetal tissue. These substances may not be regulated by the FDA, since they do not fall under its jurisdiction and their use as neural grafting material may be considered the practice of medicine. Thus, depending on what material is used, there may or may not be direct Federal oversight of neural grafting technologies.

An issue of particular concern is the procurement and use of human fetal tissue for neural grafting procedures. Because of its unique characteristics, human fetal tissue is a widely used source of neural grafting material. Although many scientists believe that it may ultimately be superseded in some proposed applications by other sources of material (e.g., cell lines, genetically manipulated cells), they also believe that this is not likely to occur in the near future. Most scientists feel that, at present, continued study of fetal tissue is needed to discern the mechanisms that underlie the ability of the nervous system to heal and to evaluate what role fetal tissue grafts can play in that process.

Many of the same concerns that have been voiced about organ transplantation in general pertain to the use of human fetal tissue for neural grafting. These include:

Table 2-3-Federal Funding of Neural Grafting Research (in millions of dollars)

Agency	1987	1988	1989	1990'
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.

- buying and selling of organs for transplantation, and
- legal authority for consent to donate organs or tissues.

Use of fetal tissue raises some additional sensitive and controversial questions. Are the issues surrounding abortion relevant to the use of fetal remains for research and medical therapy? Should the moratorium on Federal funding of abortion have any bearing on Federal funding of research employing fetal tissue for transplantation? Should cadaveric fetal tissue (i.e., tissue from dead fetuses) be discarded when this material could provide a therapy for neurological disorders? Are there potential abuses in the acquisition and use of fetal tissue for which safeguards should be developed?

In 1988, the Assistant Secretary for Health placed a moratorium on all federally funded therapeutic transplantation research that used human fetal tissue from induced abortions. This moratorium was extended indefinitely in 1989. As a result of this action, no Federal funds can be used to support the transplantation of human fetal tissue obtained from an induced abortion into a patient.

Of continuing interest to Congress is the level of funding for both basic and clinical research and the development of new technologies (table 2-3). It has been suggested that neural grafting has the potential to treat millions of Americans with certain neurological disorders. However, questions about the precise benefits of this technology, the particular disorders that may be affected, and the time frame for applying these technologies as human therapies remain to be answered.

THE OTA STUDY

This report to Congress examines the development of neural grafting into the central nervous system, i.e., the procedures and materials involved in the transplantation of tissue to the brain and spinal cord for the treatment of neurological disorders. Although other advances in neuroscience have great potential in treating neurological disorders, those advances are beyond the scope of this report.

In the six chapters that follow, OTA examines the impact neural grafting is likely to have on the treatment of neurological disorders and the legal, regulatory, and ethical issues these new procedures raise. In addition, OTA examines the role of Congress and the Federal Government in addressing these public policy issues.

Chapters 3,4, and 5 describe basic principles of neuroscience, general principles and concepts of neural grafting, and the research that has been conducted thus far on neural grafting as a treatment for neurological disorders. Chapter 6 identities some of the disorders that may be amenable to treatment by neural grafting procedures, and chapters 7 and 8 discuss the legal, regulatory, and ethical issues associated with neural grafting.

CHAPTER 2 REFERENCES

1. Apuzzo, M. L.J., Neal, J.H., Waters, C.H., et al., "Utilization of Unilateral and Bilateral Stereotactically Placed Adrenomedullary-Striatal Autografts in Parkinsonian Humans: Rationale, Techniques, and Observations," *Neurosurgery* 26:746-757, 1990.
2. Backlund, E. O., Granberg, P. O., Hamberger, B., et al., "Transplantation of Adrenal Medullary Tissue to Striatum in Parkinsonism, First Clinical Trials," *Journal of Neurosurgery* 62:169-173, *1985.*

3. Björklund, A., and Stenevi, U. (eds.), "Intracerebral Neural Grafting: A Historical Perspective," ***Neural Grafting in the Mammalian CNS*** (Amsterdam: Elsevier Science Publishers, 1985).
4. Freed, C.R., Breeze, R.E., Rosenberg, N.L., et al., "Transplantation of Human Fetal Dopamine Cells for Parkinson's Disease, Results at 1 Year," ***Archives of Neurology*** 47:505-512, ***1990.***
5. Goetz, ***C.G.,*** Tanner, C.M., Pem, M.D., et al., "Adrenal Medullary Transplant to the Striatum of Patients With Advanced Parkinson's Disease: l-Year Motor and Psychomotor Data," ***Neurology 4Q273-276, 1990.***
6. Lieberman, A., Ransohoff, J., Berczeller, P., et al., "Adrenal Medullary Transplants as a Treatment for Advanced Parkinson's Disease," ***Acta Neurological Scandinavia*** 126:189-196, ***1989.***
7. Lindvall, O., "Transplantation Into the Human Brain: Present Status and Future Possibilities," ***Journal of Neurology, Neurosurgery, and Psychiatry*** special supp.:39-54, 1989.
8. Lindvall, O., Brundin, P., Widner, H., et al., "Grafts of Fetal Dopamine Neurons Survive and Improve Motor Function in Parkinson's Disease," *Science* 247:574-577, 1990.
9. Lindvall, O., Rehncrona, S., Gustavii, B., et al., "Fetal Dopamine-Rich Mesencephalic Grafts in Parkinson's Disease" [letter], *Lancet* 2:1483-1484, 1988.
10. Madrazo, I., Drucker-Colin, R., Diaz, V., et al., "open Microsurgical Autograft of Adrenal Medulla to the Right Caudate Nucleus in Two Patients With Intractable Parkinson's Disease," New ***England Journal of Medicine*** 316:831-834, ***1987.***
11. Madrazo, I., Leon, V., Torres, C., et al., "Transplantation of Fetal Substantial Nigra and Adrenal Medulla to the Caudate Nucleus in Two Patients With Parkinson's Disease" [letter], New ***England Journal of Medicine*** 318:51, ***1988.***
12. Sladek, J.R., Jr., and Gash, D.M., "Nerve-Cell Grafting in Parkinson's Disease,' ***Journal of Neurosurgery*** 68:337-351, ***1988.***

Chapter 3

Neuroscience Primer

CONTENTS

Box

Figures

This chapter describes the major anatomical components of the nervous system, some of the basic processes underlying neural growth, development, and communication, and the response of the nervous system to injury. A grasp of these basic concepts of neuroscience is helpful to understanding neural grafting. Additional information is available from a number of sources (1,3,4).

ORGANIZATION OF THE NERVOUS SYSTEM

The nervous system can be divided into two parts: the central nervous system (CNS) and the peripheral nervous system (PNS) (figure 3-l). The CNS is made up of the brain and spinal cord. The PNS is composed of all the nerves, nerve cells, and specialized sensory receptors that lie outside the CNS. Sensory information about the outside world is brought into the CNS via the nerves and sensory receptors in the PNS; activation and regulation of activity in muscles, glands, and organs are conveyed by the motor, or outflow, component of the PNS. Most information processing, decisionmaking, and coordination of activities is under the control of the CNS.

Cellular Components

There are two major classes of cells in the nervous system: neurons, or nerve cells, and glia, or glial cells.

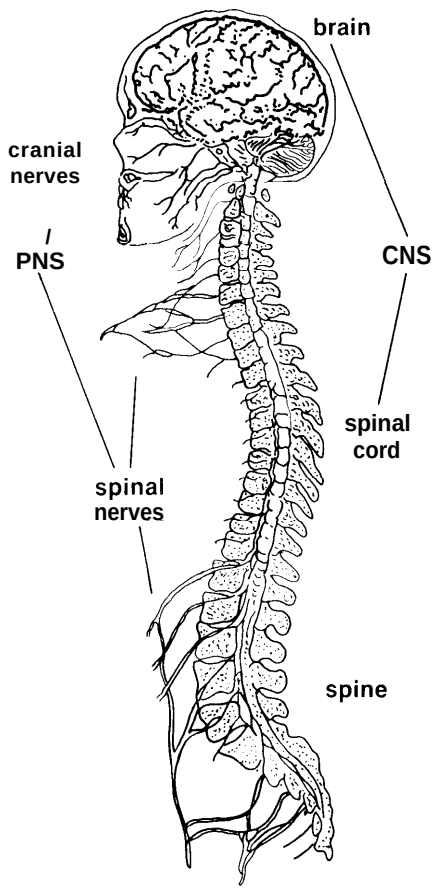
Neurons

All information processing in the nervous system is done by networks of neurons that communicate with each other. Neurons consist of a cell body with long extensions, much like branches of a tree, called dendrites. Also projecting out of the cell body is a single fiber called the axon, which can extend for great distances (figure 3-2). All nerves in the body are actually the bundled axons of many neurons conveying information to and from the CNS. The end of the axon is also branched.

Glial Cells

Glial cells support neurons by carrying on important chemical and physiological reactions and producing a variety of substances that are needed for normal neurological functioning. There are a number of different types of glial cells in the PNS and CNS--astrocytes, microglia, Schwann cells, and oligodendrocytes (figure 3-3). Schwann cells (in the PNS) and oligodendrocytes (in the CNS) produce myelin, a fatty insulating material that forms a sheath around axons and speeds the conduction of electrical impulses. Both of these types of cells play a crucial role in nerve cell regeneration: Schwann cells support regrowth of peripheral nerves, while recent evidence suggests that oligodendrocytes inhibit the regrowth of damaged axons in the CNS. The other glial cells help regulate the biochemical environment within the nervous system, provide

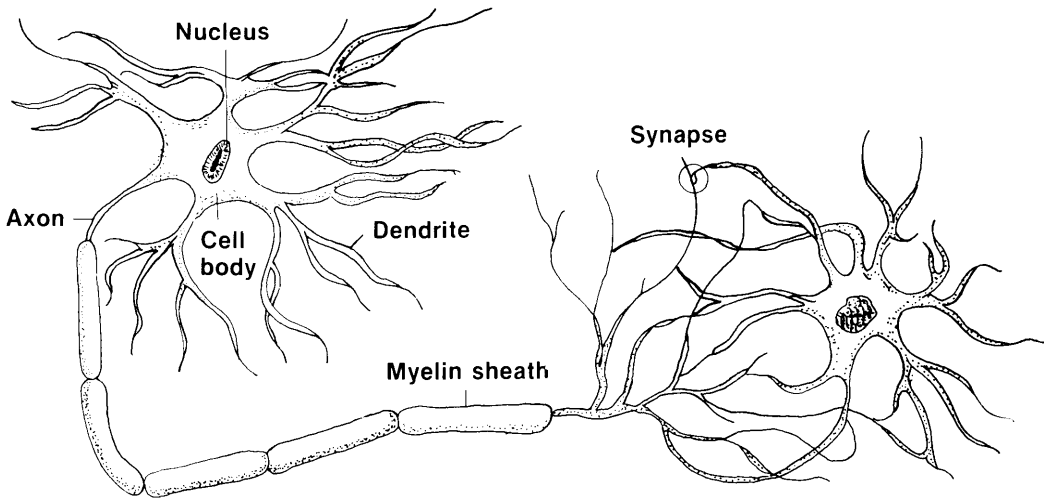
Figure 3-I-Components of the Nervous System



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).

Figure 3-2—The Neuron



Two neurons in synaptic contact.
SOURCE: R. Restak, *The* Brain (New York, NY: Bantam Books, 1984).

structural support for the neurons, and supply certain substances that are essential for the nervous system to work properly.

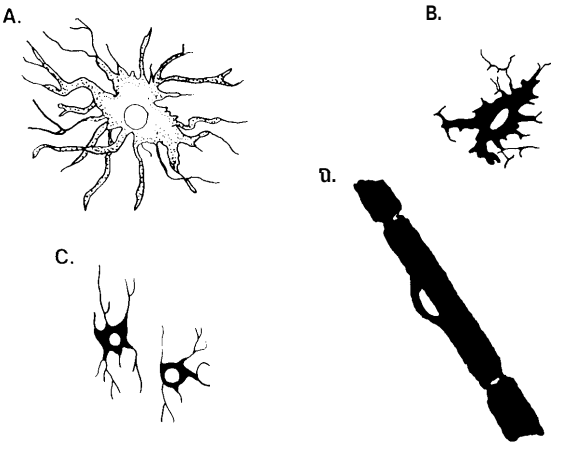
Central Nervous System

The Brain

One useful way of visualizing the brain is as a mushroom. The cap of the mushroom is the cerebral cortex, and the stem of the mushroom is the rest of the brain, which is made up of hundreds of nuclei (figure 3-4). A nucleus is a group of cells that share the same anatomical region and, to varying degrees, the same function. Information is conveyed throughout the brain and spinal cord along the axons extending from nuclei. For any given function, such as vision, a number of nuclei and areas of the cerebral cortex must act together in a coordinated and synchronized reamer so that information can be accurately analyzed.

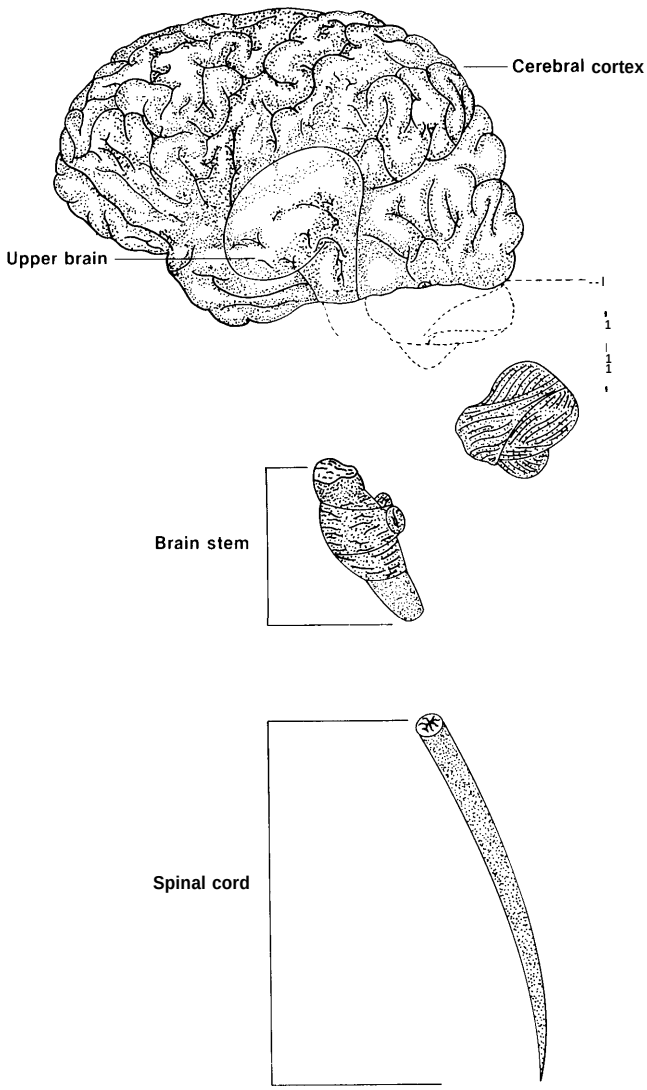
The anatomy of the brain and the intricacy of the connections among nuclei are exceedingly complex. Information from every area of the nervous system about many different functions is constantly being combined, compared, contrasted, and coordinated. The brain determines the relevance of each bit of information, fits it in with all other information available, and decides what actions should or should not be taken to regulate bodily functions and to permit successful interaction with the external environment. The result is everything that makes up life and existence as human beings perceive it—from the maintenance of heart rate to falling in love; from finding food to contemplating the nature of the universe. All of these arise from the biological events that make up the activity of the human brain.

Figure 3-3-Glial Cells



Types of glial cells include: A) astrocytes, B) microglia, C) oliogdendrocytes, D) Schwann cells (surrounding an axon).
SOURCE: Adapted from J.A. Kiernan, *Introduction to Human Neuroscience* (Philadelphia, PA: J.B. Lippincott, 1987).

Figure 3-4—The Central Nervous System



The brain (cerebral cortex, upper brain, brain stem) and the spinal cord.

SOURCE: Adapted from R. Restak, *The Mind* (New York, NY: Bantam Books, 1988).

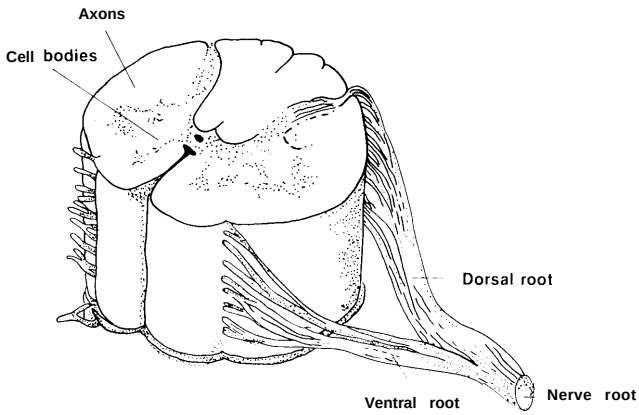
The bottom of the stem of the mushroom is the brain stem, which regulates essential bodily functions. Heart rate, blood pressure, and respiratory activity are all controlled by nuclei in the brain stem. Higher up the stem of the mushroom is the upper brain, containing other structures, such as the hypothalamus and the thalamus. Each of these is a collection of nuclei with specific functions. The thalamic nuclei are primarily involved in analyzing and relaying sensory and motor information. Some hypothalamic nuclei control behaviors such as eating, drinking, and sexual activity; others help with regulating the activity of the endocrine system. Still further up the stem of the mushroom are the basal ganglia, nuclei that help mediate movement. Also in this area are some of the nuclei of the limbic system, which is involved in emotional behaviors, and the hippocampus, a limbic nucleus that is also one of the nuclei crucial to learning and memory. These are only a sampling of the many nuclei located in the stem of the mushroom.

Overlying the stem is the cerebral cortex, the evolutionary newest part of the brain and its most advanced decisionmaking portion. The cerebral cortex consists of layers of neurons and their axons, which communicate with each other and with other regions of the brain. Roughly divided into four lobes on each side, the cerebral cortex receives sensory information and analyzes, deciphers, and puts it into context based on previous experience. Combining new input with experience, the cerebral cortex decides what actions should be taken and institutes those actions by activating the proper motor and endocrine networks. It is at the level of the cerebral cortex that differences among species become most notable. Warm-blooded animals have a more highly developed cerebral cortex than cold-blooded animals. The cortex is most fully developed in humans, with highly developed frontal lobes and specialized areas to subserve the development and use of language. The frontal lobes are thought to be the seat of higher order thinking, which gives humans the ability to engage in abstract thought and to develop philosophical concepts of morality, self, and place in the universe.

The Spinal Cord

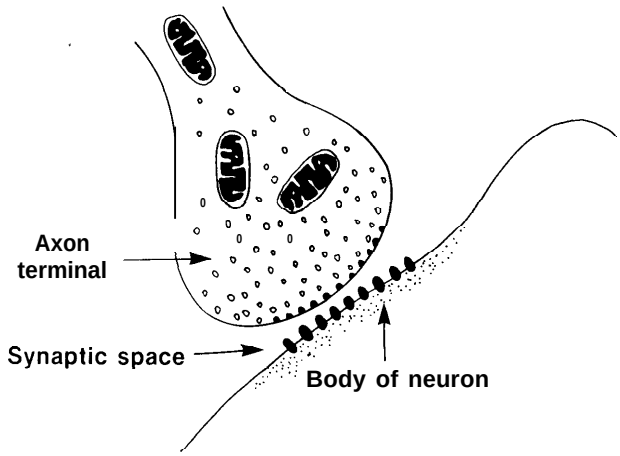
Extending downward ii-em the base of the stem of the mushroom is the spinal cord. The spinal cord is composed of a central core of cells surrounded by pathways of axons. Leaving and entering the spinal cord are the nerves that bring sensory information into the CNS and convey motor and other activating information out into the periphery (figure 3-5). The spinal cord is divided into 31 segments that are demarcated by collections of nerves called nerve roots. The spinal segments and their nerve roots serve the organs of the body and corresponding regions of muscles and skin in the limbs and along

Figure 3-5-The Spinal Cord



The spinal cord is made up of a central core of cell bodies, surrounded by axons. The nerve roots convey information into (dorsal root) and out of (ventral root) the spinal cord.
SOURCE: Adapted from A.C. Guyton, *Basic Neuroscience: Anatomy and Physiology* (Philadelphia, PA: W.B. Saunders, 1987).

Figure 3-6-The Synapse



The anatomy of a synapse.
SOURCE: Adapted from A.C. Guyton, Basic *Neuroscience; Anatomy and Physiology* (Philadelphia, PA: W.B. Saunders, 1987).

the trunk of the body. There is communication among segments and between the segments and the brain. Some basic functions, such as motor reflexes, are organized and directed from within the spinal cord. The spinal cord also contains a column of specialized cells that help control the autonomic functions of the body (see later discussion of the autonomic nervous system). All the areas within the spinal cord that control bodily activities are modulated by the brain.

Peripheral Nervous System

The PNS is made up of all the sensory nerves coming into, and motor nerves leaving, the spinal cord via the nerve roots. These include the nerves of the autonomic nervous system. In addition, the PNS includes some sensory and motor nerves that enter and exit from the brain stem.

Autonomic Nervous System

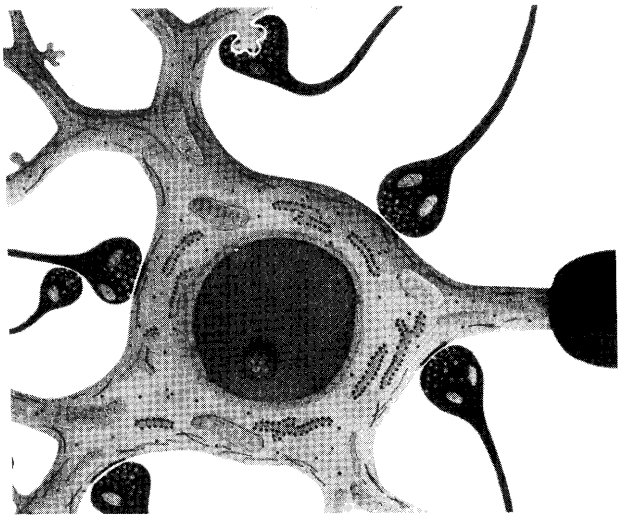
The autonomic nervous system is made up of the portions of the CNS and PNS that are concerned with the control of visceral functions. These functions include heart rate, blood pressure, digestion, and reflexive sexual activities. Within the CNS, the neurons of the autonomic nervous system are in the brain stem and the spinal cord; in the PNS, the neurons occur in specialized groups, known as ganglia. The ganglia are found in columns on either side of the spinal cord or in close association with the organs they serve (2).

NEURAL COMMUNICATION

Information in the nervous system is conveyed by chains of neurons. It usually travels through a neuron in one direction-horn the dendrites, through the cell body, and along the axon. The end of the axon of one neuron interacts with the next neuron in the chain. Information in the nervous system is coded as an electrical-chemical message that is sent from one neuron to the next. The point where the axon of one neuron connects with a dendrite or cell body of another neuron is called a synapse (figure 3-6). The two neurons never actually touch each other; instead, there is a small space between them called the synaptic space. Because the end of the axon and the dendrites of a neuron are branched, the axon of any one neuron can form synapses with thousands of other neurons and thus can send messages to and receive messages from thousands of other neurons (figure 3-7).

When a neuron generates a nerve impulse, or " fires,' an electrical message is sent along the axon toward the synapse. When the electrical message gets to the synapse, it causes the release of a chemical, called a neurotransmitter, from the axon into the synaptic space. The neurotransmitter acts as a messenger, moving across the synaptic space and binding to the membrane of the next neuron. The

Figure 3-7-A Neuron and Its Synapses



The terminals of many axons can make synapses with the dendrites or cell body of one neuron.
SOURCE: R. Restak, *The Mind(New* York, NY: Bantam Books, 1988).

binding of the neurotransmitter to the membrane then initiates, facilitates, or hinders an electrical message in that neuron. The time it takes for this process to occur, from the initiation of a message in one neuron to the release and binding of the neurotransmitter and the initiation of a message in the next neuron, is measured in thousandths of a second.

There are many different kinds of neurotransmitters. Whether and when a neuron will release a neurotransmitter is determined by the combined action of all its synapses, with their excitatory and inhibitory neurotransmitters, at any one time.

GROWTH AND DEVELOPMENT

In humans, the first signs of the developing nervous system appear in the third week of embryonic development (figure 3-8). The cells destined to form the brain and other parts of the nervous system then go through a period of proliferation, during which time they multiply. At the same time, the cells migrate to their proper positions in the developing brain. Following this period of proliferation and migration, the cells stop dividing and differentiate into the various types of neurons and glial cells that make up the nervous system. At this time, the number of neurons becomes fixed; for the rest of the person's life, no new neurons are thought to be produced. Most glial cells, on the other hand, maintain the capacity to replicate.

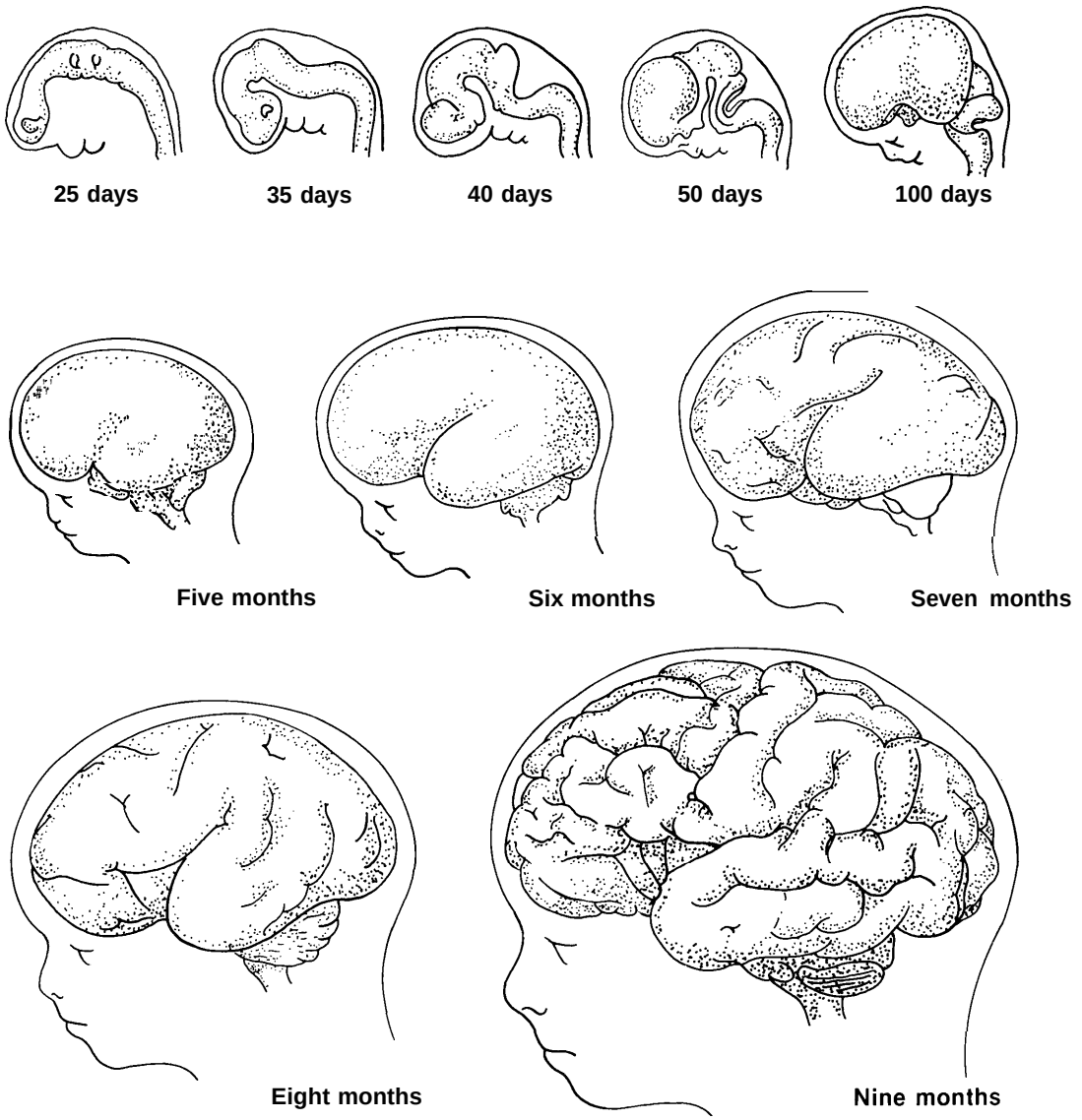
The mechanisms by which neurons migrate to the proper location and axons find their way to the proper target site and form synapses are not fully understood. The process of axonal growth is thought to include an initial, genetically predetermined map of axonal pathways. The growing axons are guided to their final destinations by chemicals called ***neurotrophic*** (nourishing) and ***neurotropic*** (guiding) factors (see box 3-A). Neurotrophic factors promote axonal growth and neuronal survival, and neurotropic factors provide a surface, or substrate, for the axon to grow along to its target. These factors act as signposts to guide the growing axons and provide chemical addresses for them to reach. Which chemical address, or target site, an axon will search for is believed to be genetically programmed within each neuron.

Once the cells are in position, differentiation occurs: the dendrites and axons of the neurons begin to grow and establish the proper synaptic contacts. In the case of some axons this can mean elongation over considerable distances, while in other cases all of the synaptic contacts of a neuron can occur within a few millimeters of the cell. The ultimate wiring of the brain, made up of billions of synapses and connections, is extremely complex. Although in humans most axons reach their target sites before birth, the final configuration of the synaptic contacts is not completed until well after birth.

There are many more neurons in the developing nervous system than there are in the mature nervous system. It has been estimated that about half of the cells initially generated die. Death is caused by competition between the growing neurons for available synaptic sites and a matching of the number of neurons to the needs of the developing nervous system. This process results in the survival of those neurons that have grown properly. There are about 200 billion neurons in the mature human brain.

Although the general pattern of synapses established once an axon reaches its target is both genetically predetermined and under the control of chemical factors, the final, precise synaptic pattern of an axon can also be shaped by other factors. These include the amount and kind of activity that occur in the pathway in response to outside stimulation. This flexibility in synapse formation in response to

Figure 3-8-The Development of the Human Brain



The human brain shown in its developmental sequence, starting at 25 days and progressing through birth.
SOURCE: R. Restak, *The Brain (New York, NY:* Bantarn Books, 1984).

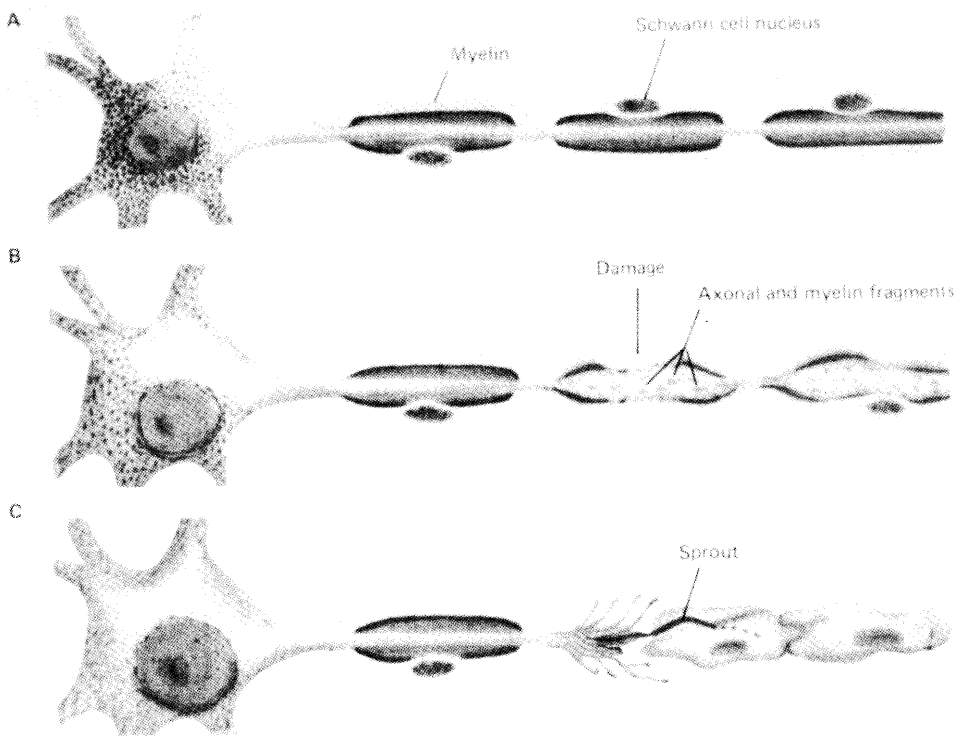
environmental stimuli is maintained throughout life and may play a role in learning and memory.

RESPONSE TO INJURY

The CNS and PNS respond differently to injury. When a peripheral nerve is damaged, the axons of the damaged neurons can regrow; but when damage occurs in the CNS, axonal regrowth is limited. Research on animals has shown that this difference is due not to differences in peripheral and central neurons (in fact, many peripheral nerves arise from cell bodies in the CNS), but to variations in the environment surrounding the axons in the CNS and PNS.

The key element in axon regrowth in the PNS is the presence of Schwann cells and the growth factors they secrete. Schwann cells normally surround each axon, supplying its fatty myelin sheath. When a peripheral nerve is damaged and dies, the bundled axons die and leave behind the Schwann cells that

Figure 3-9—The Response of a Neuron in the Peripheral Nervous System to Injury



A) The normal neuron and part of the axon; B) the axon is injured and the section away from the cell body dies; C) the end of the injured axon begins to grow into the remaining Schwann cells.

SOURCE: Reprinted by permission from "Reactions of Neurons to Injury," *Principles of Neuroscience*, 2d ed., E.R. Kandel and J.H. Schwartz (eds.) (New York, NY: Elsevier Science Publishers, 1985), p. 191.

had surrounded them. When the nerve regenerates, its axons grow within the column of remaining Schwann cells to the sense organ or muscle to which they were originally connected (figure 3-9). Schwann cells release neurotrophic and neurotropic factors that promote elongation and provide a pathway for the regenerating axons.

When the CNS is damaged, there is some regrowth that is limited to a small area around the wound. A process called synaptic sprouting occurs, whereby fibers from nearby, undamaged axons form new branches and make new synapses to replace some of the lost ones. However, unlike Schwann cells, the myelin-producing oligodendrocytes of the CNS do not promote regrowth of the damaged axons. In fact, recent studies have shown that oligodendrocytes actively block regeneration. Furthermore, following an injury, another type of glial cell, the astrocyte, forms a scar at the site of the wound and blocks regrowth. Why there are mechanisms in the CNS that actively block healing is not known. It is thought that once all the wiring of the brain is established, the growth-promoting mechanisms that were present during development are no longer needed, and these inhibitory mechanisms take over to prevent any further growth that could short-circuit the completed brain. By learning more about the differences in the environments that allow regeneration in the PNS and block it in the CNS, scientists may ultimately be able to control the processes involved and enable CNS damage to be repaired.

Box 3-A—Neurotrophic and Neurotropic Factors

During the last few years, neuroscientist have learned that the development, maintenance of function, and response to injury of neurons are influenced by chemicals called neurotrophic and neurotropic factors. These substances are produced by some neurons and glial cells and can affect the nervous system in two ways. Some are secreted by a cell into the spaces between cells in the nervous system; they can then be absorbed by neurons to initiate an intracellular process, such as growth of an axon. Other factors can act externally to guide the growing axon along a particular path to its region of synaptic contact. A chemical that stimulates growth or development is called a neurotrophic agent, while one that helps guide a growing neuron is called a neurotropic agent.

Only a few substances have been positively identified as neurotrophic or neurotropic factors. Of them, nerve growth factor (NGF) has been the most extensively studied NGF is a protein that is known to promote growth in specific areas of the peripheral nervous system and to play a role in the development of vertebrate sensory systems. What role NGF plays in the central nervous system (CNS) is not well understood. It seems that NGF has a selective effect on certain populations of cells in the brain that use acetylcholine as their neurotransmitter. NGF promotes growth and development of these cells in the fetal brain and, when extra amounts are administered in experimental conditions, can promote growth and prevent cell death following an injury in the adult brain. It has also been shown that NGF can facilitate the incorporation of some neural grafts. The observation that NGF seems to exert this effect only on certain cells in the brain suggests that there maybe different neurotrophic factors for different groups of brain cells. Thus far, other substances that have been identified as having possible neurotrophic or neurotropic effects include ciliary neurotrophic factor, brain-derived neurotrophic factor, neurotrophin-3, glia-derived nexin, fibroblast growth factors, insulin and insulin-like growth factors, epidermal growth factor, S100 protein, and laminin. What role these play in CNS regeneration is unclear at this point.

Neurotrophic and neurotropic factors are known to be present in the developing CNS and to play an important role in the formation of neuronal circuitry. Much less is known about their role in the mature CNS. When an injury occurs in the brain, there is an increase in neurotrophic activity at the site of the wound. This activity seems to promote the limited amount of healing and cell survival that is seen following some injuries. It is also thought that some of these factors are important for maintaining normal function and structural integrity in the adult brain. It has been observed that some neurons die in the absence of neurotrophic factors. It is possible that some of the factors associated with growth and development are either no longer present or are somehow inactivated within the adult CNS. Introducing missing factors or stimulating deactivated ones in the CNS by implanting tissues that produce neurotrophic and neurotropic factors may reestablish the environment needed for growth.

SOURCE: Office of Technology Assessment, 1990.

CHAPTER 3 REFERENCES

1. Adelman, G. (cd.), ***Encyclopedia of Neuroscience,*** vols. I and II (Cambridge, MA: Birkhauser Boston, 1987).
2. Coquelin, A., professor, Texas Tech University Health Sciences Center, Lubbock, TX, personal communication, Apr. 25, 1990.
3. Ferry, G., ***"Getting Wired Up," New Scientist,*** Mar. ***4, 1989, pp.*** 1-4.
4. Kandel, E. R., and Schwartz, J. H., ***Principles of Neuroscience (New*** York, NY: Elsevier Science Publishing, 1985).

Chapter 4

General Features of Neural Grafting

CONTENTS

Box

Figures

Chapter 4
General Features of Neural Grafting

Neural grafting has been hailed as.. one of the most promising approaches to have come from experimental neurobiology as a potential therapy for a variety of disorders involving damage to the central nervous system" (41). It has also triggered a debate among physicians and medical researchers about when a medical procedure should be advanced from a research tool in animals to a treatment in humans. The use of neural grafting to treat patients suffering from Parkinson's disease has led to both dramatic claims of success and more cautious statements of results. A proposal for neural grafting research prompted the Executive Branch of the U.S. Government to forbid Federal support of transplantation procedures employing human fetal tissue from induced abortions. All of this controversy begs a clear answer to the question, What is neural grafting?

The term neural grafting, as used in this report, refers to the transplantation of tissue into the brain or spinal cord. 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 as a drug delivery system, providing chemical substances to the central nervous system (CNS) of the graft recipient, or that it may be used to promote recovery of the host's injured brain or spinal cord. In addition, a neural graft may be derived from various types of tissues, including fetal CNS tissue, peripheral nervous tissue, cells from other organs, or cell lines sustained in the laboratory. Thus, neural grafting is a generic term that embraces many different treatment goals and materials.

This chapter focuses on the salient features of neural grafting and issues related to its potential use to treat the diseased or injured CNS. Unless otherwise specified, data discussed in this chapter are derived from animal studies. Despite the publicity that has recently attended neural grafting attempts in patients suffering from Parkinson's disease, the clinical usefulness of this approach is not certain. In the case of Parkinson's disease, optimal methods for using neural grafting are still under investigation. In general, the development of innovative techniques, including the use of genetically engineered cells, relies on extensive basic research. Furthermore, many questions concerning the functional effects of neural grafts, as well as the problems presented by their use, are unanswered. Neural grafting may, however, lead to promising treatments for neurological disorders, which often resist therapeutic intervention. Issues addressed in this chapter include:

- What therapeutic strategies are possible through neural grafting?
- What tissues and cells can be used for neural grafting?
- What factors influence the successful survival and function of neural grafts?
- What potential risks are presented by neural grafting?

THERAPEUTIC STRATEGIES

How a neural graft improves CNS function within the recipient is not completely understood. A neural graft may simply provide a depleted chemical substance to the brain or it may permit other therapeutic strategies as well (5,33,61). In fact, neural grafts display a wide range of capabilities. These diverse functions lead researchers to predict that neural grafts will 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 (37). In this section, potential therapeutic strategies are discussed. Neural grafts may:

- provide a source of depleted chemical substances,
- stimulate neuron growth and promote survival of neurons, and
- replace lost structures in the brain and spinal cord.

Source of Depleted Chemical Substances

Neural grafts may supply chemical substances that have been depleted in the CNS by injury or disease.

The loss of neurons within the brain or spinal cord can severely impair memory, the control of muscle

movement, and other functions performed by the nervous system. Impaired CNS function may result from a depletion of the chemical substances normally produced by the degenerating or missing neurons. Conventional drug therapy can be employed to replenish the supply of a depleted chemical in the brain. However, several factors can make drug therapy problematic. For example, some administered substances are prevented from entering the CNS by the blood-brain barrier, which excludes many cells and molecules in the blood from the CNS (11,74).

The current limited success in treating CNS disorders via drug therapy may be circumvented by the use of neural grafts. Cells that synthesize and secrete a neurotransmitter (a messenger molecule used by neurons in communication) or other chemical substance may be implanted in the CNS; it is thought such implants may provide a continuous supply of chemicals directly to the depleted region of the brain or spinal cord.

It is postulated that neural grafts supply chemical substances in one of two ways (5). If the graft is composed of cells that do not form connections (synapses) with the host neurons, it may simply synthesize and release a steady and diffuse supply of chemical substances to adjacent regions of the CNS, acting as a localized pump, or drug delivery system. If synapses are forged between graft and host neurons, integrating the graft into a neuron network, the release of chemicals may be more carefully regulated by the host neurons. In this case, rather than indiscriminately spewing chemicals near the graft site, the grafted neurons may discharge the chemicals in a more controlled fashion at synapses abutting host neurons.

Promotion of Neuron Growth and Survival

Neural grafts may introduce new substances or cells that promote and guide host neuron regrowth, prevent host neuron death, or both.

The complex network of nerve fibers within the mature brain and spinal cord attests to the tremendous neuron outgrowth and synapse formation that occurs during development. Developing neurons may form long fibers and establish contact with as many as 1,000 other neurons. While mature neurons do enjoy some regenerative potential, the ability to extend long fibers appears to be masked or inhibited in the mature CNS. Anything more than modest injury of mature neurons often proves fatal to them. In general, glial cells inhibit neuron regrowth following injury (20,76,84). Injured neurons may be permanently disconnected from their targets within the CNS, they may degenerate and die, or both. Furthermore, neurons that die are not replaced, since they lack the ability to reproduce themselves.

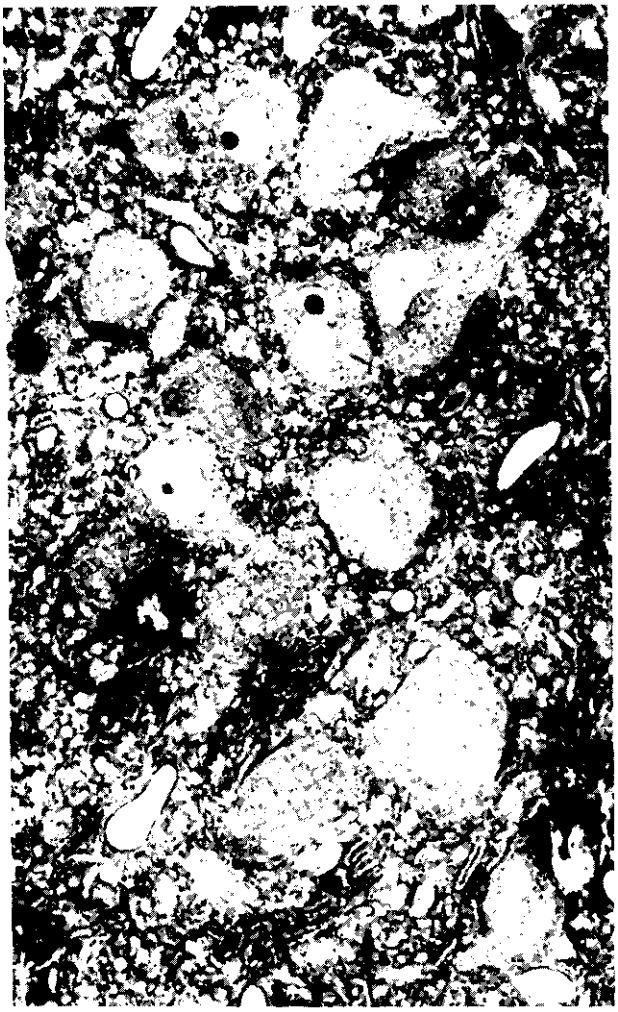


Photo credit: Laura Lee Hall

Injured nerve ceils.

Experimental evidence suggests that the degenerative consequences of neuronal injury in the mature brain and spinal cord can be prevented, or at least ameliorated, if a growth-promoting environment, such as that found in the developing brain, is provided. In other words, recovery of injured neurons within the mature CNS may be enhanced by cells or chemical factors that promote neuron regrowth, neuron survival, or both (figure 4-l). It is

speculated that neural grafts may be used in this capacity, stimulating neuron functions such as nerve fiber and synapse growth or preventing neuron death (21).

A neural graft may lead to the recovery of injured neurons in several ways. Grafted cells may synthesize and release growth-promoting factors near the injured neurons, preventing neuron death and promoting neuron regrowth. Neural grafts may also be used to form a bridge between a group of neurons and their target within the CNS, bypassing the unfavorable environment of the mature CNS. These graft materials may enhance neuron outgrowth and provide a terrain over which it is directed. Neural grafts may also serve to reduce scar formation within the injured CNS or neutralize the growth-inhibiting effect of the mature CNS (85,90). Other graft activities, such as the removal of toxic substances, may also be possible (34).

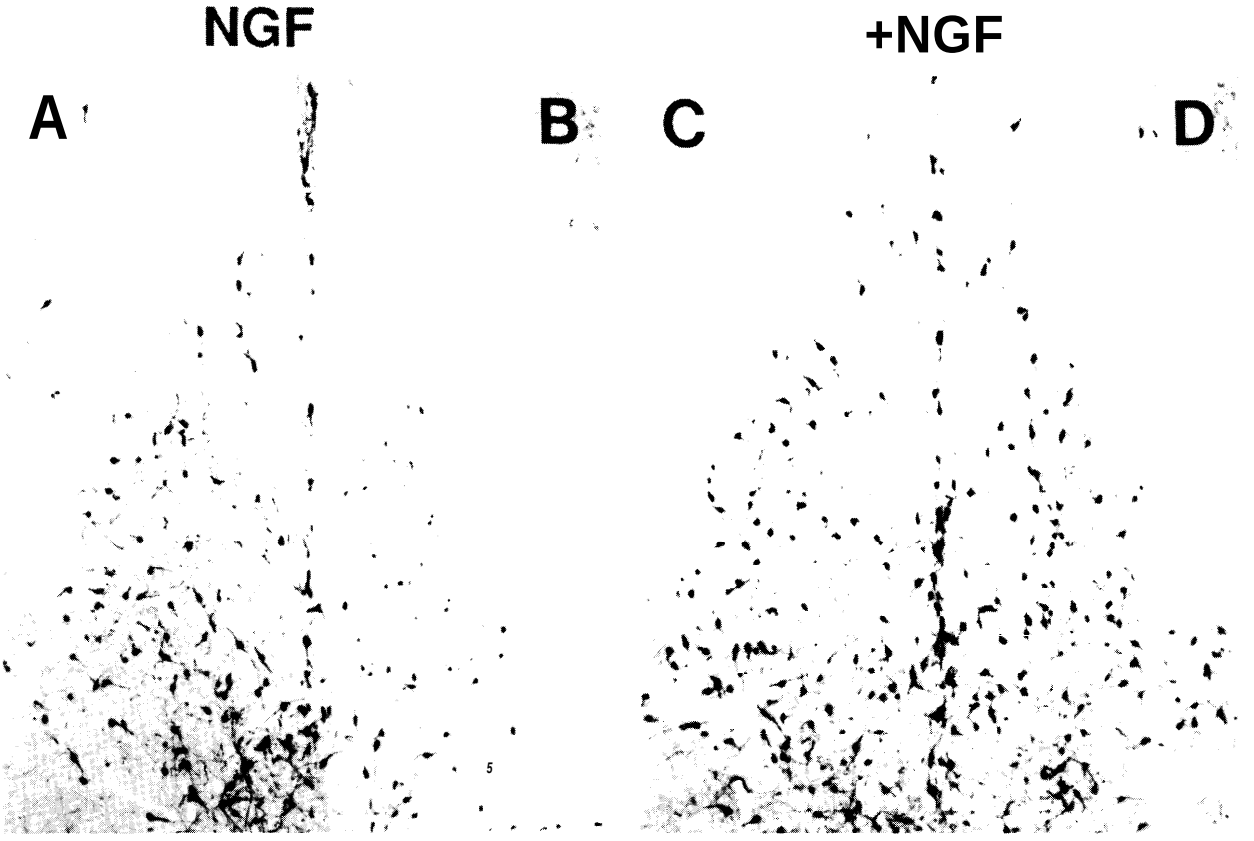
A neural graft used to promote regrowth and recovery of the host's own brain or spinal cord tissue may be required only temporarily, thus making long-term graft survival, which may be difficult to achieve, unnecessary.

Replacement of Lost Structures in the Brain and Spinal Cord

A neural graft may be used to replace nerve cells in the CNS that were lost to injury or disease.

Normal aging, injury, disease, or lack of oxygen can precipitate the death of nerve cells within the CNS. Since neurons generally are not replaced within the brain and spinal cord of adult mammals, their death leads to a permanent decrease in the number of neurons in the brain and creates a missing link in neuronal networks. This loss of neurons and disruption of neuronal networks may result in the

Figure 4-1—injured Nerve Cells With and Without Growth Factor Treatment



Photograph of brain section; nerve cells are darkly stained. Injured nerve cells on side D received nerve growth factor (NGF) and therefore survived injury. Injured nerve cells on side B, in the absence of NGF, degenerated.

SOURCE: S. Varon, "Neuronal Growth Factors," *Neural Regeneration and Transplantation, Frontiers of Clinical Neuroscience*, vol. 6, F.J. Seil (cd.) (New York, NY: Alan R. Lies, 1989).

permanent impairment of a CNS function. Another therapeutic use for neural grafts may be the replacement of degenerated neurons.

Replacement of neurons and the reconstitution of neuronal networks within the adult CNS seem a remote possibility, considering the intricate interactions that occur between neurons within the nervous system. A single neuron may receive thousands of contacts from different regions of the brain. Despite this complexity, grafted fetal neurons demonstrate a remarkable ability to integrate into the mature CNS of a recipient. Grafts of fetal neurons can send nerve fibers into the host CNS and form synapses with host neurons, often in an appropriate and recognizable pattern. Grafted fetal neurons may also receive synaptic input from the host.

Complete and literal replacement of a group of neurons is probably impossible. For example, when neurons that normally project long distances within the CNS degenerate, replacement neural grafts are generally implanted near the target in the host CNS rather than in the original site of nerve cell degeneration. In this situation, juxtaposition of graft and host CNS target can be important for their interaction (41). Although the graft will probably not receive the full range of normal inputs from other CNS regions, it may be sufficiently integrated into host neuronal networks to restore a useful degree of function.

MATERIALS FOR NEURAL GRAFTING

Several types of biological materials may be used for neural grafting. The first and perhaps most important determinant of a particular material's usefulness is its ability to improve CNS function with minimal risk to the recipient. The availability and source of the graft material will also significantly influence its application in humans. Currently, several sources of tissue for neural grafting in humans seem possible, including human fetuses, cells maintained in cultures, or tissue from graft recipients themselves. Nonhuman species also represent a potential source of neural grafting material, although they may present serious functional and immunological problems (30,52,67,70). Each of these sources presents unique technical issues and questions about availability. In addition, the type and source of material used are central to the ethical and legal questions surrounding neural grafting (see chs. 7 and 8). In this section, general features of the following potential neural grafting materials are discussed:

- tissue from the fetal central nervous system;
- tissue from the peripheral nervous system;
- peripheral autonomic neurons;
- tissue from outside the nervous system; and
- isolated, cultured, or genetically engineered cells.

Fetal Central Nervous System Tissue

Animal experiments have shown that fetal tissue,[1] unlike mature CNS tissue, readily develops and integrates within a host organism following grafting. A majority of neural grafting research in animals has made use of tissue from the fetal brain and spinal cord. In pioneering experiments, fetal CNS tissue often displayed a considerable capacity for survival within the CNS of the graft recipient (for reviews see 7,35,89). During the 1960s and 1970s, technological advances heralded a new era of neural grafting with fetal CNS tissue. Reliable methods for distinguishing surviving graft tissue within the host were developed, as were improved surgical methods for inserting the graft material. When fetal CNS tissue was transplanted into the CNS of young animals, it matured and interacted with the host brain for a substantial period of time. Subsequent studies revealed that fetal CNS tissue could also be successfully grafted into the mature brain. In fact, the grafted fetal CNS tissue was shown not only to survive and develop in the host, but to integrate into the host brain in a predictable manner.

Research further established that grafted fetal nervous tissue often produced functional improvements in animals with neurological deficits. For example, in several studies grafted neurons were seen to increase brain hormone production in animals that demonstrated a deficiency of hormones (38,40,58). The absence of the hormones impaired the brain's regulation of kidney or reproductive organ function. When the appropriate fetal nerve cells from the same species were introduced into the CNS of the impaired animals, they produced the deficient hormones and restored control of kidney or reproductive function. More recent studies, directed toward the analysis of biological rhythms, have

[1]In this chapter, when referring to humans, the fetal stage is considered the period from the end of the eighth week after fertilization until birth.

shown that fetal tissue from a region of the brain called the suprachiasmatic nucleus could be grafted and subsequently control daily cycles of behavior in hamsters (73).

Animal models for parkinsonism were employed to evaluate the effectiveness of grafted fetal nervous tissue (6,72). In rodents and nonhuman primates, chemicals were used to destroy the nerve cells that degenerate in humans suffering from Parkinson's disease. The chemically induced nerve cell death is manifested as abnormal rotatory movement in rodents and as abnormal body movements (similar to those seen in humans with Parkinson's disease) in nonhuman primates. When fetal neurons are grafted to replace the destroyed cells, the movement disorder is partially reversed. The success of this technique led to its adaptation for studies in humans suffering from Parkinson's disease. Ongoing clinical trials are examining the effectiveness of neural grafting with human fetal tissue for the treatment of persons with Parkinson's disease (see ch. 5).

Many different animal models of neurological deficits are being used to study the effects of grafted fetal CNS tissue. Results suggest that neural grafting with fetal neurons may one day be developed to treat several neurological disorders (see ch. 6).

The number of fetal nerve cells needed for neural grafting may be of critical importance, especially when the graft recipient's brain is relatively large, as is the adult human 's. While too many grafted fetal neurons pose the threat of excessive growth and overenlargement within the CNS of the host, too few cells (a more common occurrence) may fail to improve CNS function significantly. For example, the amelioration of symptoms of Parkinson's disease reported in a single patient following neural grafting required CNS tissue from four human fetuses (62). Invariably, some neurons are lost while collecting the fetal tissue. In addition, identification of the region of the fetal brain required for grafting is difficult; the desired fetal brain region transplanted into humans with Parkinson's disease is approximately 1 millimeter long (less than 4/100 of an inch) (figure 4-2). Human fetal CNS tissue for neural grafting is derived from first-trimester elective abortions, which are commonly performed via vacuum aspiration; this results in fragmented fetal tissue, the transplantable components of which maybe difficult to identify (18). Some researchers have estimated that human fetal tissue for neural grafting in Parkinson's disease is correctly identified in only 10 to 50 percent of aborted tissue analyzed (27,61). Furthermore, only 5 to 10 percent of the transplanted neurons may survive the grafting procedure. Improving graft retrieval and survival could diminish the amount of fetal tissue necessary for transplantation.

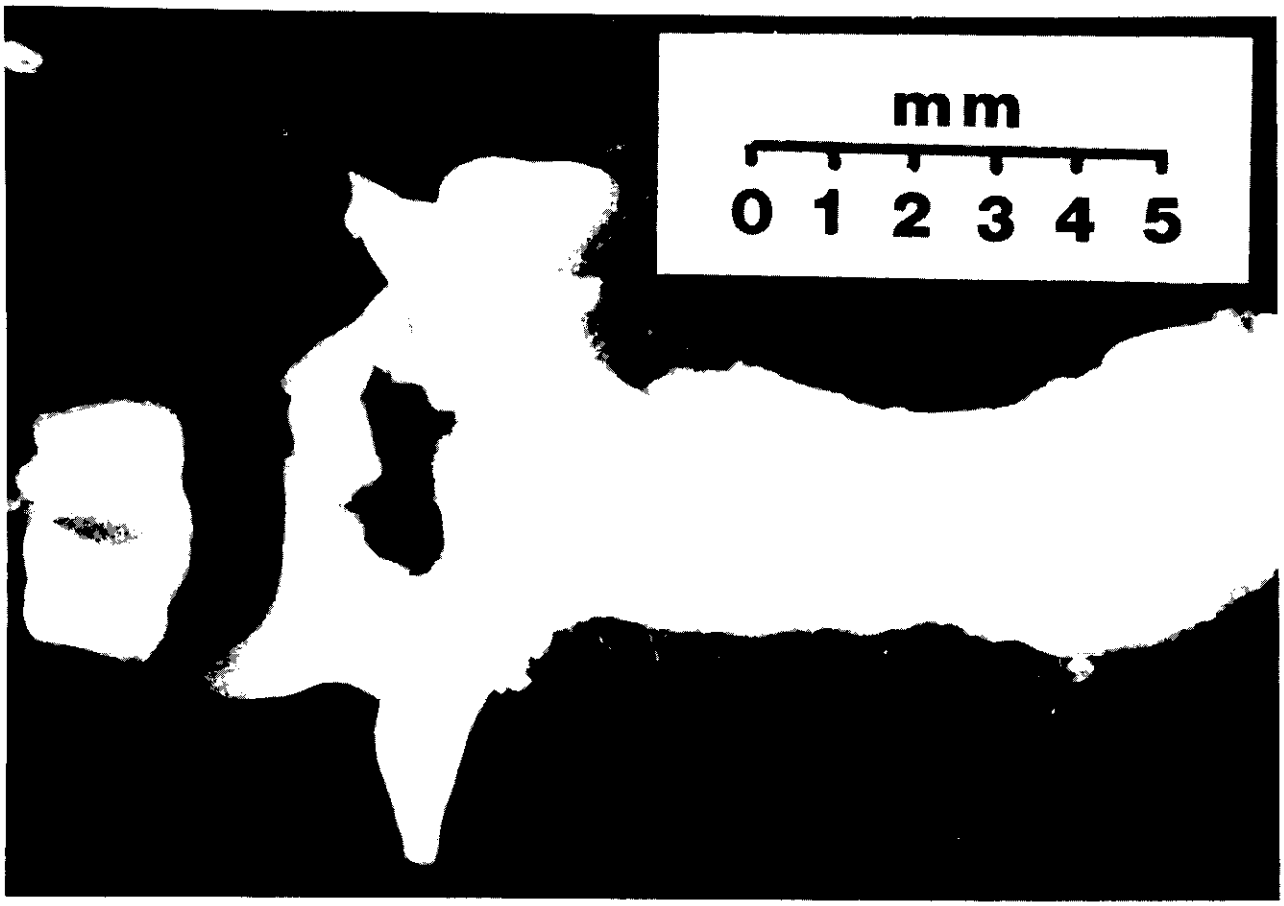
Like other tissue used for neural grafting, fetal CNS tissue presents some risks (see discussion of risks later in this chapter). However, many scientists consider fetal CNS tissue to be the most effective material currently available for neural grafting (46,93). Fetal CNS cells appear to be less vulnerable than adult cells to damage from, for example, lack of oxygen, which is encountered during the transplantation process. Also, cells within fetal CNS tissue can readily mature and integrate within the host; mature CNS tissue has lost these capabilities. Of all the graft materials available at the present time, fetal CNS tissue is most capable of reconstituting nerve cell structure and function within the host CNS. In addition, fetal CNS tissue may enjoy at least a temporary immunological advantage (see later discussion) and, like other potential graft materials, is amenable to long-term storage via cryopreservation (figure 4-3) (box 4-A). Despite the usefulness of fetal tissue for neural grafting, ethical, social, and political issues have created a barrier to its use in the United States and propel the search for alternative neural grafting materials.

Peripheral Nerve Tissue

The permanent deficit in function that frequently results from injury to the mature CNS reflects, in part, the stymied regrowth of neurons within the CNS. In contrast, axons in the peripheral nervous system (PNS), which lies outside the brain and spinal cord, can regrow following injury. Components of the PNS, including Schwann cells, a type of glial cell that produces the insulating myelin sheath around axons, promote axon growth (19).

Investigators have attempted to harness the growth-promoting capacity of peripheral nerves by grafting segments of peripheral nerve into the CNS. Early animal experiments showed that a piece of peripheral nerve placed into a lesion in the CNS would bridge the lesion, allowing host nerve fibers

Figure 4-2—Fetal Central Nervous System



A portion of the dissected human fetal central nervous system.
SOURCE: Curt Freed, Department of Medicine and Pharmacology, University of Colorado,

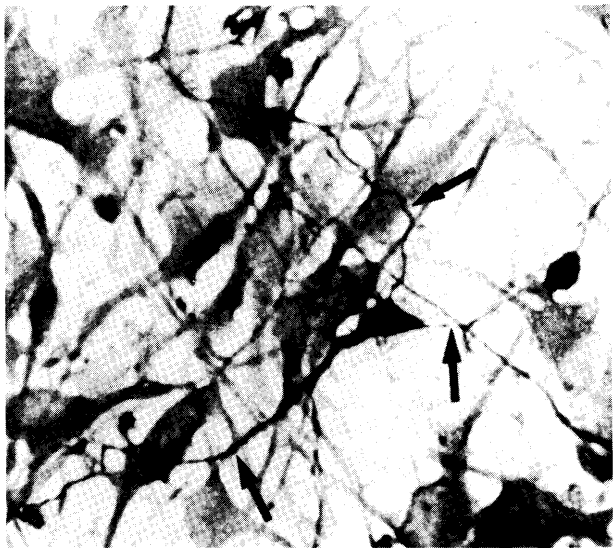
to penetrate and completely traverse the graft (22) (figure 4-4). Nerve fibers that regenerate through a grafted peripheral nerve penetrate only a short distance on reentry into the host CNS. However, even this shallow penetration back into the host brain permits some reconnection with target neurons. Thus, some recovery of function may be obtained by using this approach (55). This approach may be limited to certain regions of the CNS due to geometric constraints on nerve graft placement. For example, it may be impossible to interconnect deeply embedded regions of the brain with a nerve graft without damaging the surrounding brain tissue.

Most of these animal experiments have involved autografts; that is, the graft material has come from the animal itself. An autograft provides two advantages: rejection of the graft by the host immune system is avoided, and the graft recipient serves as a readily available source of material.

Peripheral Autonomic Tissue

Some neurons are located outside the brain and spinal cord and interact directly with various organs, regulating body temperature, metabolism, and the body's response to stress. These peripheral neurons are part of the autonomic nervous system, and they synthesize neurotransmitters and other chemical substances that are similar to those found in the CNS. In addition, mature peripheral autonomic neurons can survive injury and redevelop nerve fibers. Because this class of neurons is easily accessible and exhibits a great potential for regrowth, several investigators have examined the usefulness of peripheral autonomic neurons for neural grafting. Autonomic neurons have been

Figure 4-3-Transplanted Fetal Nerve Cell



Photograph of a fetal nerve cell following cryopreservation and transplantation.

SOURCE: D.E. Redmond, Jr., F. Naftolin, T.J. Collier et al., "Culture and Transplantation of Human Fetal Mesencephalic Tissue Into Monkeys," *Science* 242:788-771, 1988.

grafted into the mature brain in a few animal experiments, and in some cases these grafted neurons survived and led to improvement in function within the injured CNS (54, 83).

Tissue From Outside the Nervous System

Some nonneuronal cells located outside the central and peripheral nervous systems share a common heritage with nervous tissue; i.e., they develop from the same type of embryonic precursor cell as nervous system cells. These cells (sometimes referred to as paraneurons) produce neurotransmitters and can be stimulated to extend nerve fibers. Included in this category are some cells in the adrenal gland, as well as other, smaller collections of cells in the body (e.g., carotid body cells, which monitor the concentration of oxygen in the blood). Because such cells resemble neurons, they have been considered potential candidates for neural grafting. Cells from the adrenal gland have been studied extensively.

The adrenal glands are located above each kidney, and they produce various hormones. The innermost region of the adrenal gland is the adrenal medulla. One type of adrenal medullary cell, the chromaffin cell, is derived from precursor cells that also generate neurons in the autonomic nervous system.

Figure 4-4—Peripheral Nerve Graft

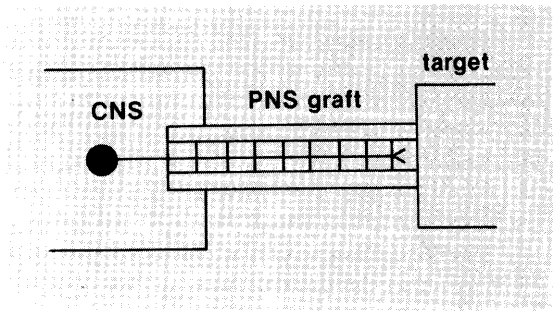


Diagram of graft from the PNS, permitting CNS nerve fiber regrowth to target.

SOURCE: A.J. Aguayo, "Regeneration of Axons From the Injured Central Nervous System of Adult Mammals," Encyclopedia *of Neuroscience, vol.* II, *G.* Adelman (cd.) (Boston, MA: Birkhäuser, 1987).

Chromaffin cells produce neurotransmitters chemically related to those made in the nervous system. One of the neurotransmitters produced by chromaffin cells is dopamine, the chemical that is deficient in the brain of persons with Parkinson's disease.

The finding that fetal neurons which produce dopamine could reverse parkinsonian symptoms in animals suggested the use of adrenal medulla cells for neural grafting (6,72). In the latter case, animals could provide their own chromaffin cells for grafting, thus eliminating concerns about a source of tissue and possible rejection of the graft. The adrenal medulla grafts were shown to reverse some of the abnormal body movements in animal models of parkinsonism (see ch. 5).

A few recent experiments have employed another nonneuronal tissue, human amnion membrane matrix (HAMM), taken directly from the discarded human placenta, as a neural graft material (23,32). When positioned in an animal's brain, HAMM appears to serve as a bridge that supports neuron outgrowth. HAMM does not contain cells; rather, it contains a chemical substance that promotes and guides neuron regrowth. It does not seem to provoke rejection of the graft by the host immune system, and it is available in abundance. Although more research is necessary to evaluate the usefulness of HAMM in neural grafting, these experiments suggest that manmade materials, coated with a growth-promoting chemical, may ultimately be developed and used in neural grafting.

Box 4-A—The Deep Freeze: Cryopreservation of Fetal CNS Tissue

Neural grafting with fetal CNS tissue is constrained by the need for rapid implantation of freshly collected tissue into the graft recipient. The viability of fetal CNS tissue diminishes within hours of procurement. Extending the interval between tissue collection and implantation would greatly ease the logistics of neural grafting and allow assessment of tissue contamination, vitality, and genetic compatibility with the intended recipient. Cryopreservation, or freezing of cells and tissue at very low temperatures, can be used to extend the time between tissue collection and neural grafting. This technique is routinely used for the storage of continuous cell lines and other types of cells. In fact, cryopreservation of fetal CNS tissue has a long history.

Prior to cryopreservation, cells or tissue are typically treated with a cryoprotectant, a chemical that limits tissue damage during the freezing process. The cryoprotected material is then either abruptly or more gradually lowered to -l%" C, the temperature of liquid nitrogen. Once at this temperature, cells or tissue can be stored for a long time; frozen cells can also be transported readily between clinical centers.

Fetal CNS tissue from several species, including humans, has been examined following cryopreservation. In general, cryopreserved fetal CNS tissue demonstrated a significant reduction in viability when thawed. Recently, however, improved cryopreservation of human fetal tissue has been reported, resulting 'in ***95*** percent viability of thawed fetal neurons. Furthermore, cryopreserved human fetal tissue has been shown to survive following grafting into monkeys and humans.

SOURCES: T.J. Collier, D.E. Redmond, Jr., CD. Sladek et al., "Intracerebral Grafting and Culture of Cryopreserved Primate Dopamine Neurons," Brain Research 436:363-366, 1987; T.J. Collier, C.D. Sladek, M. J. Gallagher et al., "Cryopreservation of Fetal Rat and Non-human Primate Mesencephalic Neurons: Viability in Culture and Neural Transplantation," *Progress in Brain Research,* vol. 78, *Transplantation Info the Mammlian CNS,* D.M. Gash and J.R. Sladek, Jr. (eds.) (Amsterdam.: Elsevier Science Publishers, 1988); D.E. Redmond, Jr., "Fetal Tissue Transplantation: Animal and Human Studies,' paper presented at the American Association for the Advancement of Science annual meeting, New Orleans, LA, 1990, D.E. Redmond, Jr., F. Naftolin, T.J. Collier et al., "Culture and Transplantation of Human Fetal Mesencephalic Tissue Into Monkey s," *Science* 242:768-771, 1988; D.E. Redmond, Jr., D. Spencer, F. Naftolin et al., "Cryopreserved Human Fetal Neural Tissue Remains Viable 4 Months After Transplantation Into Human Caudate Nucleus,' paper presented at the Society for Neuroscience 19th annual meeting, Phoenix, Arizona, 1989; V. Silani, A. Pizzuti, O. Strada et al., ''Human Neuronal Cell Viability Demonstrated in Culture After Cryopreservation," *Brain Research 473:169-174, 1988;* T. Sorensen, S. Jensen, A. Moller et al., "Intracephalic Transplants of Freeze-stored Rat Hippocampal Tissue, ' *Journal of Comparative Neurology 252:468-482, 1986.*

Isolated, Cultured, or Genetically Engineered Cells

The graft materials discussed thus far have been distinct types of tissue harvested directly from a donor organism. Technical developments that permit the separation of individual cells from a solid block of tissue, the maintenance of living cells in the laboratory, and the manipulation of genes within cells may expand the types and forms of materials available for neural grafting. The methods described in this section can be applied to many cell types. In this report, however, the cells derived from each tissue source via the methods described are treated as a separate neural grafting material because each gives rise to unique technological issues. The forms of neural graft materials presented in this section include:

- cell suspensions,
- **cells in** culture, and
- **genetically** engineered cells.

Cell Suspensions

Neural grafting can involve the placement of small, solid pieces of tissue into the brain ***(8,61);*** however, solid pieces of tissue cannot be implanted and sustained in all locations within the ***CNS. In*** order to overcome this limitation, procedures have been developed in which solid tissue is dispersed into individual cells or, more often, aggregates of cells prior to grafting ***(8,16).*** Dispersed cells in a supporting fluid are known as a cell suspension. Use of cell suspensions for grafting involves: 1) removal of the required tissue from a donor organism, 2) dissociation of the tissue into individual cells or small aggregates of cells, ***3)*** suspension of the individual cells or aggregates in a supporting fluid, and 4) injection of the suspension into the host CNS.

Cell suspensions from several types of tissue have been used for neural grafting in animals (71). **Experiments have shown that fetal neurons grafted in the form of a cell suspension are capable of long-term survival and interaction**

with the host CNS and can restore function in a damaged region of the brain (8). In fact, neuron suspension grafts may provide more rapid and complete integration into the host brain than solid grafts. Another advantage of using cells in suspension rather than solid tissue for neural grafting is the ease with which suspensions can be manipulated. A solid piece of tissue contains a heterogeneous population of cells, the number and viability of which cannot be determined. In contrast, cell number and viability can be monitored more accurately in suspensions, and it may be possible to isolate a single type of cell for transplantation (16,63). Also, neural grafting with a cell suspension may provoke a less severe immune system response than solid tissue grafts.

Cells in Culture

Once solid tissue is dissociated into a suspension of cells, the living cells can be maintained in the laboratory for several weeks or months in culture. For primary culture, cells are taken directly from an organism and grown in vitro (literally, in glass). Culturing cells prior to grafting them increases the opportunity for manipulating the cells and thus may increase the versatility of neural grafting.

A vast amount of information concerning the in vitro culturing of different groups of nerve cells, each with its specific requirements, has emerged from basic neuroscience research (9), including a recent report of successful culturing of human neurons (78). Primary cultures of nerve cells, which are generally derived from embryonic or fetal tissue, have demonstrated the ability to survive implantation in the host CNS, to integrate into the host brain, and to promote recovery following an induced injury (15,39,51). In general, culturing fetal neurons diminishes their survival in the host following grafting.

The use of primary cultures of glial cells for neural grafting has also been studied. For example, neural grafts of astrocytes from the developing brain can reduce scar formation following CNS injury in animal experiments (90) and promote recovery of brain function (56). Schwann cells and oligodendrocytes, both myelin-producing glial cells, have also been grown in primary cultures and used for neural grafting. Cultured Schwann cells and oligodendrocytes have been implanted into the CNS of myelin-deficient rats, resulting in the formation of myelin within the host CNS (31,45).

Photo credit: National Institute of Neurological Disorders and Sfroke, Bethesda, MD, 1990

Nerve cells in culture.

Most cells survive for only a limited period in primary culture, either replicating a freed number of times or not at all. However, some cells can continue to replicate and thus can potentially survive indefinitely. These continually self-propagating cells may arise spontaneously, may be derived from tumors, or may be created via genetic engineering. Sustained, self-propagating cells in culture are known as continuous cell lines (CCLs). Because CCLs can produce a large number of cells and are in a sense immortal, they have been extremely useful in a number of areas of research.

Several CCLs have been studied extensively as model systems for neuron development and function, including PC12 and neuroblastoma cells. These neuronal CCLs, originally derived from tumors, can be induced to stop replicating and to develop features of adult neurons (e.g., formation of long nerve fibers and secretion of neurotransmitters). Experiments have shown that neuronal CCLs

can be successfully grafted into the CNS and may attenuate functional problems produced by lesions in the CNS (29,36,48,57).

Because CCLs are capable of continuous self-replication, they could provide an inexhaustible source of donor tissue for neural grafting; however, this very trait presents a critical obstacle to their use. As is true of all replicating cells, their potential for uncontrolled growth in the host CNS may lead to tumor formation. Tumor formation has been observed in some, but not all, animal experiments using CCLs for neural grafting (29,53,57). In order to eliminate the threat of tumor formation, strategies for chemically controlling the occurrence and arrest of cell replication are being evaluated (2,57). Although CCLs may offer an attractive option for neural grafting in the future, more research is necessary to characterize and control cell replication in tissue culture and in the graft recipient.

Figure 4-5-Genetic Engineering of Graft Tissue

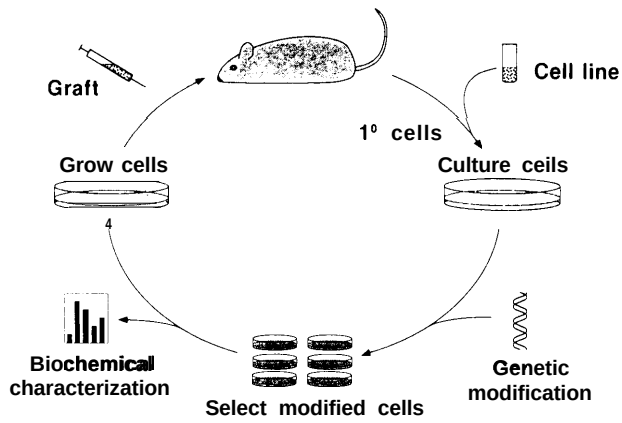


Diagram of methods used to graft genetically modified cells.
SOURCE: Fred H. Gage, Department of Neuroscience, School of Medicine, University of California, San Diego.

Genetically Engineered Cells

Research is demonstrating that cells may be designed to synthesize a specific chemical substance or to perform a specific function before being implanted into a recipient. This customized approach to neural grafting is made possible by the use of genetic engineering techniques. Genetic engineering permits the insertion of new genes into a cell. Genes code for proteins, which carry out many cell functions, and different genes direct the synthesis, or expression, of different sets of proteins. Cells derived from fetal CNS tissue, the prospective host, primary cell cultures, or a CCL can be genetically engineered.

Genetic engineering techniques have been applied to tissue from the CNS. In one approach, immature precursor cells from the developing CNS of rats, which are capable of developing into mature brain cells, were isolated and maintained in primary cell culture (42,66). There they replicated for a finite period and then matured. Genetic engineering methods were designed to permit the immature precursor cells to replicate indefinitely in the laboratory, but then subsequently to mature and to stop replicating when transplanted into a host brain or spinal cord. Using this approach, specific CCLs from the brain and spinal cord may be developed for use in neural grafting (10). The hope is that specific "immortal" precursors for each type of cell within the brain and spinal cord can be isolated and made available to replace diseased or injured cells through neural grafting.

Two types of nonneuronal cells have been used for genetic engineering and neural grafting: astrocytes and fibroblasts (cells found in connective tissue) (figure 4-5). Early research demonstrated that genetically engineered cells can survive and function within the host CNS (34). In more recent experiments, fibroblasts have been genetically engineered to synthesize: 1) an enzyme important for the production of the brain chemical L-dopa, which is a precursor of the brain chemical dopamine; and 2) nerve growth factor (NGF) (25,79,97). When used for neural grafting, these genetically engineered cells enhanced survival and growth of neurons, improved CNS function, or both.

The use of genetically engineered fibroblasts, which are easily derived from the skin, as neural graft material has all the advantages of autografts: a ready source of tissue and no worry about immune system rejection of the graft. Although the use of nonneuronal cells precludes the graft from forming synapses with host neurons, genetically engineered nonneuronal cells may be able to function as a drug delivery system in the host. Fibroblasts, like other replicating cells, do present some risk of excessive replication within the host. However, since fibroblasts are primary cells, not derived from a CCL, their multiplication is inhibited by contact with other cells, minimizing the threat of tumor formation.

Many important questions remain concerning the grafting of genetically modified cells into the human brain. Perhaps most important, the genes controlling various cell functions within the CNS (e.g., neurotransmitter synthesis and growth factor production) must be identified. Once the genes controlling CNS function and disease are identified, they must be isolated and made available for genetic engineering. Providing multiple genes to cells for neural grafting and controlling their expression are long-term goals requiring extensive research. Nevertheless, current research represents an encouraging start toward many of these revolutionary therapeutic strategies.

DETERMINANTS OF SUCCESSFUL NEURAL GRAFTING

To survive grafting, cells must endure mechanical and metabolic disruption during their preparation for grafting, and they must incorporate into the foreign, and potentially hostile, environment of the host. The surgical technique and tissue used for neural grafting are important determinants of success. Several additional characteristics may figure prominently in the survival of a neural graft, including:

. the developmental state of the graft material,
• the host's immune system response,
. blood vessel formation into the graft, and
. the age of the host.

Developmental State of the Graft Material

In general, immature tissue can survive grafting more readily than its mature counterpart. Several characteristics of immature tissue, especially fetal tissue, make it well-suited for grafting (l). In general, cells from fetal tissue replicate rapidly and can differentiate into functioning mature cells. Nutritional support provided by blood vessels from the host is easily accepted and probably promoted by fetal tissue. Fetal tissue is amenable to cell culture and storage techniques, thereby expanding its flexibility for use in grafting. These features, which make fetal tissue especially suitable for grafting, are diminished or lost with maturity.

Early experiments in neural grafting of tissue from the adult brain and spinal cord indicated that this tissue survives poorly in the host CNS (7,35,89). In contrast, tissue from the CNS of a fetus or newborn exhibits great potential for survival and development following neural grafting. Neural grafting experiments in which cell suspensions are used demonstrate an even greater reliance on the use of fetal nervous tissue (8).

Although CNS tissue in later stages of development has been used with some success for neural grafting in rodents and nonhuman primates, survival is greatest when fetal CNS tissue is used (17,86). Apparently, immature neurons, which have not yet grown long and elaborate fiber-like extensions, are less vulnerable to the mechanical disruption associated with tissue collection. In addition, immature cells may be more resistant to other stresses' associated with the grafting procedure, such as a temporary reduction in oxygen supply. Because neurons throughout the CNS develop and mature asynchronously, different groups of neurons reach the optimal developmental stage for neural grafting at different fetal ages. The developmental stage of the CNS tissue used for grafting may present immunological considerations. Grafts of fetal CNS tissue fail to provoke an immediate immune response, probably because the cells and molecules that trigger graft rejection by the host immune system have not yet developed within fetal tissue. Fetal CNS tissue does possess the capability of expressing immunoreactive molecules on maturity, hence it could provoke a delayed immune system response.

The optimum donor age of non-CNS tissues for neural grafting has not been as extensively evaluated. Adrenal medulla transplants in rats demonstrate greater functional effects when derived from younger rather than older animals (28). Thus, optimal success in adrenal grafting maybe obtained by using young, and perhaps even fetal, adrenal medulla tissue. Grafted nerve cells from the autonomic nervous system do not survive well when derived from the fetus; however, mature autonomic nerve cells regenerate briskly when transplanted (82).

Immune System Response

Mammals have evolved an immune system to protect them from disease-causing agents encountered in the environment. This system is a finely tuned collection of tissues, organs, cells, and molecules that seek out, identify, destroy, and remember foreign cells and molecules. An individual's immune system vigilance against cells and mole-

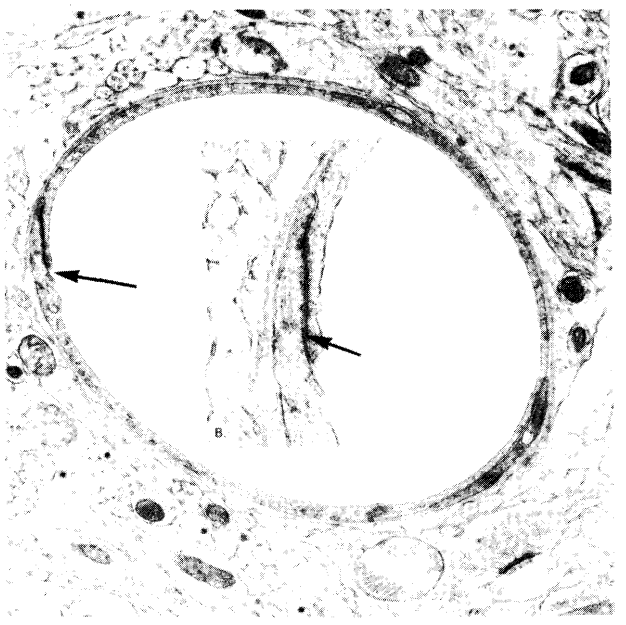
cules that do not originate within itself presents a major obstacle for organ or tissue transplantation. In order for a graft to survive for an extended period of time in the host, the host's immune system must be contravened or suppressed.

Rejection of a graft can be prevented by using tissue from the host's own body. As noted earlier, such a graft is called an autograft. Graft material from an identical twin-an isograft--should behave immunologically like an autograft. After these two types of grafts, compatibility is increasingly rare. Either an allograft--tissue transferred between different members of the same species--or a xenograft--tissue transferred between individuals of different species-can lead to graft rejection. Host rejection of grafted tissue may be prevented by reducing the genetic disparity between the donor and the host and by using drugs that suppress the action of the immune system.

It has long been thought that the CNS enjoys relative isolation from the immune system because it permits the entry of few cells from the immune system that recognize foreign cells or molecules (for review, see 69,94). This isolation has given rise to the concept of immunological privilege; i.e., the CNS is not subjected to the same degree of scrutiny by immune system components as the rest of the body. However, although allografts within the CNS seem to survive frequently without inducing rejection, xenografts in the CNS do provoke graft rejection (69). These data and others demonstrate that the immune system can penetrate the CNS and lead to graft rejection, thus casting doubt on the degree to which immunological privilege operates in the CNS.

Many immune system components are excluded from the CNS by the blood-brain barrier, an important agent of immunological privilege (figure 4-6). Injury, surgery, or infection can disturb the blood-brain barrier, allowing cells and molecules from the immune system to enter the CNS and cells from the CNS to enter the bloodstream. While there is debate about whether the blood-brain barrier is permanently disrupted by the implantation of tissue in the CNS (12,81), it is undoubtedly disrupted for at least a few days (13). The type of grafting material used also appears to affect the development of the blood-brain barrier within the graft (13,83).

Figure 4-6—Blood-Brain Barrier in Transplanted Tissue



Blood vessel surrounded by brain tissue shown in photograph. Inset B displays the source of the blood-brain barrier, i.e., the tight adhesion of endothelial cells, which line blood vessels.

SOURCE: Richard D. Broadwell, Division of Neurological Surgery, University of Maryland School of Medicine.

A second feature of the CNS which was believed to isolate grafts and hinder graft rejection is the lack of extensive lymphatic drainage. Lymphatic drainage returns fluids, molecules, foreign particles, and cells from various tissues in the body through the lymphatic system back to the immune and circulatory systems. It is through this drainage that grafted cells capable of triggering rejection reach the host's immune system. The CNS had been thought not to experience lymphatic drainage; however, some studies have suggested that molecules and cells can leave the CNS and enter the lymphatic system. Thus the CNS may indeed experience some lymphatic drainage and therefore be capable of provoking rejection (96).

The use of CNS tissue as a grafting material often fails to provoke rejection by the immune system, at least in the short term. Cells within the CNS normally lack, or express very few, immunoreactive molecules, i.e., molecules that trigger rejection by

the host's immune system (88,98).[2] Also, tissue from 'the CNS was thought not to contain cells that enter the immune system and trigger an immune response (47). Unfortunately, recent experiments suggest that the CNS can be provoked to produce immunoreactive molecules and that the CNS does possess cells which may reach the immune system and initiate graft rejection (3,50,92,98).

Another cell type that can provoke an immune response is endothelial cells (49,65), which form the inner walls of blood vessels and are commonly found in grafts of solid pieces of tissue. This cause of graft rejection can be eliminated by using neural grafts composed of a single type of cell, as in cell cultures or purified suspensions of cells, which do not contain blood vessels or endothelial cells.

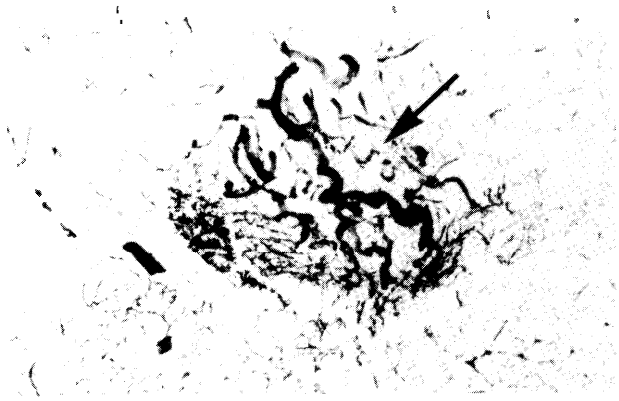
The fact that many types of neural grafts survive in the host CNS suggests that the brain and spinal cord do enjoy some immunological privilege. However, research indicates that some grafts can be identified and destroyed by the host's immune system. Further experiments and analyses are required to delineate the precise relationship between the immune system and the CNS, as well as the immune system's response to neural grafts.

Blood Vessel Formation

The neural graft's ability to obtain ready access to nutritional support and a supply of oxygen from the host is critical for its survival. The failure of many early neural grafts may reflect inadequate incorporation of the grafted tissue into the host blood supply (8). Solid tissue grafts into the CNS may not receive an adequate blood supply for more than 1 week (13).

Several approaches to neural grafting have been developed to accelerate the provision of nutritional support to the graft. One entails placing the graft near a CNS surface that is naturally rich in blood vessels. The brain ventricles were a favored site for graft placement in animal experiments for this reason (82). Ventricles are cavities within the brain that contain cerebrospinal fluid (CSF). CSF may provide immediate nutritional support to the solid graft, and regions rich in blood vessels within the ventricles provide long-term support. Another approach is to create a rich vascular surface within the brain (91). Under normal conditions, new blood vessels are very rarely formed in the brain. However, when a cavity is produced surgically in the CNS, new blood vessel growth is stimulated and the cavity walls become heavily invested with blood vessels. Placing a graft within the cavity often results in a good supply of blood vessels to the grafted tissue. Greater blood vessel growth is produced by graft placement than by a wound alone (59). The choice of grafting material may also influence blood vessel formation: blood vessels can grow into suspensions of cells more readily than into solid pieces of tissue, and fetal tissue seems to stimulate blood vessel development better than adult tissue (figure 4-7) (77). Finally, certain drugs may be used to enhance blood vessel development within a graft (26).

Figure 4-7—Blood Vessel Growth in Transplant



Darkly stained blood vessels invading neural graft tissue in brain.
SOURCE: Richard D. Broadwell, Division of Neurological Surgery, University of Maryland School of Medicine.

It has been debated whether blood vessels within a neural graft are derived from the donor or the host. The relative contribution of each may depend on the type of tissue transplanted, whether it is transplanted as a solid piece or in a cell suspension, and the amount of tissue damage sustained by the recipient during placement of the graft (13,24,60,69,83). Blood vessels within the graft may or may not fully develop a blood-brain barrier, depending on the type of tissue utilized (13,14,68,80,95). Both of these observations, the presence of donor cells in the graft blood vessels and the formation of the blood-brain barrier, have important implications for graft rejec-

[2]The presence of specific molecules, including the major histocompatibility complex, or MHC antigens, is an important determinant of a tissue's immunogenicity. Detection and measurement of these molecules can be difficult (71).

tion. (See the earlier discussion of immune system response.)

The Age of the Host

In general, the younger the graft recipient, the more likely the graft is to survive and integrate within the host brain. A younger host animal, especially a newborn, maybe better able to support grafted material because it can more vigorously form blood vessels (8). Furthermore, an adult recipient rejects neural grafts more rapidly than an immature recipient (64). The age of the host, however, is less critical to graft survival than the age of the donor, immunological response, and extent of blood vessel formation.

POTENTIAL RISKS

A major goal of neural grafting is to improve CNS function following disease or trauma. As with any surgical intervention, however, neural grafting presents risks to the recipient. Problems may result from:

- immune system reaction or suppression,
- . unwanted psychological effects,
- . the surgical procedure itself,
- excessive growth of graft material, or
- infection or other effects on the host CNS.

Unfortunately, many of the risks attributed to neural grafting are either poorly understood or simply speculative. Before any routine application of neural grafting in humans, the risks must be carefully delineated, minimized, and measured against expected benefits.

Immune System Reaction or Suppression

The transplantation of tissue from one individual to another presents the risk of graft rejection. The foreign tissue triggers a cascade of events in the graft recipient, culminating in destruction of the graft. In general, allografts implanted in the CNS do not appear to suffer immediate rejection by the host's immune system, although rejection in the long term may be possible.

When tissue transplantation is performed outside the CNS, drugs that suppress the immune system are employed to prevent rejection and promote survival of the graft. Immunosuppression poses serious risks to the graft recipient, including increased susceptibility to infection and the development of some forms of cancer (87). Uncertainty about immune system reactions in the CNS complicates attempts to balance the risks of immunosuppression against those of neural graft rejection. Studies of fetal CNS tissue grafting in humans with Parkinson's disease have both applied and abstained from applying immunosuppression therapy (27,62,75).

Unwanted Psychological Effects

Implantation of tissue into the human brain raises the possibility of unwanted psychological effects. Assessment of adrenal medulla grafts in humans with Parkinson's disease indicates that some psychological changes consistently accompany this procedure, including hallucinations, confusion, and somnolence (43,44). These psychological responses proved, in general, to be transient. How such changes are produced is unknown, but they may reflect either trauma to the brain from the surgical procedure itself or the effects of chemical substances released by the grafted adrenal tissue. Similar effects have not been reported in the few Parkinson's patients who have received fetal CNS tissue grafts.

Effects of the Surgical Procedure

Aside from its suspected role in producing temporary psychological changes in the recipient, the surgical procedure used to insert a neural graft presents other serious risks. Graft placement in the brain, especially the more invasive surgical procedures (see ch. 5), can cause serious damage, such as excessive bleeding or injury to brain tissue. Injury may result in the loss of CNS function or exacerbate the recipient's immune response to the grafted tissue (41). In addition, surgery disrupts the blood-brain barrier for at least a week; even the less invasive method of graft insertion probably disrupts the blood-brain barrier for 1 to 3 days (14,94). The CNS's protected environment may thus be lost temporarily near the graft site, posing a risk to the graft recipient.

Excessive Growth of Graft Material

Fetal CNS tissue, some nonneuronal tissues, and continuous cell lines can continue to replicate in the CNS of the graft recipient, presenting the risk of excessive graft enlargement. Brain tissue can be compressed and permanently damaged by an expanding mass of tissue. In addition, an enlarging neural graft placed in the brain ventricles can

obstruct the flow of CSF, which can dangerously increase pressure in the brain. The number of cells used for neural grafting is thus an important consideration; the number chosen must reflect a balance between the risk of overenlargement and the more common problem of inadequate cell survival. As discussed earlier, some replicating cells pose the added threat of tumor formation.

Infection and Other Effects on the Host CNS

Transplanted cells can transmit bacterial and viral infections, placing the graft recipient at risk for such diseases as hepatitis, AIDS, or herpes simplex encephalitis. Several actions can reduce this risk. The likelihood of a potential donor carrying an infectious agent can be assessed. The potential donor or graft material can be screened for infectious agents. In addition, graft material can be treated with drugs, such as antibiotics, to destroy susceptible infectious agents prior to implantation.

Materials used for neural grafting may disrupt or alter CNS function in the recipient. For example, non-CNS tissue, such as cells from the adrenal medulla or fibroblasts, may prevent the reestablishment of the blood-brain barrier near the graft (13,59,83). The implantation of certain fetal CNS tissue has been shown to produce seizures in some experimental animals (33). In addition, injection of brain tissue into the abdomen of animals has led to experimental allergic encephalomyelitis (EAE) (4), a potentially fatal inflammatory disease of the CNS in which immune cells attack components of nerves. Although EAE has not been reported in neural grafting experiments in animals, it represents a serious risk, especially in the case of xenografts. Finally, the graft may be susceptible to the pathological processes that underlie the neurological disorder being treated. Since many neurological disorders are of unknown etiology, it is difficult to assess the likelihood of this risk factor.

SUMMARY AND CONCLUSIONS

Neural grafting involves many therapeutic goals, materials, and procedures. Tissue or cells may be transplanted to the brain and spinal cord in order to deliver chemical substances, to promote neuronal growth and survival following injury, or to replace lost nerve cells. Numerous materials have been used for neural grafts, including fetal CNS tissue, peripheral nerve tissue, and tissue from outside the nervous system. In addition, several types of tissue have been manipulated, using cell culture and molecular biological techniques, in preparation for neural grafting. While genetically engineered cells present an exciting possibility for the future of neural grafting, at present fetal CNS tissue is demonstrably the most effective graft material available. The developmental stage of the grafted material, the host's immune response, vascular support within the host, and the age of the host also influence graft survival and function. Depending on the material chosen and the surgical procedures employed, neural grafting technology does present some risk to the host.

The potential use of neural grafting for the routine treatment of the diseased or injured CNS requires much more research, even for Parkinson's disease, where the technology is most highly developed at present. Research is necessary to evaluate and optimize transplant procedures. Other neural grafting approaches, including the use of genetically engineered cells, will require even more extensive basic research. Factors that determine the long-term survival and function of a neural graft, especially the immune system reactions, must be probed more deeply. The influence of the disease process on the grafted material must also be addressed. Perhaps most important, a more complete understanding of the basis of disease and malfunction within the CNS is required for the development of treatments such as neural grafting.

CHAPTER 4 REFERENCES

1. Auerbach, R., "Qualities of Fetal Cells and Tissues," ***Report of the Human Fetal Tissue Transplantation Research Panel,*** vol. II (Bethesda, MD: National Institutes of Health, 1988).
2. Barnes, D., "Serum-free Animal Cell Culture," *Biotechniques* 5:534-541, ***1987.***
3. Bartlett, P.F., Kerr, R. S. C., and Bailey, K.A., "Expression of MHC Antigens in the Central Nervous System," ***Transplantation Proceedings*** 21: ***3163-3165, 1989.***
4. Bauer, H.J., ''Umstrittene MS-Therapie," *Nervenarzt* 54:400-405, **1983.**
5. Björklund, A., Lindvall, O., Isacson, O., et al., "Mechanisms of Action of Intracerebral Neural Implants: Studies on Nigral and Striatal Grafts to the Lesioned Striatum, " ***Trends in Neuroscience*** 10:509-516, ***1987.***
6. Björklund, A., and Stenevi, U., "Reconstruction of the Nigrostriatal Dopamine Pathway by Intracerebral Nigral Transplants," ***Brain Research*** 177:555-560, ***1979.***

7. Björklund, A., and Stenevi, U., "Intracerebral rafting: A Historical Perspective," *Neural Grafting in the Mammalian CNS*, A. Björklund and U. Stenevi (eds.) (Amsterdam: Elsevier Science Publishers, 1985).
8. Björklund, A., Stenevi, U., Schmidt, R.H., et al., "Intracerebral Grafting of Neuronal Cell Suspensions, I: Introduction and General Methods of Preparation," *Acta Physiologic Scandinavia* supp. 522:1-7, 1983.
9. Bottenstein, J.E., "Growth and Differentiation of Neural Cells in Defined Media," *Cell Culture in the Neuroscience,* J.E. Bottenstein and G. Sato (eds.) (New York, NY: Plenum Press, 1985).
10. Bredesen, D.E., Hisanaga, K., and Sharp, F.R., "Neural Transplantation Using Temperature-Sensitive Immortalized Neural Cells: A Preliminary Report," *Annuls of Neurology* 27:205-207, *1990.*
11. Brightman, M.W., and Reese, T. S., "Junctions Between Intimately Opposed Cell Membranes in Vertebrate Brains," *Journal of Cell Biology 40%48-677,1969.*
12. Broadwell, R.D., "Absence of a Blood-Brain Barrier Within Transplanted Brain Tissue," *Science 241: 473, 1988.*
13. Broadwell, R.D., Charlton, H.M., Ebert, P., et al., "Allografts of CNS Tissue Possess a Blood-Brain Barrier, II: Angiogenesis in Solid Tissue and Cell Suspension Grafts," *Experimental Neurology,* submitted.
14. Broadwell, R.D., Charlton, H.M., Ganong, W.F., et d., "Allografts of CNS Tissue Possess a Blood-Brain Barrier, I: Grafts of Medial Preoptic Area in Hypogonadal Mice,' *Experimental Neurology* 105: *135-151, 1989.*
15. Brundin, P., Barbin, G., Isacson, O., et al., "Survival of Intracerebrally Grafted Rat Dopamine Neurons Previously Cultured In Vitro," *Neuroscience Letters* 61:79-84, *1985.*
16. Brundin, P., Isacson, O., and Björklund, A., "Monitoring of Cell Viability in Suspensions of Embryonic CNS Tissue and Its Use as a Criterion for Intracerebral Graft Survival," *Brain Research* 331:251-259, *1985.*
17. Brundin, P., Isacson, O., Gage, F. H., et al., "Intracerebral Grafts of Neuronal Cell Suspensions," *Neural Grafting in the Mammalian CNS*, A. Björklund and U. Stenevi (eds.) (Amsterdam: Elsevier Science Publishers, 1985).
18. Brundin, P., Nilsson, O.G., Strecker, R.E., et al., "Behavioral Effects of Human Fetal Dopamine Neurons Grafted in a Rat Model of Parkinson's Disease," *ExperimentalBrain Research* 65:235-240, *1986.*
19. Bunge, R.P., "The Cell of Schwann," *Diseases of the Nervous System: Clinical Neurobiology,* A.K. Asbury, G.M. McKhann, and W.I. McDonald (eds.) (Philadelphia, PA: W.B. Saunders, 1986).
20. Caroni, P., Savio, T., and Schwab, M.E., "Central Nervous System Regeneration: Oligodendrocytes and Myelin as Non-permissive Substrates for Neurite Growth,' *Progress in Brain Research,* vol. *78, Transplantation Into the Mammalian CNS*, D.M. Gash and J.R. Sladek, Jr. (eds.) (Amsterdam: Elsevier Science Publishers, 1988).
21. Cotman, C.W., and Kesslak, J.P., "The Role of Trophic Factors in Behavioral Recovery and Integration of Transplants," *Progress in Brain Research, VOL 78, Transplantation Into the Mammalian CNS*, D.M. Gash and J.R. Sladek, Jr. (eds.) (Amsterdam: Elsevier Science Publishers, 1988).
22. David, S., and Aguayo, A.J., "Peripheral Nerve Transplantation Techniques to Study Axonal Regeneration From the CNS of Adult Mammals," *Neural Grafting in the Mammalian CNS*, A. Björklund and U. Stenevi (eds.) (Amsterdam: Elsevier Science Publishers, 1985).
23. Davis, G.E., Blaker, S.N., Engvall, E., etal., "Human Amnion Membrane Serves as a Substratum for Growing Axons In Vitro and In Vivo," *Science* 236:1106-1109, *1987.*
24. Dusart, I., Nothias, F., Roudier, F., et al., "Vascularization of Fetal Cell Suspension Grafts in the Excitotoxically Lesioned Adult Rat Thalamus," *Developmental Brain Research* 48:215-228, *1989.*
25. Ernfors, P., Ebendal, T., Olson, L., et al., "A Cell Line Producing Recombinant Nerve Growth Factor Evokes Growth Responses in Intrinsic and Grafted Central Cholinergic Neurons," *Proceedings of the National Academy of Sciences, U.S.A* 86:4756-4760, 1989.
26. Finger, S., and Dunnett, S. B., "Nimodipine Enhances Growth and Vascularization of Neural Grafts," *Experimental Neurology* 104: *1-9,* 1989.
27. Freed, C., "Fetal Mesencephalic replants for Parkinson's Disease," presentation at the Office of Technology Assessment, U.S. Congress, Washington, DC, December 1989.
28. Freed, W.J., Cannon-Spoor, H.E., and Krauthamer, E., "Factors Influencing the Efficacy of Adrenal Medulla and Embryonic Substantial Nigra Grafts," *Neural Grafting in the Mammalian CNS*, A. Björklund and U. Stenevi (eds.) (Amsterdam: Elsevier Science Publishers, 1985).
29. Freed, W.J., Patel-Vaidya, U., and Geller, H.M., "Properties of PC12 Pheochromocytoma Cells Transplanted to the Adult Rat Brain," *Experimental Brain Research* 63:557-566, *1986.*
30. Freeman, T.B., Wojak, J. C., Brandeis, L., et al., "Cross-species Intracerebral Grafting of Embryonic Swine Doparninergic Neurons," *Progress in Brain Research, VOL 78, Transplantation Into the Mammal-*

ian CNS, D.M. Gash and J.R. Sladek, Jr. (eds.) (Amsterdam: Elsevier Science Publishers, 1988).
31. Friedman, E., Nilaver, G., Carmel, P., et al., "Myelination by Transplanted Fetal and Neonatal Oligodendrocytes in a Dysmyelinating Mutant," ***Brain Research*** 378:142-146, 1986.
32. Gage, F.H., Blaker, S.N., Davis, G.E., et al., "Human Amnion Membrane Matrix as a Substratum for Axonal Regeneration in the Central Nervous System," ***Experimental Brain Research*** 72:371-380, ***1988.***
33. Gage, F.H., and Buzsaki, G., 'CNS Grafting: Potential Mechanisms of Action," ***Neural Regeneration and Transplantation,*** F. Seil (cd.) (New York, NY: Alan R. Liss, 1989).
34. Gage, F.H., Wolff, J.A., Rosenberg, M. B., et al., "Grafting Genetically Modified Cells to the Brain: Possibilities for the Future," ***Neuroscience 23:795-807, 1987.***
35. Gash, D.M., "Neural Transplants in Mammals, A Historical Overview," ***Neural Transplants: Development and Function,*** J.R. Sladek, Jr., and D.M. Gash (eds.) (New York, NY: Plenum Press, 1984).
36. Gash, D.M., Netter, M.F.D., Okawara, S.H., et al., "Amitotic Neuroblastoma Cells Used for Neural Implants in Monkeys," ***Science*** 233:1420-1422, ***1986.***
37. Gash, D.M., and Sladek, J.R., Jr., "Neural Transplantation: Problems and Prospects-Where Do We Go From Here?" ***Mayo Clinics Proceedings 64:363-367, 1989.***
38. Gash, D.M., Sladek, J.R., Jr., and Sladek, C.D., "Functional Development of Grafted Vasopressin Neurons," ***Science*** 210:1367-1369, ***1980.***
39. Gibbs, R. B., Pixley, S.K.R., and Cotman, C.W., "Transplantation of Septal Neurons Maintained in Long-Term Culture,' ***Brain Research*** 382:409-415, ***1986.***
40. Gibson, M.J., Krieger, D.T., Charlton, H.M., et al., "Mating and Pregnancy Can Occur in Genetically Hypogonadal Mice With Preoptic Area Brain Grafts," ***Science*** 225:949-951, ***1984.***
41. Gill, T.J., and Lund, R.D., "Implantation of Tissue Into the Brain," ***Journal of the American Medical Association*** 261:2674-2676, ***1989.***
42. Giotta, G.J., Heitzmann, J., and Cohn, M., "Properties of Two Temperature-Sensitive Rous Sarcoma Virus Transformed Cerebella Cell Lines," ***Brain Research*** 202:445-448, ***1980.***
43. Goetz, C.G., Olanow, C.W., Keller, W. C., et al., "Multicenter Study of Autologous Adrenal Medullary Transplantation to the Corpus Striatum in Patients With Advanced Parkinson's Disease,' New ***England Journal of Medicine*** 320:337-341, 1989.
44. ***Goetz, C.G.,*** Tanner, C.M., Penn, R.D., et al., "Adrenal Medullary Transplant to the Striatum of Patients With Advanced Parkinson's Disease: l-Year Motor and Psychomotor Data, ***Neurology 40:273-276, 1990.***
45. Gumpel, M., Baumann, N., Raoul, M., et al., "Survival and Differentiation of Oligodendrocytes From Neural Tissue Transplanted in New-Born Mouse Brain," ***Neuroscience Letters*** 37:307-311, ***1983.***
46. Hansen, J.T., and Sladek, J.R., Jr., "Fetal Research," ***Science*** 246:775-779, ***1989.***
47. Hart, D. N.J., and Fabre, J.W., "Demonstration and Characterization of Ia-positive Dendritic Cells in the Interstitial Connective Tissue of Rat Heart and Other Tissues, But Not Brain," ***Journal of Experimental Medicine*** 154:347-361, 1981.
48. Hefti, F., Hartikka, J., and Schlumpf, M., "Implantation of PC12 Cells Into the Corpus Striatum of Rats With Lesions of the Dopaminergic Nigrostriatal Neurons," ***Brain Research*** 348:283-288, ***1985.***
49. Hickey, W. F., and Kimura, H., "Perivascular Microglial Cells Are Bone Marrow-Derived and Present Antigen In Vivo," ***Science*** 239:290-292, ***1988.***
50. Hickey, W.F., Osborn, J.P., and Kirby, W.M., "Expression of Ia Molecules by Astrocytes During Acute EAE in the Lewis Rat," ***Cellular Immunology*** 91:528-533, ***1985.***
51. Hisanaga, K., Tsukui, H., Takei, N., et al., "Transplantation of Fetal and Early Postnatal Rat Septal Cholinergic Neurons Cultured in Serum-free and Serum-containing Medium With Nerve Growth Factor," ***Brain Research*** 475:349-355, ***1988.***
52. Huffaker, T.K., Boss, B.D., Morgan, A. S., et al., "Xenografting of Fetal Pig Ventral Mesencephalon Corrects Motor Asymmetry in the Rat Model of Parkinson's Disease,' ***Experimental Brain Research*** 77:329-336, ***1989.***
53. Jaeger, C. B., "Immunocytochemical Study of PC12 Cells Grafted to the Brain of Immature Rats," ***Experimental Brain Research*** 59:615-624, ***1985.***
54. Kamo, H., Kim, S.U., McGeer, P.L., et al., "Functional Recovery in a Rat Model of Parkinson's Disease Following Transplantation of Cultured Human Sympathetic Neurons," ***Brain Research 397: 372-376, 1986.***
55. Keirstead, S.A., Rasminsky, M., Fukuda, Y., et al., "Electrophysiologic Responses in Hamster Superior Colliculus Evoked by Regenerating Retinal Axons," ***Science*** 246:255-257, ***1989.***
56. Kesslak, J.P., Nieto-Sampedro, M., Globus, J., et al., "Transplants of Purified Astrocytes Promote Behavioral Recovery After Frontal Cortex Ablation," ***Experimental Neurology*** 92:377-390, ***1986.***
57. Kordower, J.H., Netter, M.F.D., Yeh, H., et al., "An In Vivo and In Vitro Assessment of Differentiated Neuroblastoma Cells as a Source of Donor Tissue for Transplantation," ***Annals of the New York Academy of Sciences*** 495:606-621, ***1987.***

58. Krieger, D.T., Perlow, M.J., Gibson, M. J., et al., "Brain Grafts Reverse Hypogonadism of Gonadotropin Releasing Hormone Deficiency," *Nature* 298:468-471, *1982.*

59. Krum, J.M., and Rosenstein, J. M., "Patterns of Angiogenesis in Neural Transplant Models: I. Autonomic Tissue Transplants,' *Journal of Comparative Neurology* 258:420-434, *1987.*

60. Krum, J.M., and Rosenstein, J. M., "Patterns of Angiogenesis in Neural Transplant Models: II. Fetal Neocortical Transplants," *Journal of Comparative Neurology* 271:331-345, 1988.

61. Lindvall, O., "Transplantation Into the Human Brain: Present Status and Future Possibilities," *Journal of Neurology, Neurosurgery, and Psychiatry* supp.: *39-54, 1989.*

62. Lindvall, O., Brundin, P., Widner, H., et al., ''Grafts of Fetal Dopamine Neurons Survive and Improve Motor Function in Parkinson's Disease, " *Science* 247:574-577, 1990.

63. Lopez-Lozano, J.J., Gash, D.M., Leary, J.F., et al., "Survival and Integration of Transplanted Hypothalamic Cells in the Rat CNS After Sorting by Flow cytometry," *Cell and Tissue Transplantation Into the Adult Brain,* E.C. Azmitia and A. Björklund (eds.) (New York, NY: New York Academy of Sciences, 1987).

64. Lund, R. D., Rae, K., Hankin, M., et al., "III: Transplantation of Retina and Visual Cortex to Rat Brains of Different Ages: Maturation Patterns and Immunological Consequences, " *Annals of the New York Academy of Sciences* 495:227-241, *1987.*

65. McCarron, R. M., Kempski, O., Spatz, M., et al., "Presentation of Myelin Basic Protein by Murine Cerebral Vascular Endothelial Cells," *Journal of Immunology* 134:3100-3103, *1985.*

66. McKay, R., Frederiksen, K., Jat, P. J., et al., "Reconstructing the Brain From Immortal Cell Lines, ' *Progress in Brain Research, VOL 78, Transplantation Into the Mammalian CNS*, D.M. Gash and J.R. Sladek, Jr. (eds.) (Amsterdam: Elsevier Science Publishers, 1988).

67. Mason, D. W., Charlton, H. M., Jones, A. J., et al., "The Fate of Allogeneic and Xenogeneic Neuronal Tissue Transplanted Into the Third Ventricles of Rodents," *Neuroscience* 19:685-694, *1986.*

68. Naradzay, J.F., and Rosenstein, J. M., "Vascular Morphology and Permeability in Fetal CNS Grafts to the Renal Capsule, " *Experimental Neurology* 104:284-291, *1989.*

69. Nicholas, M. K., and Arnason, B. G. W., "Immunologic Considerations in Transplantation to the Central Nervous System," *Neural Regeneration and Transplantation,* F.J. Seil (cd.) (New York, NY: Alan R. Liss, 1989).

70. Olson, L., Stromberg, I., Bygdeman, M., et al., "Human Fetal Tissues Grafted to Rodent Hosts: Structural and Functional Observations of Brain, Adrenal and Heart Tissues in Oculo,'' *Experimental Brain Research* 67:163-178, 1987.

71. Patel-Vaidya, U., Wells, M.R., and Freed, W. J., "Survival of Dissociated Adrenal Chromaffin Cells of Rat and Monkey Transplanted Into Rat Brain," Cell *and Tissue Research* 240:281-285, *1985.*

72. Perlow, M. J., Freed, W. J., Hoffer, B. J., et al., "Brain Grafts Reduce Motor Abnormalities Produced by Destruction of Nigro-Striatal Dopamine System," *Science* 204:643-647, 1979.

73. Ralph, M.R., Foster, K. G., Davis, F. C., et al., ''Transplanted Suprachiasmatic Nucleus Determines Circadian Period," *Science 247: 975-978,* 1990.

74. Rapaport, S.I., *Blood-Brain Barrier in Physiology and Medicine (New* York, NY: Raven Press, 1976).

75. Redmond, D. E., Jr., "Fetal Tissue Transplantation: Animal and Human Studies,' paper presented at the American Association for the Advancement of Science annual meeting, New Orleans, LA, 1990.

76. Reier, P. J., Eng, L. F., and Jakeman, L., "Reactive Astrocyte and Axonal Outgrowth in the Injured CNS: Is Gliosis Really an Impediment to Regeneration?" *Neural Regeneration and Transplantation,* F.J. Seil (cd.) (New York, NY: Alan R. Liss, 1989).

77. Risau, W., "Developing Brain Produces Angiogenesis Factor,' *Proceedings of the National Academy of Sciences, U.S.A.* 83:3855-3859, *1986.*

78. Ronnett, G.V., Hester, L. D., Nye, J. S., et al., "Human Cortical Neuronal Cell Line: Establishment From a Patient With Unilateral Megalencephaly,'' *Science* 248:603-605, *1990.*

79. Rosenberg, M, B., Friedmann, T., Robertson, R. C., et al., "Grafting Genetically Modified Cells to the Damaged Brain: Restorative Effects of NGF Expression," *Science* 242:509-516, *1988.*

80. Rosenstein, J. M., ''Neocortical Transplants in the Mammalian Brain Lack a Blood-Brain Barrier to Macromolecules,' *Science* 235:772-774, 1987.

81. Rosenstein, J. M., ''Absence of a Blood-Brain Barrier Within Transplanted Brain Tissue?" *Science* 241:473-474, 1988.

82. Rosenstein, J. M., and Brightman, M. W., "Intact Cerebral Ventricle as a Site for Tissue Transplantation," *Nature* 276:83-85, 1978.

83. Rosenstein, J. M., and Brightman, M. W., "Circumventing the Blood-Brain Barrier With Autonomic Ganglion Transplants,' *Science* 221:879-881, 1983.

84. Savio, T., and Schwab, M.E., "Rat CNS White Matter, But Not Gray Matter, Is Nonpermissive for Neuronal Cell Adhesion and Fiber Outgrowth," *Journal of Neuroscience* 9:1126-1133, 1989.

85. Schnell, L., and Schwab, M.E., "Axonal Regeneration in the Rat Spinal Cord Produced by an Antibody

Against Myelin-Associated Neurite Growth Inhibitors," ***Nature*** 343:269-272, ***1990.***

86. Seiger, A., and Olson, L., "Quantitation of Fiber Growth in Transplanted Central Monoamine Neurons," Cell ***and Tissue Research*** 179:285-316, ***1977.***

87. Shevach, E.M., "The Effects of Cyclosporin-A on the Immune System," ***Annual Review of Immunology*** 3:397-424, ***1985.***

88. Skoskiewicz, M.J., Colvin, R. C., Scheenberger, E.E., et al., "Widespread and Selective Distribution of Major Histocompatibility Complex Determined Antigens In Vivo by Interferon,' ***Journal of Experimental Medicine*** 152:1645-1664, 1985.

89. Sladek, J.R., Jr., and Gash, D.M., "Nerve-cell Grafting in Parkinson's Disease,' ***Journal of Neurosurgery*** 68:337-351, ***1988.***

90. Smith, G. M., and Silver, J., "Transplantation of Immature and Mature Astrocytes and Their Effect on Scar Formation in the Lesioned Central Nervous System," ***Progress in Brain Research,*** vol. ***78, Transplantation Into the Mammalian CNS,*** D.M. Gash and J.R. Sladek, Jr. (eds.) (Amsterdam: Elsevier Science publishers, 1988).

91. Stenevi, U., Kromer, L.F., Gage, F.H., et al., "Solid Neural Grafts in Intracerebral Transplantation Cavities," ***Neural Grafting in the Mammalian CNS***, A. Björklund and U. Stenevi (eds.) (Amsterdam: Elsevier Science Publishers, 1985).

92. Ting, J.P.Y., Nixon, D.R., Weiner, L.P., et al., 'Brain Ia Antigens Have a Bone Marrow Origin," ***Immunogenetics*** 17:295-301, ***1983.***

93. Weiss, R., "Bypassing the Ban," ***Science News*** 136:378-379, ***1989.***

94. Widner, H., and Brundin, P., "Immunological Aspects of Grafting in the Mammalian Central Nervous System, A Review and Speculative Synthesis," ***Brain Research Reviews*** 13:287-324, ***1988.***

95. Widner, H., Brundin, P., Björklund, A., et al., "Immunological Aspects of Neural Grafting in the Mammalian Central Nervous System," ***Progress in Brain Research, vol. 78, Transplantation Into the Mammalian CNS,*** D.M. Gash and J.R. Sladek, Jr. (eds.) (Amsterdam: Elsevier Science Publishers, 1988).

%. Widner, H., Johansson, B.B., Moller, G., et al., "QualitativeDemonstration of aLink Between Brain Parenchyma and the Lymphatic System After Intracerebral Antigen Deposition," ***Journal of Cerebral Blood Flow Metabolism*** 5:88-89, 1985.

97. Wolff, J.A., Fisher, L.J., Xu, L., et al., "Grafting Fibroblasts Genetically Modified To Produce L-dopa in a Rat Model of Parkinson's Disease,' ***Proceedings of the National Academy of Sciences, U.S.A.*** 86:9011-9014, ***1989.***

98. Wong, G. H.W., Bartlett, P. F., and Clark-Lewis, I., "Interferon Induces the Expression of H-2 and Ia Antigens on Brain Cells," ***Journal of Neuroimmunology*** 7:255-278, ***1985.***

Chapter 5

Applications of Neural Grafting Into the Brain and Spinal Cord

CONTENTS

Boxes

Figures

Chapter 5

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 in the initial stages of development. Research in animals has indicated that neural grafting may provide beneficial therapeutic effects in some neurological disorders, 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. The research currently being conducted in this field is aimed at learning more about basic mechanisms involved in grafting tissues into the central nervous system (CNS) and the actions and effects neural grafts can exert there. Information is being sought in three broad areas:

- the conditions necessary for graft survival and incorporation into the host,
- the functional role grafted material can play in alleviating deficits caused by disease or injury, and
- the mechanisms by which grafts produce any functional recovery that is observed..

Scientists use many different kinds of experiments with animals to obtain this information. Some experiments are designed to gain information about basic mechanisms related to brain development, the brain's response to injury, and the regenerative capabilities of nervous tissue. Others examine the ability of grafts to ameliorate or reverse experimentally induced deficits. Still others use animal models that either replicate or share features of human disorders in order to determine whether grafting could result in improved function. Thus, experimental work in the field of neural grafting provides information about basic brain mechanisms as well as the role grafts can play in neurological disorders.

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. Animal models of a disease or injury can be either homologous (sharing a common origin with the human condition) or analogous (sharing similar organ damage, though not necessarily via the same disease mechanism). Currently, there are very few homologous models of human neurological disease. The closer an animal model is to the human condition under study (in terms of the neurological damage induced and the resulting behavioral effects), 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 grafting experiments.

Theoretically, the applications of neural grafting technologies into the brain and spinal cord could encompass many types of neurological disorders. The possible therapeutic applications of neural grafting range from the highly speculative to the actually implemented. This chapter provides an overview of some of the possible applications of neural grafting into the brain and spinal cord, the research that has been conducted so far, and the current status of each. In addition, the possible mechanism of therapeutic action of neural grafts for each condition is discussed. The neurological disorders are presented according to type, with an emphasis on those that have been studied most extensively.

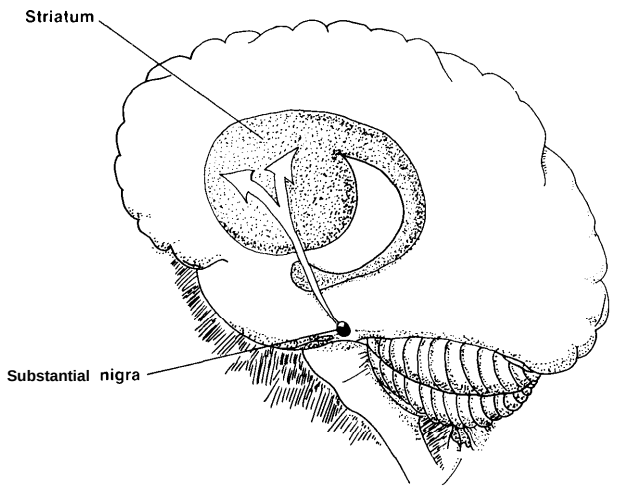
NEURODEGENERATIVE DISORDERS

Parkinson's Disease

The clinical use of neural grafting in the treatment of Parkinson's disease, begun in the early 1980s, has generated controversy in the scientific and medical communities. While more is known about neural grafting in Parkinson's disease than in any other neurological disorder, the efficacy of grafting in humans is unclear, and ethical concerns are unresolved. The concern about the discrepancy between the base level of knowledge and the actual clinical use of these procedures, even under experimental conditions, has increased public awareness of this controversy. This section provides a summary of the animal research and clinical use of neural grafting in persons with Parkinson's disease.

Parkinson's disease is well suited to the application of neural transplantation because the disease results from the degeneration of a discrete population of neurons located in an area of the brain called

Figure 5-l—The Substantial Nigra and the Striatum



The cells of the substantial nigra send their axons to the striatum. This pathway degenerates in Parkinson's disease.
SOURCE: R. Restak, *The Brain (New* York, NY: Bantarn Books, 1984).

the substantial nigra. These neurons produce dopamine, a neurotransmitter, and form synapses with neurons in another area of the brain, the striatum (figure 5-l). The neurons in the striatum are not destroyed in Parkinson's disease (67); however, the depletion of dopamine in the striatum, caused by the loss of cells in the substantial nigra, is associated with the symptoms of tremor, rigidity, difficulty in standing, and slowness of movement that are characteristic of Parkinson's disease. Neural grafting in Parkinson's disease has been aimed at correcting the loss of the dopamine-producing pathway between the substantial nigra and the striatum by either replacing the dying cells or supplying additional dopamine. To do this, neural grafting materials from two main sources have been used: 1) tissue from the adrenal gland and 2) tissue from the fetal CNS. A graft that would survive indefinitely could produce continuous relief from symptoms, but evidence suggests that the degeneration of the dopamine-producing neurons in the substantial nigra would continue. All research to date has been aimed at the ability of grafts to provide relief from symptoms and reduced disability, not cessation or reversal of the degenerative process.

The most obvious site for transplantation of dopamine-producing cells in Parkinson's disease would seem to be the locus of the degenerating cells, i.e., the substantial nigra. While cells placed in this site might receive some inputs from neurons in other areas of the brain that normally send fibers to the substantial nigra, axons from the grafted cells would have to grow several centimeters through the brain to connect with their targets in the striatum. Unfortunately, nerve fibers do not readily grow over such distances in the adult brain, and it has been shown that dopamine-producing grafts implanted into the experimentally damaged substantial nigra of rodents have no effect on the parkinsonian symptoms such damage causes (40).

Instead, dopamine-producing cells have been grafted (either as a cell suspension or as solid pieces) to sites close to their targets in the striatum, in order to facilitate formation of synapses. In fact, it is unclear whether the formation of synapses is actually necessary to produce an effect—it is possible that some of the effects of dopamine produced in the

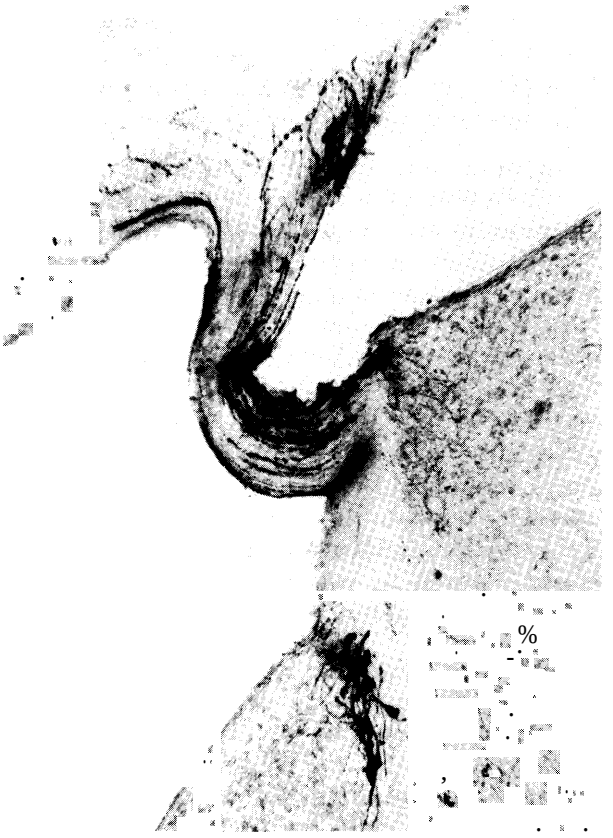


Photo credit: J.R. Sladek, Jr., University of Rochester Medical Center

Picture of a graft of monkey fetal tissue implanted into an adult monkey.

striatum by grafts may result simply from the diffuse release of chemicals in the area and thus do not require specific, point-to-point synaptic connections and precisely timed release.

Animal Research

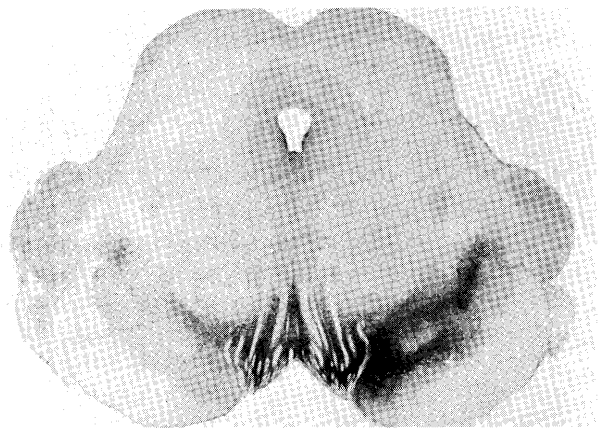
Fetal Tissue—The first indication that grafts might be effective in the treatment of Parkinson's disease was observed in experiments conducted in 1979 (19,1 19). These experiments used rats in which the pathway between the substantial nigra and the striatum had been destroyed by the neurotoxin 6-OHDA,[1] thus chemically affecting the same site that is thought to be central to the clinical signs of Parkinson's disease. Grafts of dopamine-producing neural tissue from rat fetuses, implanted into the striatum, were able to reduce some deficits caused by the wound (40,41); however, the extent and type of function that was restored depended on where in the striatum the graft was placed (40,41).

Since these initial experiments, many others using the same animal model have shown that implanted fetal tissue sends out fibers and makes contact with the host tissue, receives inputs from the host tissue, and performs typical neuronal functions within the host (3,20,54,55,103,131,139,141, 153).

Although some of the functional recovery produced by neural grafting may be due to the nonspecific release of dopamine into the host brain, studies have shown that much of the observed recovery is related to the extent to which the implanted tissue becomes incorporated within the host brain--i.e., the degree to which the graft sends connections to, and receives connections from, the host brain. This finding indicates that more than just a diffuse release of dopamine into the striatum is involved. In fact, when the graft is removed, the corrective effects disappear, suggesting that they are due to a direct action of the graft and not to an effect unrelated to it (17,42).

Dopamine-producing fetal tissue has also been studied in the MPTP model of parkinsonism (figure 5-2).[2] While it takes only days for MPTP to produce the symptoms of parkinsonism in laboratory animals, as compared to years for the disease itself in humans, most scientists still regard this as the best animal model of the disease (see box 5-A). Also, since MPTP is particularly effective in monkeys, it has provided scientists with an important primate model of parkinsonism. (Data derived from experiments using monkeys are more easily extrapolated to humans than are data from nonprimate animal models.) As with the 6-OHDA experiments, it was shown that grafted dopamine-producing fetal neural tissue can become incorporated into the striatum of treated monkeys and result in significant, long--lasting reductions in movement abnormalities, including tremor, rigidity, and slowness of movement (7,8,31,49,124,135). Recently, this effect of fetal tissue grafts in monkeys has been linked to the ability of the grafts to stimulate new growth from undamaged neurons (10).

Figure 5-2—Monkey Brain Exposed to MPTP



The brain of a monkey that was exposed to MPTP on one side. 'The substantial nigra on the unexposed side (right) is normal (black band). On the MPTP exposed side (left) the cells of the substantial nigra are destroyed.

SOURCE: R.A.E. Bakay, Section of Neurological Surgery, The Emory Clinic.

In Summary, a number of different studies have demonstrated that dopamine-producing fetal tissue can counteract some of the effects produced in the 6-OHDA and MPTP animal models of parkinsonism. In particular, some of the results seen following grafting in nonhuman primates treated with MPTP have been promising. However, in

[1] This analogous animal model is produced by the neurotoxin 6-hydroxydopamine (6-OHDA), which selectively destroys dopamine-producing neurons. In this model, the 6-OHDA is injected directly into the substantial nigra. While the lesion produced by this injection destroys the same neurons that are lost in Parkinson's disease, the action of the chemical and the temporal course of the neuron destruction do not mimic what occurs in the disease. Also, the functional deficits produced, while in some respects similar to those produced by Parkinson's disease, are not exactly the same.

[2] MPTP (1-Methyl-4-phenyl-1-2-3-6-tetrahydropyridine) is a chemical that, when administered, causes a syndrome similar to Parkinson's disease. Thus, the drug is said to result in parkinsonism rather than Parkinson's disease (see box 5-A).

Box 5-A—MPTP, a Key to Parkinson's Disease

On a July morning in 1982, a patient was brought into the emergency room of a hospital in Santa Cruz, California. He was stooped over and displayed the symptoms of rigidity and inability to initiate movement typically seen in persons in their sixties or seventies who have been suffering from Parkinson's disease for many years. The clinical picture was that of classic, late-stage Parkinson's disease. However, this patient was 24 years 014 and his symptoms had developed virtually overnight. With this startling patient began one of the most interesting and important chapters in the history of Parkinson's disease research and treatment.

A closer examination of this patient and five others who came to hospital emergency rooms in the northern California area at about the same time revealed that they were all heroin addicts who had injected some homemade narcotics that contained an impurity. The impurity was determined to be the chemical 1-methy1-4-phenyl-1,2,3,6-tetrahydropyridine, or MPTP. It was thought that the MPTP might have caused brain damage that mimicked Parkinson's disease, resulting in identical symptoms, This hypothesis was lent further credence by an autopsy report on another individual who had been exposed to MPTP. The report noted that the man's brain looked like that of someone who had suffered from Parkinson's disease for years: The dopamine-containing neurons in the substantial nigra, which are lost in Parkinson's disease, were destroyed. It was also found that when given L-dopa, the most common medicine for treating Parkinson's disease, the patients exposed to MPTP improved dramatically. However, the effectiveness of the L-dopa began to wear off after 2 to 3 years, just as it does in most Parkinson's patients after 5 to 10 years.

Immediately after the identification of MPTP as the agent responsible, scientists began to study the compound to find out how it causes this model of parkinsonism. They found that MPTP can enter the bloodstream through direct injection, inhalation, or contact with the skin. Inside the brain, an enzyme called monoamine oxidase B (MAO-B) breaks down MPTP into other chemicals, including an electrically charged molecule called methylpyridine (MPP+). The MPP+ molecules are taken up selectively by dopamine-producing neurons. It is thought that, once inside these dopamine neurons, the MPP+ may cause another chemical reaction to take place. This reaction produces toxic substances, such as peroxides, and other charged particles, called free radicals. The production of these substances destroys the cell. It was also found that if the breakdown of MPTP to MPP+ is prevented by blocking the activity of MAO-B, MPTP has no effect.

This understanding of the chemistry of MPTP has led to a new understanding of what might be occurring in persons with Parkinson's disease. It is possible that the same sorts of toxin-producing chemical reactions that MPTP causes in the brain occur in Parkinson's patients, What causes the chemical reactions to take place in the disease is unclear, but it may be some disruption in the normal biochemical activity of the dopamine-producing neurons. Indeed, it has been known for some time that MAO-B is also involved with the normal breakdown of dopamine in these cells. It is possible that this normal process gets disrupted somehow and that when the dopamine is broken down, peroxides and free radicals are produced. Based on these new MPTP data, a drug called deprenyl, which is known to block the action of MAO-B, was studied. It has been shown, at least in one study, that deprenyl appears to have a retarding effect on the progression of the disease. While this finding needs to be confirmed, it indicates how the information gained from the MPTP model of parkinsonism is giving scientists and doctors valuable new information about the disease,

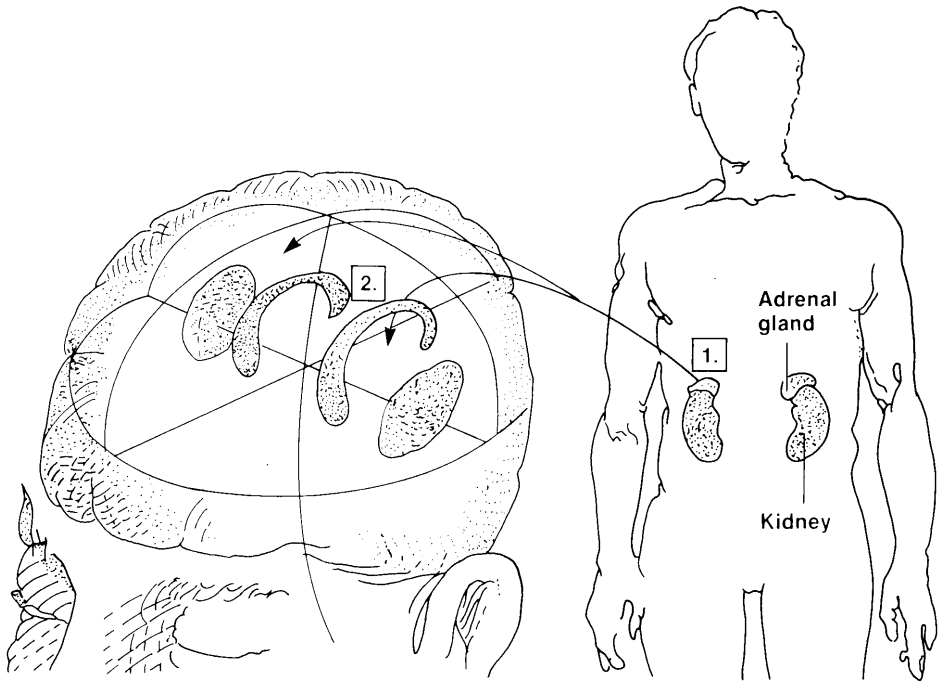
Another theory that has been proposed as a result of the discovery of MPTP is that Parkinson's disease might be caused by environmental exposure to MPTP or a chemical like it. While this is a possibility, no strong evidence of any link between the incidence of Parkinson's disease and exposure to MPTP in the environment has been found to date.

Interestingly, it has been found that MPTP does not affect all species. While it produces symptoms of parkinsonism in humans, nonhuman primates, and mice, it has little or no effect in rats, cats, rabbits, and a number of other species. The reason for this is not clear, but it is thought to be due to differences in the blood-brain barrier.

The discovery of MPTP has greatly advanced the understanding of Parkinson's disease. Not only has it provided important new insights into the possible mechanism that causes the disease, but it has given scientists an important and extremely useful new tool to study Parkinson's disease. The nonhuman primate MPTP model has been and will continue to be one of the best experimental tools for dete**rmining *the efficacy*** of the use of neural grafting to treat Parkinson's **disease.**

SOURCE: Office of Technology Assesstment, 1990.

Figure 5-3—Adrenal Medulla Neural Graft for Parkinson's Disease



Tissue from a patient's adrenal gland, which lies atop the kidney(1), is implanted into the striatum (2).
SOURCE: *Newsweek*, Apr. 14, 19S6, I.B. Ohlsson.

addition to the need to replicate and expand these findings, there is a need to answer the following questions by means of additional animal studies:

. Where in the striatum should material be grafted to achieve maximum effect?
• How long do the effects of the graft last?

Adrenal Medullary Tissue—There is considerable interest in finding alternative sources of dopamine-producing grafting material, for two reasons. First, there are ethical, legal, and technical obstacles to procurement of human fetal tissue for transplantation. Second, the use of autografts (tissue from the person's own body) eliminates possible immunological rejection of the graft. While other types of tissue for autografts have been studied [sympathetic ganglia, carotid body glomus cells, (15,83)], tissue from the medulla of the adrenal gland has attracted the greatest interest. In animal experiments, the adrenal tissue is collected from donor animals; in humans with Parkinson's disease, the patient's own adrenal tissue can be used for the graft (figure 5-3).

The efficacy of adrenal tissue is more uncertain than that of fetal CNS tissue. Questions have been raised about how effective adrenal tissue is in producing fictional recovery, what mechanism induces functional effects, and whether any observed functional effect is actually due to a direct effect of the graft or to some other factor.

Implantation of adrenal medullary tissue can ameliorate some of the deficits created in the 6-OHDA model in rodents; however, the range of functions recovered is narrower than when fetal tissue is used (52,96). The beneficial effects are thought to result from either a nonspecific, diffuse release of dopamine by the adrenal cells (53) or an increase in the number of new dopamine fibers near the graft site (112). The latter presumably reflects the degree to which the grafted adrenal medulla cells are converted into neuron-like cells that produce dopamine.

The number of adrenal cells that survive implantation is very low in both rodents (15) and monkeys (1 1,75,108). If the cells do not survive, the chance of functional recovery is small and any long-term

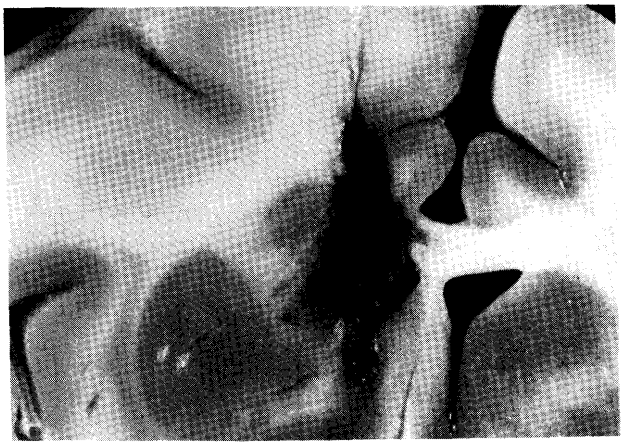


Photo credit: R.A.E.Bakay, The Emory Clinic

Section of a monkey brain showing a surviving graft of adrenal medulla tissue that was implanted along with other tissues that produce neurotrophic substances.

recovery that does occur is probably due to some effect unrelated to continued graft function. Adrenal cell survival is enhanced when neurotrophic factors, including nerve growth factor (NGF), are added to the graft site (16,88,140). In monkeys, increased fictional recovery is observed when adrenal cells are grafted along with cells that produce neurotrophic factors (88), although it has been observed in rats that the same level of functional recovery occurs when NGF is given in conjunction with either adrenal grafts or grafts of nondopamine-producing material (121). This suggests that the functional recovery observed in the latter case resulted, in part, from activation of the brain's injury response mechanisms due to surgical injury (including release of growth factors) and the nonspecific action of NGF to promote axon growth.

Another issue surrounding adrenal tissue grafts is the influence of donor age on graft efficacy. Grafts from younger rats are more effective than those from older rats in promoting functional recovery following destruction of dopamine-producing cells with 6-OHDA (51). Also, older tissue is less likely to undergo the conversion from adrenal medulla cells to dopamine-producing neurons (9). This may be due to a lack of growth-promoting factors, perhaps NGF, in the older tissue. When NGF is administered to rats in conjunction with grafts of older adrenal tissue, more conversion of cells to dopamine-producing neurons is seen and a greater improvement in movement occurs (140). Since many Parkinson's disease patients are elderly, donor age may be one reason for the limited effect of adrenal autografts used in these patients (see later discussion).

The data collected on adrenal grafts in the MPTP nonhuman primate model of parkinsonism agree with the data obtained in 6-OHDA experiments with rats. As noted previously, only limited survival of grafted tissue following implantation has been observed (11,75). This raises the question of what is responsible for the functional recovery that has been seen. New dopamine fibers growing in the host brain (47) and functional improvement (11) have been observed in both grafted animals and animals that had the surgery performed without tissue implantation. This suggests that the surgical procedure itself has some effect. As was true of the rats, the degree of functional recovery in nonhuman primates is less with adrenal medullary tissue than with fetal CNS tissue (100).

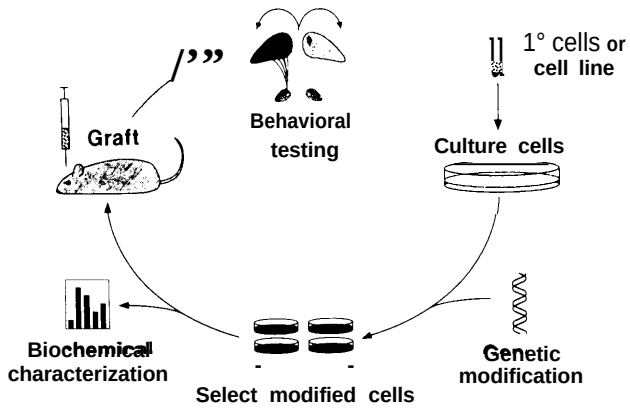
In summary, the ability of adrenal medullary tissue to ameliorate the deficits caused in animal models of parkinsonism is unclear. Questions that need to be answered include:

- Are the functional improvements that have been observed the result of the adrenal graft or the surgical procedure?
- If adrenal grafts do have a beneficial effect, what is the range of deficits that can be improved?
- What role can concomitant application of growth-promoting factors play in the survival and efficacy of adrenal grafts?

Genetically Engineered Cells-Genetically engineered cells have been shown to survive grafting into the CNS (58). The ability of genetically manipulated cells to decrease the abnormal behavior caused by administration of 6-OHDA to rats has recently been investigated (151). Certain skin cells, called fibroblasts, were taken from rats and genetically modified to produce the enzyme tyrosine hydroxylase (TH), which is required for the production of dopamine (figure 5-4). It was hoped that inserting these cells into the 6-OHDA rats would cause the animals to produce dopamine and thus reduce their abnormal behavior. The grafts of the genetically engineered cells did reduce abnormal behavior, by about 40 percent.

Although this important study indicates that genetically altered cells might be an effective grafting material, it was noted that the extent of

Figure 5-4-Grafting Genetically Modified Fibroblasts



The process of grafting genetically engineered fibroblasts consists of: 1) culturing the fibroblasts, 2) genetically modifying them, 3) selecting which cells to use, 4) testing them, 5) grafting into the brain, and 6) behavioral testing of the animal to determine the effect of the graft.

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

recovery was less than that which has been observed when fetal CNS tissue is used. One possible reason for this difference is that the manipulated cells do not produce as much dopamine as normal fetal brain cells. Nonetheless, since the use of genetically manipulated cells lines would circumvent the problems associated with fetal tissue and the immunological considerations connected with other sources, continued exploration of their use is an important area of research.

Human Application

Human trials of neural grafting in persons with Parkinson's disease have used both adrenal and fetal CNS tissue. In both cases, some observers have held that the trials were premature (137). 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 animal experiments. This question may place scientists who are doing the research at odds with patients and doctors, who must deal with the realities of devastating illness on a daily basis. The participants in this debate include scientists performing basic research, desperately ill patients who are willing to undergo virtually anything that might help them, and clinicians, who are motivated by the altruistic desire to help their patients and, perhaps, by the ambition to be on the cutting edge of a new and exciting field.

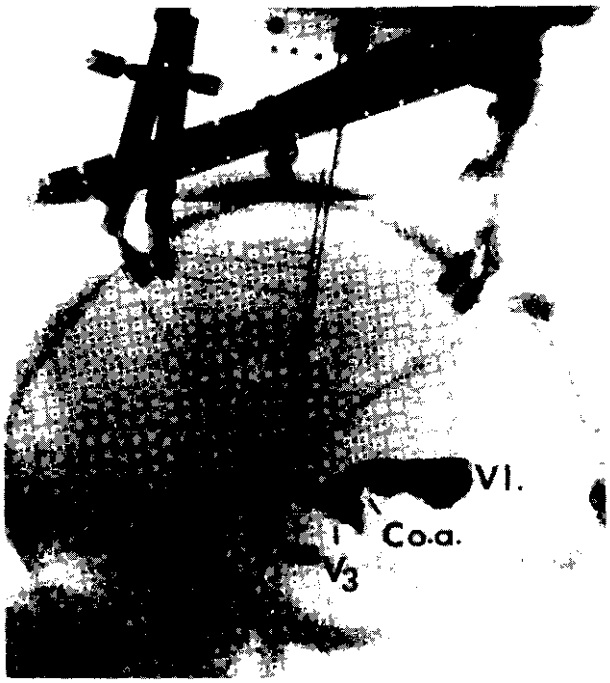
As of 1990, between 300 and 400 persons with Parkinson's disease had received neural grafts worldwide. About 100 of them have been implanted with fetal CNS tissue, the remainder with adrenal tissue. In the United States, approximately 130 patients have been treated with adrenal tissue, while fewer than 10 have had fetal tissue implants. The use of fetal tissue for implantation in this country is limited to privately funded ventures because of the moratorium on Federal funding for such research (see app. A).

Surgical Procedures--Implantation of adrenal or fetal tissue into the brain can be done using either a stereotactic or an open surgical approach. In a stereotactic procedure, the tissue is implanted by means of a long needle inserted into the brain through a small hole made in the skull; this procedure is guided by various computer-assisted imaging procedures and brain scans (figure 5-5). In an open surgical procedure, the area where the graft is to be placed is exposed so it can be seen by the neurosurgeon. This procedure, therefore, is more invasive than the stereotactic procedure. In addition, a patient undergoing an adrenal transplant must also undergo surgery to remove one of his or her adrenal glands for implantation.

Most stereotactic procedures are performed under local anesthesia, although general anesthesia is sometimes used. Implantation of tissue using a stereotactic procedure usually takes 1 to 1 1/2 hours. Following surgery, patients are often observed in a neurological intensive care unit overnight in case surgical complications develop. Provided there are no complications, the patient could recover from the operation within 24 to 48 hours and be fit for discharge a few days after that. In the case of experimental procedures, however, it is likely that the patient would be kept in the hospital longer, for observation and for comprehensive testing.

While an open approach is more invasive, it provides more flexibility in the way graft tissue can be implanted. A general anesthetic is given, and a portion of the skull is removed. For grafting in Parkinson's disease patients, the surface of the striatum is exposed by incising the overlying brain

Figure 5-5-Stereotactic Surgery



An X-ray of a patient in a streotactic apparatus.
SOURCE: E.A. Spiegel, *Encyclopedia of Neuroscience, vol.* II, G. Adelman (cd.) (New York, NY: Birkhauser Boston, 1987).

tissue; a cavity is made on the surface of the striatum, and the graft tissue is placed into that cavity. Sometimes the graft is held in place by surgical staples or by a covering of a specially treated material. The piece of bone that was removed from the skull is replaced, and the scalp wound is closed. This operation generally takes 3 to 4 hours. The patient is usually returned to the neurological intensive care unit for observation. In general, recovery from the operation takes several weeks.

When adrenal medullary tissue is used for grafting, one of the patients two adrenal glands has to be removed. This procedure is called an adrenalectomy. Since the adrenal gland lies atop the kidney, its removal requires abdominal surgery. Access to the adrenal gland is obtained through an incision in either the abdomen or the side of the patient. Normally, an adrenalectomy is performed by a surgeon working in tandem with a neurosurgeon, who is simultaneously preparing for the implantation. In the future, techniques such as cryopreservation may make it possible to retrieve the adrenal tissue, preserve it, and then wait until the patient has recovered from the abdominal surgery before performing the grafting procedure.

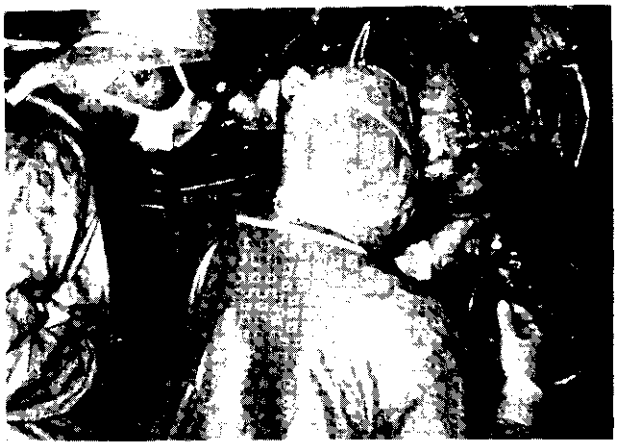


Photo *credit: R.A.E. Bakay, The Emory Clinic*

Adrenal medulla graft surgery.

Thus far, the majority of patients who have received adrenal grafts have had both the adrenalectomy and the brain surgery done at the same time. The procedure is quite debilitating, and recovery takes a long time, often weeks. Patients may also experience the surgical complications that can accompany abdominal surgery and neurosurgery. Based on the results presented by different groups in the United States that have done adrenal grafts, the mortality rate and the rate of complications have each been estimated at 5 to 10 percent (100).

Adrenal Medulla Grafts—Based on the early success obtained in rodent experiments using adrenal tissue, the first grafts of adrenal medullary tissue in humans were performed on two Parkinson's patients in Sweden in 1982; both patients had been experiencing severe fluctuations in the management of their disease by medications (the so-called on-off phenomenon[3](5). In a subsequent study, two additional patients were operated on (97). In all four patients, a stereotactic technique was used to transplant medullary tissue from the patient's own adrenal gland into the striatum on one side of the brain. These patients showed minor improvements in motor function that lasted for about 2 months. By

[3]The on-off phenomenon refers to sudden and unpredictable shifts between periods in which the symptoms of Parkinson's disease are waler control (on), and periods in which they are severe and uncontrolled (off). This occurs regardless of when and how much medication patients aregiven.It is thought that the phenomenon results from the continued progression of the disease. Most patients will eventually experience dose-related fluctuations in their symptoms, but the on-off phenomenon is more rare.

6 months, no positive effects remained. No adverse effects of the procedure were reported. Long-term followup of these patients has not shown any influence of the transplant on the course of the disease (96). In the face of these modest effects and the simultaneous development of the MPTP primate model of parkinsonism, it was widely considered that further animal research was needed before attempting additional grafts in patients.

In 1986, however, a group in Mexico conducted similar grafting experiments on patients with Parkinson's disease. These experiments differed from those done by the Swedish group in that the adrenal grafts were performed using an open surgical procedure and the tissue was placed into the brain in a slightly different fashion. Furthermore, the patients were generally younger and in a less advanced stage of the disease. In 1987, the Mexican group reported dramatic and persistent improvements in the first two patients (102). The surgeons placed several fragments of adrenal tissue into a single cavity on the surface of the striatum on one side of the brain and anchored them with miniature staples. Improvements in muscle movements were seen almost immediately after recovery from surgery, with continued improvement over the next 10 months. In a second report, in 1988, the outcomes for the Mexican group's first 11 grafting patients were described (38). All patients (ages 35 to 65) were said to have improved in gait and writing capability; tremor and rigidity were lessened and movement was improved in most cases; and medication could be reduced in all. The Mexican group has now performed the operation on more than 40 Parkinson's disease patients. Four of the patients have subsequently died (the relation of death to the surgery is not clear); no postmortem confirmation of surviving adrenal cells has been reported.

Despite the discrepancies between the Mexican and Swedish results, the 1987 Mexican report led to a torrent of adrenal medullary operations on Parkinson's patients around the world. Approximately 300 operations using adrenal medulla autografts have been carried out worldwide. In many of these operations, the neurosurgeons attempted to follow the procedure of the Mexican group, with only minor modifications. A detailed observation of 19 patients over a period of 6 months in Chicago, Tampa, and Kansas City has been published (69,1 18). A modest reduction in these patients' off periods (when symptoms are most severe) was found, but the patients were still disabled by the disease. Also, the grafting procedure did not permit dosages of their medications to be decreased. Frequent medical complications were associated with the procedure. A followup study of 7 of the 19 original patients reported that, 12 months after their operations, the overall amount of on time was increased and the severity of symptoms during off time was decreased (71).

Other studies, including one involving a group of 18 patients treated in Nashville (1) and several involving smaller groups of patients (2,94,95, 117,148), have been published or presented in abstract form at scientific meetings. They have reported variable results with the use of adrenal grafts. In an effort to establish a centralized repository for the data collected from these procedures, two registries have been established (see box 5-B). The results collected by each of these registries have been published (6,70), with the data from some centers included in both reports. One registry indicated that there was "a rather diffuse response with a general trend for improvement, but mostly modest improvement" (6) 1 year following surgery, and the other reported a statistically significant decrease in disability, as indicated by an increase in on time and less severe symptoms during off periods 1 year after surgery (70). Neither registry found that it was possible to decrease the medication patients received, and both reported a number of postoperative complications. The complications, which in some cases were transitory (lasting less than 3 months) but in others persisted for as long as a year, included respiratory problems, pneumonia, urinary tract infections, and a number of transitory psychiatric problems, including hallucinations or delusions, sleepiness, and confusion.

Data from both registries clearly show that there are fewer complications associated with removal of the adrenal gland through the patient's side as opposed to the abdominal cavity and by stereotactic placement of the tissue into the brain versus an open neurosurgical approach. Older, more severely affected patients were more likely to have adverse effects and less likely to benefit from the procedure, leading to the conclusion that, based on the data collected thus far, the ideal patient ". . . would be less than 55 years of age and only moderately disabled" (6). The mortality rate according to the data collected by one of the registries was 10 percent, though not all the deaths were thought to

Box 5-B—The Use of Registries To Collect Data

In 1987, in an attempt to document the activity occurring in the field of adrenal-neural grafting, the American Association of Neurological Surgeons (AANS), in collaboration with the National Institute of Neurological Disorders and Stroke (NINDS), established the General Registry of Adrenal-Fetal Transplantation (GRAFT'). Like the National Heart Transplant Registry established in the early 1980s to track the work being done in heart transplantation, the idea behind GRAFT is to provide a central clearinghouse where researchers in the field can send their data so that sufficient information can be collected to evaluate the various methodologies being used. Following the report from Mexico of successful adrenal grafting in persons with Parkinson's disease, a number of centers began trying to replicate the results. These studies usually involved small numbers of patients and used various modifications in the surgical technique. It was thought that, by pooling data from the various sources, an ongoing analysis could be performed . . of the evolving transplantation experience to document the potential risk factors and to guide future studies" (Bakay et al., in press).

At about the same time that GRAFT was established, the United Parkinson Foundation (UPF) announced formation of its own registry. In order to avoid duplication and competition between the two groups, it was decided that the focus of the two registries would be different. GRAFT would focus on safety, efficacy, and surgical issues by collecting data from as many centers as were willing to participate. The UPF registry would collect data from a smaller, more uniform group of investigators. Due to different methods of data acquisition, the UPF would be able to make a more quantitative evaluation of efficacy, as opposed to GRAFT, which would have to rely on qualitative measures of efficacy. As a result of this arrangement, some research teams have contributed data to both registries.

As of mid-1990, the GRAFT registry had collected data on 135 patients from 24 centers. Most are from the United States, with two centers each from Canada and South America and one from Europe and Mexico. The database includes preoperative information on demography, medical history, and prior treatment of parkinsonism, as well as qualitative evaluation of patients' responses to the procedure and complications at 3, 6, and 12 months after the operation. Followup information more than 1 year later is currently being collected.

The UPF registry has collected information on 61 patients from 13 centers in the United States and Canada. The same kind of demographic information was collected, but the pre- and post-operative data were collected in a more uniform manner: All the centers were asked to analyze the patients and their responses to the surgical procedure using the same rating scale. This made it possible to compare and evaluate the data from all the centers more easily. These data were collected 12 months tier the operation,

The l-year data from both registries have been published and both registries are continuing to collect information. Registries are an effective way of collecting and comparing information derived from a variety of sources in order to evaluate progress in the development of a surgical procedure. Their success depends on the willingness of investigators to supply their data and in some cases to comply with requests to collect data using standardized methods. When these criteria are met, data from registries are invaluable guides for future investigations.

SOURCES: R.A.E. Balmy, G.S. Allen, M.L.J. Apuzzo et al., "Preliminary Report on Adrenal Medullary Grafting From the American Association of Neurological Surgeons GRAFT Project," *Progress in Brain Research, in* press; C.G. Goetz, G.T. Stebbins, H.L. Klawans et al., "United Parkinson Foundation Neurotransplantation Registry Multicenter United States and Canada Database Presurgical and 12-Month Followup," *Proceedings of the Third International Congress of Neurotransplantaion: Cambridge (Amsterdam:* Elsevier Science Publishers, 1989).

have been due to the surgical procedure (70). The overall level of improvement and number of complications observed led to this summary of the data collected by both groups:

> This strongly suggests that there is an effect from the transplantation, although the effect inmost cases is not very dramatic. The mild-to-moderate improvement would be more enthusiastically received if the surgical morbidity were less (6).

The original Swedish results also inspired a series of adrenal medullary autografts in Beijing, China, beginning in 1986. The Chinese group used a stereotactic technique similar to that of the Swedish group, but it used a larger total mass of implanted tissue and administered antiparkinson drugs after the operation. Substantial improvements in movement and lessening of rigidity and tremor were observed in the first four patients for at least 6 months after surgery. To date, this group has operated on at least 10 patients, with claims of varying degrees of improvement in all cases (84). However, some scientists believe that it is difficult to interpret and compare the results of this study and others (60,143)

due to differences in the methods used for assessing benefit to patients and in the medical treatment they received pre- and post-operatively.

Adrenal medullary autografts have also been performed in the United States in a small number of patients with progressive supranuclear palsy (PSP), a neurodegenerative disorder marked by loss of neurons at various locations in the brain, including the substantial nigra. PSP, though much less common than Parkinson's disease, has many of the same symptoms, including difficulty in moving and standing up. The disease is invariably fatal and there are no satisfactory pharmacological therapies. One report (87) described three patients with PSP who had tissue from one of their adrenal glands grafted into the striatum. Only one of the three patients showed a small degree of improvement, mostly in his ability to stand. The authors conclude from these data that "adrenal medullary transplantation has only limited efficacy in progressive supranuclear palsy.'

To date, the success reported by the Mexican group in 1987 has been difficult to replicate. The reason for this is unclear. Questions about diagnostic and other criteria used for inclusion of patients, the methods used to measure the severity of the disease preoperatively, the handling of the patients' medications, and the methods used to quantify the improvements in movement that were observed have been raised about the Mexican study.

Based on the available data, the efficacy of adrenal medulla autografts is unclear. The relative effectiveness of the various open and stereotactic procedures used, their modes of action, and the existence of surviving, functional adrenal medullary cells have not yet been conclusively established. The efficacy of adrenal grafts has yet to be demonstrated in experiments using nonhuman primates, and the human clinical data are inconsistent, with several studies suggesting that there may be only minimal, perhaps transitory, improvement. Judging from animal experiments and the small amount of postmortem human data available, the ability of adrenal tissue to survive in the brain seems to be limited (80,120). Survival may be improved by concurrent administration of growth-promoting factors, but this needs to be explored further in the laboratory. If adrenal tissue does not survive, it is unclear whether any observed improvement is the result of the graft or of nonspecific effects. The observation made in many of the clinical trials that improvement was

Photo credit: R.A.E. Bakay, The Emory Clinic

Dissecting tissue to be used as a graft.

seen on both sides of the body when the graft was placed in only one side of the brain also suggests a general effect, perhaps circulation of graft-related factors in the cerebrospinal fluid, rather than a direct action of the graft. Additional animal experimentation can provide more information and help answer these questions. Regarding the use of the procedure in humans, the adrenalectomy and open neurosurgical procedures most widely used are associated with risk of severe complications in older, more profoundly afflicted patients. Also, the best age for donor tissue and a clarification of which Parkinson's patients are most likely to benefit fromthe procedure needs to be delineated.

Fetal Neural Tissue-Only about 100 persons worldwide have received grafts of fetal CNS tissue for the treatment of Parkinson's disease. Clinical trials with such tissue are going on in Sweden, England, Mexico, the People's Republic of China, Czechoslovakia, Spain, and Cuba. Approximately 10 patients have undergone the procedure in the United States. While the results of some of these procedures have been reported at various scientific and medical meetings, there are very few published

Some of the most thoroughly documented research has been conducted in Sweden, where two patients underwent this procedure in 1987 (100).

Dopamine-producing tissue from four human fetuses, 7 to 9 weeks (postconception) of age, was implanted as a cell suspension, stereotactically, on one side of the brain in each patient. Both patients received drugs to keep the graft from being rejected. Up to 6 months after the operation, although both patients showed some minor improvement in how quickly they could move and how well they responded to a single dose of antiparkinson drugs, the scientists reported that ". . . no major therapeutic effect from the operation was observed" (96). This same research group reported a greater degree of improvement in another patient, for whom they used different methods of handling and implanting the fetal tissue and thus may have increased the ability of the graft to survive (99). This patient exhibited a lessening of his symptoms and an increased response to his medications for the 6 months he was observed after the surgery.

Other positive results have been reported from groups in Mexico and England, but these reports have not been in the form of published papers in scientific journals providing information on how the procedure was performed, what criteria were used for assessing patients pre- and post-operatively, and giving all the details necessary to analyze the results.

In the United States, observations of a patient who was operated on in Colorado in November 1988 were reported 15 months after the operation (50). In this case, drugs to prevent graft rejection were not used. Some improvement in movement and motor coordination was observed in this patient, and the patient has reported increased ease in doing daily tasks (cutting food, brushing teeth, and so on). Also, the patient's medication could be decreased without any adverse effects. While the investigators involved state that the patient is not cured, they believe that the implants can reduce disability, smooth out medication-related fluctuations in symptoms, and increase mobility.

The limited data collected to date suggest that fetal CNS grafts may have a beneficial effect in controlling some of the symptoms of Parkinson's disease. However, more information must be derived before an ultimate determination of the efficacy of this procedure can be made. How long the grafted tissue survives, the optimal placement of tissue in the striatum, and the time course for seeing an improvement are unknown. Additional animal research can answer these questions. Then the details of how much tissue is needed to achieve a worthwhile therapeutic effect and the susceptibility of the grafted tissue to immunological rejection and to the underlying destructive mechanism of Parkinson's disease can be derived from human experimentation. As stated by the Swedish research group:

> Although our findings support the idea that neural grafting can be developed into an effective therapy in Parkinson's disease, further work is necessary to optimize the transplantation procedure. . . (99).

What Is the Next Step?

Whether clinical neural grafting experiments should continue before additional data are gathered from animal experiments is still a subject of scientific debate (93). In the case of adrenal tissue grafts, the lack of replication of successes and the lack of a solid basis in animal experimentation have made many persons in the medical and scientific communities retreat from the rush of enthusiasm that accompanied the initial reports.

The effectiveness of fetal tissue grafting in animal models and the initial reports of some success with its use in humans indicate that fetal tissue grafting may have a more solid scientific basis than adrenal grafting. The question that now arises is how to proceed from here. Many persons in the scientific and medical communities feel that the questions concerning fetal CNS tissue grafting can best be answered with additional basic animal research, coupled with limited human experimentation. Then expanded human trials could proceed to determine whether fetal CNS grafts area genuinely efficacious treatment for persons with Parkinson's disease. This evaluation has been expressed in the following statement by two prominent scientists:

> . . . too many questions remain unanswered about the use of embryonic nerve cells to propose anything more than limited fetal grafting in humans as a requisite next step. Although scientifically it seems logical to proceed, considerable information is needed before therapeutic success might be predicted . . . . We are still at a stage at which basic scientific studies are needed to elucidate important details. . . (60).

When clinical experiments do proceed, it will be necessary to standardize their designs, the criteria used for assessing pre- and post-operative levels of disability, and the methods of reporting results. For the most part, this has not been done in the clinical experiments carried out so far, making it difficult to interpret and compare studies.

Beyond the scientific issues, the legal and ethical controversies that surround the use of fetal tissue could impede the initiation of clinical trials. In the United States, the Federal ban on funding of transplants using human fetal tissue from induced abortions will limit clinical research (see app. A).

Huntington's Disease

Huntington's disease is a genetic disorder, the major pathological hallmark of which is a loss of neurons in the striatum. Symptoms of the disease include abnormal movements, especially of the face and extremities, and a progressive deterioration in mental ability. Unlike Parkinson's disease, where only one population of cells dies, Huntington's disease involves the destruction of several populations of neurons, generally located in the striatum, that contain different neurotransmitters. An animal model in which chemicals known as excitotoxins are used to destroy the cells in the striatum[4] has been employed to see whether implantation of fetal striatal tissue could reverse some of the deficits caused by the injury. This animal model exhibits some of the same characteristics as persons suffering from Huntington's disease (e.g., abnormal movements, inability to respond to sensory stimuli, and deficits in learning and memory). In most of these experiments, grafts have been inserted in hopes of replacing the lost striatal neurons rather than supplying a single neurotransmitter, as in the Parkinson's disease research.

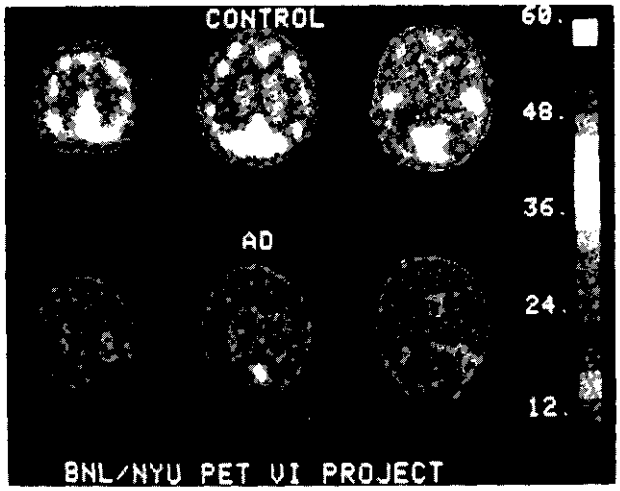
Studies have shown that rat fetal striatal tissue can survive following implantation into the striatum of adult rats that have been injected with excitotoxins (114). These grafts have also been shown to decrease some of the abnormal movement (36,66,81,129) and learning and memory deficits (35) produced in this model; however it has been reported that the animals' behavior is not returned to normal (114).

The mechanism by which the fetal tissue grafts act is not entirely clear. There are two possibilities. First, the grafted tissue may grow into the host brain, forming synapses and thus directly and actively play a role in the function of the striatum. Experimental evidence to support this includes the need for an intact, undamaged graft (66) at a specific region of the striatum in order to achieve a functional effect (82) (indicating the importance of graft integration into the host), coupled with the observation of an interaction between host and grafted tissues (128,147). The second possibility is that the grafted tissue could be exerting a growth-promoting effect that causes the undamaged parts of the host striatum to grow and assume some of the fictional activity of the damaged parts. Experimental evidence supporting this idea includes the conflicting observations that integration does not occur (101,146) but a functional effect may nevertheless take place (113) and that fetal grafts may be able to protect against excitotoxins (145) [although this has not been conclusively proven (11 l)]. Although the majority of the evidence indicates that grafts do integrate into the host, the data preclude an unequivocal statement. The possible role of fetal striatal tissue in the treatment of Huntington's disease must await further elucidation of both the graft's mechanism of action and the underlying mechanism of the disease itself.

There has been one report, not published in a research journal, that grafting of rat adrenal medulla tissue into the rat striatum can protect neurons against the destructive action of excitotoxins (132). Since one theory holds that excitotoxins may be involved in Huntington's disease, adrenal tissue could possibly play a role in treating this disorder. Despite the lack of conclusive evidence to support this hypothesis, a patient with Huntington's disease has received an adrenal medulla autograft (132). It was reported that the patient received no beneficial effect from the procedure. At this time, there is no evidence to support the idea that adrenal tissue can ameliorate any of the symptoms associated with Huntington's disease: the role of excitotoxins in the disorder has yet to be clarified, and the effect of adrenal tissue on the action of excitotoxins has yet to be proven.

[4]In this model, excitotoxins (kainic acid, ibotenic a@ quinolinic acid) are injected directly into the striatum. These toxins stimulate sites 011 neurons that are normally activated by certain neurotransmitters; however, these acids activate the cells so much (hence the name "excito") that they kill the cells. Whether these excitotoxins are actually involved in Huntington's disease in humans is unclear.

Figure 5-6-Brain Activity in an Alzheimer's Disease and a Normal Brain



Brain scans showing the activity (white areas) in a normal brain (control) and the brain of an Alzheimer's disease patient (AD). The scan of the Alzheimer's disease patient shows that many areas in the brain are not functioning properly.
SOURCE: R. Restak, *The Mind* (New York, NY: Bantam Books, 19S8).

Alzheimer's Disease

Unlike Parkinson's or Huntington's diseases, in which there is either a loss of a specific population of neurons or localization of cell destruction in one region of the brain, Alzheimer's disease involves a much more diffuse loss of neurons and affects a number of different groups of cells (figure 5-6). Cells in the front of the brain that contain the neurotransmitter acetylcholine and cells in the middle of the brain that contain norepinephrine are particularly affected in Alzheimer's disease. The acetylcholine-containing areas are involved with memory and learning, while the norepinephrine-containing regions are thought to be associated with controlling moods. Destruction of these areas results in the dementia and depression that are characteristic of Alzheimer's disease. Due to the diffuse nature of the damage in Alzheimer's disease, it is thought that if neural grafts have a role, it maybe to supply growth-promoting substances or to supply lost neurotransmitters rather than to replace lost structures.

At present there is no fully satisfactory animal model of the symptoms of Alzheimer's disease. The closest is aged monkeys, which can exhibit some of the memory and cognitive deficits or abnormal changes in brain cells, or both, seen in persons with Alzheimer's disease (122). To date no neural grafting experiments have been conducted on such monkeys; however, experimentation has been conducted on aged rats and rats that have had injuries made in the same areas of the brain that are destroyed in Alzheimer's disease. These animals exhibit some of the same types of memory and learning problems seen in humans with the disease, even though they do not truly mimic Alzheimer's disease.

To create animal models, wounds are made in some of the same areas of the front or middle part of the brain that are destroyed in Alzheimer's disease or in the pathways that connect these areas to other parts of the brain.[5] The result is that the animals have difficulty learning and remembering certain tasks, such as running through a maze. When rat fetal tissue is grafted into wounded adult rats near the areas to which the acetylcholine fibers project, the grafts take hold and there is a partial improvement in the rats' ability to learn and remember specific tasks (42,43,48,86,150). This occurs if the fetal tissue implanted is taken from areas in the fetal brain that correspond to the wounded areas in the adults. Similar results have been observed in adult rats when either grafts of fetal tissue from mice (32) or cultured cells that naturally produce acetylcholine (89) were implanted.

The ability of acetylcholine-producing grafts to reverse memory deficits caused by the ingestion of alcohol has also been examined(4). Large quantities of alcohol cause brain damage in rats, as in humans, especially in the regions of the cortex and hippocampus containing acetylcholine; this damage causes memory and learning deficits. When acetylcholine-producing tissue from the front part of the brain is implanted into either the cortex or the hippocampus of rats given alcohol, the deficits decreased. This does not occur when other tissue, not containing acetylcholine, is grafted. It is postulated that the positive effects are due to the increased supply of acetylcholine into the cortex and hippocampus.

[5]The acetylcholine-containing cells in the front part of the brain send their fibers to the hippocampus and specific parts of the cerebral cortex. Both the hippocampus and these cortical areas are very important in mediating learning and memory. The norepinephrine-containing neurons in the middle of the brain also connect to cortical areas. The wounds result in the loss of these acetylcholine or norepinephrine pathways and the cells giving rise to them.

Aged rats are also known to have more difficulty learning certain types of tasks than younger animals. Implantation of acetylcholine-producing fetal tissue into the hippocampus (56,57) or norepinephrine-containing fetal tissue into 'the middle of the brain (30) improves the performance of some aged rats on certain learning and memory tests.

It is thought that the grafts in these studies exerted their effect by releasing acetylcholine or norepinephrine into the brain. While the research conducted to date has provided invaluable information about the ability of neural grafts to decrease experimentally induced deficits in cognitive performance and deficits in learning and memory in aged rats, the extrapolation of that information to patients with Alzheimer's disease is problematic. These models share, at best, only a few characteristics of the disease. In addition, when injuries are produced in experiments, they are very specific to the area that is damaged, whereas in Alzheimer's disease the damage is not restricted to a single group of neurons.

Since acetylcholine-producing cells are one of the major populations of cells affected in Alzheimer's disease and nerve growth factor (NGF) is known to act on acetylcholine neurons, investigators have studied the ability of NGF to protect these cells. The implantation of cells that have been genetically engineered to produce NGF has been shown to prevent the acetylcholine neurons in the front part of the brain from dying following destruction of the pathway that connects them to the hippocampus (127) and other areas of the brain (45). In addition, the protected cells apparently started to grow new fibers in the direction of the implanted NGF-producing cells. Whether NGF can affect the progression of Alzheimer's disease is a question being investigated extensively.

A number of important points must be addressed before the potential value of grafting therapy in Alzheimer's disease can be determined. A better understanding of the mechanisms underlying the disease is needed in order to determine the types of graft tissue likely to have the broadest possible effect on the disease. Also, development of a valid animal model of the disease or its symptoms is necessary.

Motor Neuron Disease

Motor neuron disease (MND) is a family of disorders marked by degeneration of neurons located in the spinal cord and brain that are involved with regulating movement. Probably the best known MND is amyotrophic lateral sclerosis (Lou Gehrig's disease).

As in some other neurodegenerative disorders, such as Parkinson's and Huntington's diseases, the hallmark of MND is a selective loss of certain populations of cells. Since Parkinson's and Huntington's diseases are thought to be candidates for symptom amelioration by neural grafting, it can be speculated that persons with MND may also benefit from this procedure. The same strategy of replacing the lost cell populations with grafts may be applicable. The ability of fetal spinal motor neurons to become incorporated into the spinal cord of an adult has been demonstrated in rats (134) and mice (37). To date, no research on the ability of neural grafts to restore functional deficits caused by induced injuries to these cell populations has been conducted. Whether MND would be at all amenable to this therapeutic strategy is purely conjectural. The fact that the populations of cells lost in MND are distributed throughout the spinal cord and the brain may be a hindrance to the effective use of implants. It is also possible that the mechanisms involved in the development and progression of MND are such that graft technologies would not be suitable.

CENTRAL NERVOUS SYSTEM INJURY

Spinal Cord Injury

Injury **to the** spinal cord occurs most often when the bones of the spinal column (vertebrae) are pushed into the soft neural tissue of the spinal cord, bruising or tearing it. This ensues when a strong, rapid, mechanical force is applied to the back or neck, as can occur in automobile collisions or sporting injuries. Incidents such as these are the leading cause of spinal cord injury. Damage to the spinal cord can also be caused by a projectile or knife wound. In such cases the amount of tissue damaged is directly related to the strength of the force applied. A third cause of damage to the spinal cord is disruption of its blood supply or gradual compression (caused by various types of intruding bodies, such as tumors or blood clots).

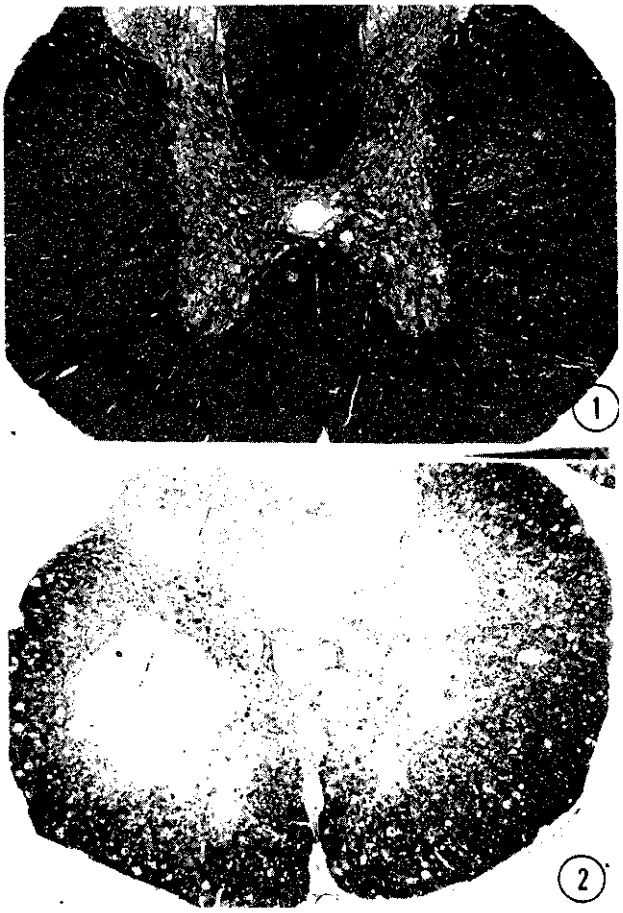


Photo credit: P.J.Reier, University of Florida

A cross-section through a normal(1) and an injured (2) rat spinal cord.

The spinal cord is made up of a central core of neuronal cell bodies surrounded by collections of axons. These axons make up the long pathways that connect the spinal cord and brain and the shorter pathways that connect areas within the spinal cord. Injury to the spinal cord, whatever the cause, can destroy both axons and neurons located in the damaged region. In addition, neurons that are located away from the injury site, whether higher up in the spinal cord or in the brain, and that contribute to the damaged pathways can die as a result of the injury (retrograde cell death). The functional deficits associated with spinal cord injury range from paralysis (loss of the power of voluntary movement in the extremities) and loss of sensation to the loss of reflex activities coordinated from within the spinal cord (motor reflexes and reflexes associated with sexual activity and bladder control). In most cases, these functional deficits are permanent.

Unlike the case in neurodegenerative diseases, in spinal cord injury the original neurons are mostly present, but damaged. Repair of the long ascending and descending nerve fibers that convey movement and sensory information between the brain and spinal cord would require regrowth of these fibers to reconnect with their original targets. Repair of the short pathways within the spinal cord would involve providing a means by which the intrinsic spinal cord connections could be reestablished.

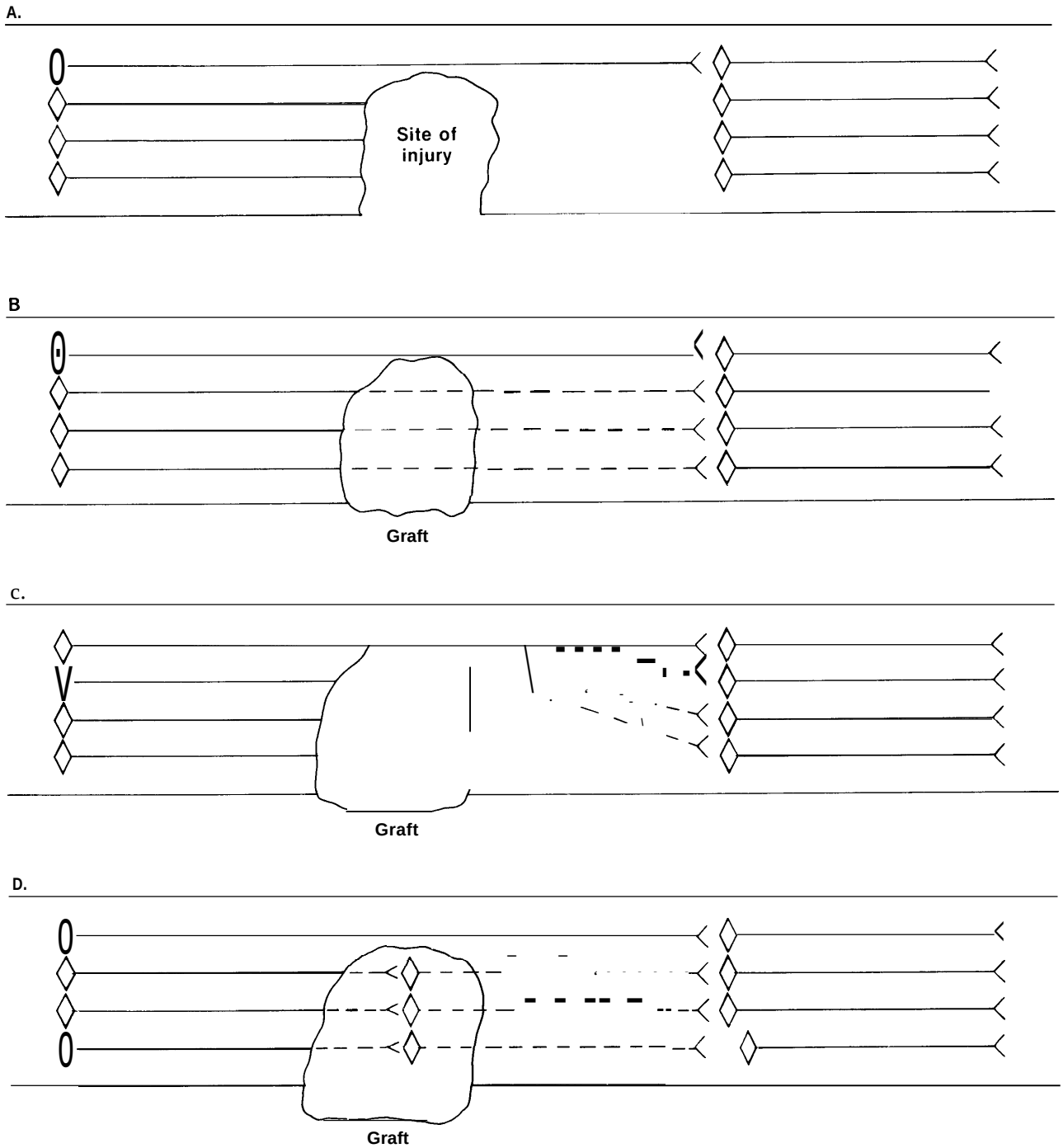
The goal of neural grafting in spinal cord injury is to repair or substitute for the damaged neuronal pathways to induce recovery of function. The aim is to achieve fictional recovery by reestablishing original synaptic contacts by the damaged axons; stimulating new outgrowth from uninjured neurons; or introducing new circuitries that would transmit functional information through the site of injury (figure 5-7). If growth of damaged neurons were to be stimulated, the grafts would serve as a substrate to induce the severed axons to reestablish their lost connections, thus regenerating the original anatomical structures. If undamaged neurons were to be stimulated, then the grafts would induce new growth from them to create alternative pathways, which would assume the role of the damaged pathways and restore functional activity without necessarily replicating the original anatomical connections (13). The third possibility is to construct a functional relay between separated regions of the spinal cord. ,

The questions to be addressed in determiningg the ultimate therapeutic role of neural grafts in spinal cord injury include:

- What grafting material will best integrate with the host spinal cord and create the environment most conducive for growth?
- Is there functional recovery following grafting?

To date, most research in this area has provided information regarding the first question; more basic research is needed to answer the second question. Scientists use a number of different types of experiments to study the mechanisms of regrowth in the damaged spinal cord. Some of the experiments closely approximate conditions that would be encountered in a human spinal cord injury. However,

Figure 5-7-Possible Actions of Neural Grafts in Spinal Cord Injury



Theoretically, neural grafts could repair the damage caused by an injury to the spinal cord (A) in three ways: B) stimulate regrowth from damaged axons; C) stimulate new growth from uninjured axons; D) provide a relay that would transmit information through the site of injury.
SOURCE: Office of Technology Assessment, 1990.

since different types of injuries can result in a wide range of insults to the spinal cord (the damage done in an automobile collision may be quite different from what occurs in a diving injury), no single model can be used to study spinal cord injury. The development of analogous animal models is a crucial step in exploring the usefulness of neural grafts in spinal cord injury.

What Makes a Good Graft?

Several sources of grafting materials have been examined in animal experiments. These include adult peripheral nerve and fetal CNS tissue, either in pieces or as cell suspensions. In general, autografts and allografts have been used in these experiments. The use of tissue from other species has not been widely examined; however, there is some evidence suggesting that such tissue is not as suitable as the others (142).

Peripheral Nerves—Nerves from the peripheral nervous system (PNS) are used to bridge a wound. They enable axons to cross the wound, reenter the far side of the spinal cord, and reinnervate their original targets. Over the past decade, some success has been achieved in implanting segments of peripheral nerves into the spinal cords of animals with experimentally induced injuries; these grafts have survived and become incorporated into the host spinal cord (126,130). The grafts support growth from the damaged tissue, but the extent to which the elongating axons can emerge from the graft and extend back into the host tissue is extremely limited (34,126).

While the ability of peripheral nerve grafts to induce growth in the injured spinal cord of experimental animals has been confined, the ability of these grafts to restore function has yet to be demonstrated.

Fetal Spinal Cord Tissue—Another major source of grafting material in many animal experiments has been fetal spinal cord tissue, usually from the same species. Given its ability to support growth, fetal tissue could act as a bridge across a wound or as a relay station between the severed axons and their target sites on the other side of the wound by providing a system of intervening neurons. Research into the use of this tissue does not have as long a history as that into peripheral nerve grafts. Experiments have shown that fetal tissue can create an environment that supports limited growth in the damaged adult spinal cord. Also fetal tissue can sometimes limit the scarring that occurs following an injury (and that can act as a barrier to growth) (77) and prevent retrograde cell death (26).

One interesting model has demonstrated the effectiveness of fetal spinal cord grafts in promoting growth at the boundary of the central and peripheral nervous systems. The fibers conveying sensory information from the body (e.g., sensing when the bladder is full) into the spinal cord are called dorsal roots. These fibers travel in both the peripheral and central nervous systems and traverse the boundary between the CNS and PNS when they enter the spinal cord (see figure 3-5). In spinal cord injuries the dorsal roots are sometimes torn. When damaged, these fibers will regenerate in the periphery until they reach the PNS-CNS boundary at the spinal cord and then stop growing. This phenomenon clearly demonstrates the ability of fibers to regrow in the peripheral but not in the central nervous system. Animal experiments have shown that if fetal spinal cord tissue is placed where the dorsal root enters the spinal cord, the severed root will continue to grow into the implant (133,144) and in some cases, to a limited extent, through it and into the host spinal cord (78). Fetal grafts, then, can support regeneration of these specialized peripheral-central fibers within the CNS and, to a certain degree, overcome the barriers present at the PNS-CNS boundary.

Fetal spinal cord implants can also support growth of CNS axons in an animal that is still growing and developing (24,25). In the newborn rat, axons from the brainstem are still growing into the spinal cord. If the spinal cord of a newborn rat is cut, the growing axons cannot reach their targets, and in many cases the neurons in the brain that send fibers into the spinal cord die. When fetal spinal cord tissue is placed into wounds made in the spinal cords of newborn rats, the tissue supports the continued development of the growing spinal cord and prevents neuron death in the brain. Although these studies clearly show that fetal spinal cord grafts can facilitate survival and regrowth of CNS axons in the immature, growing spinal cord, they do not indicate whether fetal spinal cord grafts would have any effect in the fully formed, adult spinal cord.

The ability of fetal spinal cord grafts to become integrated into the adult spinal cord in rats has been demonstrated (77,125). Fibers from the host spinal cord can grow into the grafts; however, the outgrowth from fetal grafts, whether by spinal axons

Photo credit: B. Bregman, Georgetown University

A cross-section through a rat spinal cord with a neural graft of rat fetal tissue.

transversing the graft or by neurons from within the graft sending their axons into the host spinal cord, is very limited. This again demonstrates the inability of axons to grow in the environment provided by the mature CNS.

Neurotrophic and Neurotropic Factors—The mechanism by which peripheral nerves or fetal tissue induces growth of damaged axons in the spinal cord is thought to involve certain chemical factors (see box 3-A). Neural grafting into the spinal cord may owe its success thus far to the insertion of tissues that contain the correct mix of these chemicals at the injury site, establishing the proper biochemical environment to support regrowth of the damaged axons and to allow reestablishment of lost synaptic contacts. Providing the proper chemical messengers to turn the various components of the regeneration system on and off may be a crucial element in the repair process. As more is learned about neurotrophic and neurotropic factors and the processes by which these substances regulate growth in the nervous system, abetter understanding of exactly what is necessary to produce healing can be determined.

Fetal Brain Tissue—Another grafting strategy that is being investigated involves the use of tissue from areas in the fetal brain that are known to regulate activity in the spinal cord. When the spinal cord is injured, descending fibers (originating in the brain and containing a specific class of neurotransmitters called catecholamines) are damaged. It is known that these fibers modulate the activity of local centers in the spinal cord which control certain

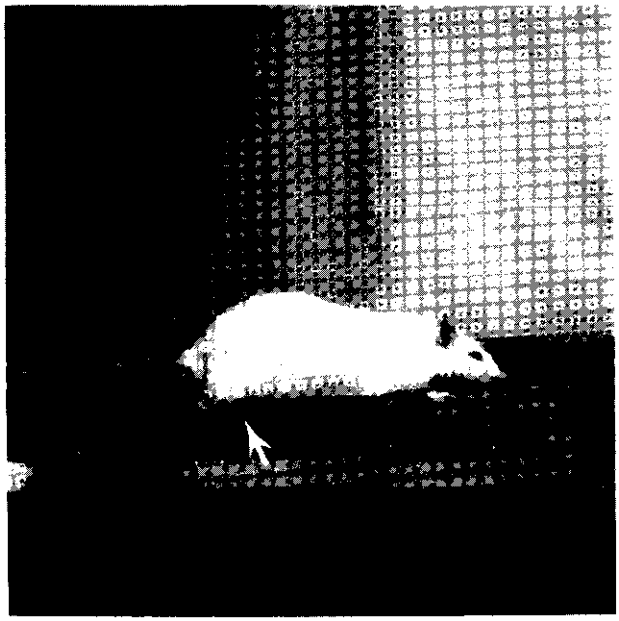


Photo credit: B. Bregman, Georgetown University

A rat being tested for the effects of a spinal cord injury. The rat has difficulty walking across the grid (arrow).

patterns of movement. There has been some investigation of whether these grafts could replace the lost catecholamines and regulate activity in the affected regions of the spinal cord. Grafts of fetal tissue from the relevant areas of the brain, implanted either as solid pieces (115,1 16) or in a cell suspension (18,123), become integrated into the host spinal cord and send fibers containing the catecholamines into the surrounding tissue.

Is There Functional Recovery?

The most important question regarding these techniques as they relate to possible clinical applications is whether there is any functional recovery from an injury after grafting. None of the studies previously discussed examined whether the grafts restored functions that were lost as a result of the injury. Most research to date has been aimed at determining and establishing the conditions most conducive to a successful implant and the degree to which the graft can integrate with surrounding host tissue. As a result, information regarding functional recovery following grafting is meager.

One study showed that grafting fetal rat spinal cord tissue into a small wound made in the spinal cords of adult rats decreased the difficulty in walking that the animals normally would have shown following such an injury (14). Significantly,

when the spinal cords of the animals that had received grafts were examined, it was seen that there had been very little regrowth of the severed fibers. The authors of the study concluded that the beneficial effects were probably" due to the growth-promoting factors in the grafts stimulating new growth from surviving neurons. They speculate that the surviving neurons assumed control of the lost functions by establishing new pathways that bypassed the injured area.

Injection of a cell suspension of rat fetal brain stem cells into the spinal cord can enhance leg reflexes in rats in which catecholamine-containing neurons have been destroyed (27). The catecholamine-containing cells in the suspension integrate into the spinal cord and establish new synaptic contacts with the spinal cord cells. It was hypothesized that some of the restoration of the leg reflexes was due to the development of new catecholamine synapses, not regeneration of damaged cells.

In neither of these studies was the functional recovery observed thought to be due to regrowth of the damaged neuronal pathways at the site of the wound. In the first study, neurotrophic factors were thought to be involved, while in the second, the enhancement of reflexes was due partly to an increase in catecholamine synapses and partly to other, unknown factors.

Some investigators have found evidence of recovery of function related to reconstruction of the neuronal pathways at the siteofawound(91). Grafts of fetal spinal cord tissue placed into the growing spinal cords of newborn rats lessen the deficits in walking that occur when the spinal cords of these animals are injured. Since neural grafts in newborns allow the growing spinal cord to assume a nearly normal circuitry, it has been proposed that the recovery of function is due to this rewiring of the spinal cord at the site of the injury by the still-growing spinal cord.

Questions That Need To Be Answered

Neural grafts may be able to ameliorate deficits caused by spinal cord injury; however, it is difficult to predict if and when these technologies will enter the clinical research arena. Animal experimentation in this area is yielding a wealth of information concerning basic biological mechanisms involved in growth and development of the nervous system, how it responds to injury, and the feasibility of grafting tissues into the site of a spinal cord injury. A number of questions remain to be answered before it can be known what clinical application, if any, this research will have.

Can Grafted Biologic Material Exert a Healing Effect on the Damaged Spinal Cord?—Implicit in this question is the notion that the spinal cord has no capacity to heal-once it is damaged, it is damaged forever. Evidence to date shows that this is false. The normal response of the spinal cord to injury indicates that it has some regenerative capacity. If this capacity, coupled with the mechanisms controlling growth in the immature spinal cord, can be harnessed and manipulated, then some form of healing can be achieved.

Can the Healing Effects of a Graft Restore Function?--The ability of grafted material to become incorporated into the damaged spinal cord serves no clinical purpose in itself. The ultimate clinical goal of grafting is to restore function. The requirements for restoration may differ from function to function. For simple functions, such as awareness of when the bladder is full, it may be possible to restore the necessary sensory input by reconnecting the dorsal root sensory nerves that convey this information to an intact area of the spinal cord. The graft would enable the sensory fibers to cross the PNS-CNS boundary and would allow the message that the bladder is full to enter the nervous system. While this may not restore complete motor control, the patient would be able to tell when it was time to empty the bladder.

In the case of more complex functions under the control of the spinal cord circuitry (blood pressure and temperature regulation, sexual reflex activity, bladder control, motor reflexes), reestablishment of function may require bridging the wound to reconnect the spinal cord control centers back into the reflex pathways or to reinstate the higher level control of these centers. The small degree of outgrowth from grafts that has been observed in many experiments may be sufficient for bridging spinal cord wounds. If the control centers themselves are damaged, then grafts would have to provide new cells to reform them. This would require a more complex interaction than just bridging an injury site. Restoration of the motor and sensory deficits that result in paralysis would require an even more comprehensive mending process, one that would initiate regeneration or generation of

pathways that could mediate the activity necessary for these functions.

The more complex and coordinated a function is, the more complex the type of repair needed to reinstate it. Exactly how much repair is necessary to restore a given function is not known. It is known from animal models that, even if only a small percentage of fibers is spared at the time of injury, there can be marked recovery of function. It may be that reestablishment of only a small proportion of connections, either by direct reconstruction or by stimulation of new pathways, may be sufficient for significant fictional recovery. In order to realize this recovery, it may be necessary to follow the reconstructive surgery with extensive rehabilitative therapy.

What Characteristics of the Graft Are Necessary for Functional Recovery?—The processes set in motion by implantation of neural tissue must be understood before this technology can be used as a therapeutic tool. At the present time, grafting into the spinal cord is analogous to inserting a "black box.' Very little information is available as to what causes the observed morphological changes and functional effects. Is an integrated, solid piece of tissue necessary to supply the proper mixture of neurotrophic factors to the right location and in the right form to induce growth? Or is it sufficient just to supply the growth-promoting factors alone? Is a mixture of the two needed? Do these needs differ depending on what type of functional recovery is desired? The answers to these questions are still being sought.

What Are the Possible Unwanted Effects of Grafting Into the Spinal Cord?—It is possible that inserting tissue into the spinal cord or stimulating growth from the damaged host tissue could cause abnormal pathways and connections to be formed. This could result in unwanted effects, notably the development of abnormal motor functions, such as muscle spasticity and increased reflex actions, or pain or other discomforting sensations (e.g., burning, tingling).

Brain Injury and Stroke

Since grafts may serve to replace lost or damaged tissue or to stimulate growth from damaged areas, it is possible that neural grafts could restore functional losses caused by injury to the brain. Animal experiments have demonstrated that fetal tissue can survive and become incorporated into a wound made in the brain of an adult (e.g.,33,72,110). This includes tissue damage caused by inducing a stroke in the experimental animal (usually rats) (104,109). The stroke is caused by clamping one of the vessels that supplies blood to the brain, thus mimicking what happens in humans suffering a stroke. The area of the brain that loses its blood supply dies. When rat fetal tissue corresponding to the damaged area is placed in the wound, the graft integrates into the host brain and becomes incorporated into the host blood supply. The cells in the graft send signals like normal neurons, indicating that the graft is active. The grafts survive best when they are implanted at least 1 week after the stroke, a phenomenon that is observed when wounds are made in either the brain or spinal cord. Neither the stroke studies nor the others previously mentioned examined whether the grafts reversed any functional deficits caused by the wounds.

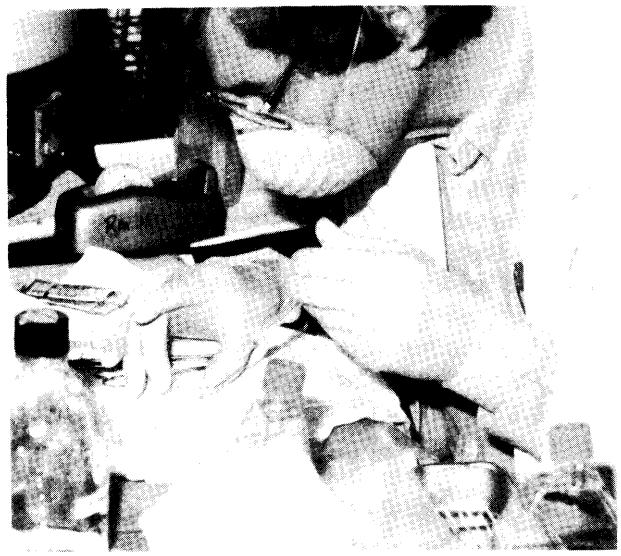


Photo credit: R.A.E. Bakay, The Emory Clinic

Preparing a cell suspension for grafting.

Studies of other kinds of brain injury in rats have shown that implantation of rat fetal tissue into wounds made in the cerebral cortex can help alleviate the deficits caused by the wounds (46,92,152). Grafting of fetal tissue into these models results in functional improvement, but only if the tissue implanted is from regions of the fetal brain that correspond to the areas destroyed in the adult.

The mechanism by which grafts exert their effects in these animal models of brain injury is unclear. Recovery may be due either to integration of the grafted material into the host brain or to effects not related to integration or even graft survival. It has been observed that the beneficial effect occurs for only a short time after implantation of the tissue (44) and that the same degree of functional recovery is seen whether a fetal graft, a suspension of glial cells, or a piece of sponge that has been sitting in the wound of another animal is placed into the wound (85). This indicates that part of the remedial effect may result from the presence of neurotrophic factors produced when the wound was made or secreted by cells other than neurons contained in the graft. These factors could stimulate growth from the injured host brain. Thus, both incorporation of the graft into the host and the effects of growth-promoting factors could play a role in recovery of function. Some investigators have stated:

> It appears. . . that transplants can facilitate functional recovery by more than one mechanism, including promotion of survival and reactive synaptogenesis [synapse formation] of host neurons, stabilization of the damaged environment and replacement of neurons (85).

The ability of grafts to reverse functional deficits caused by brain injury is still unclear. If a functional effect can be produced, the underlying mechanism of that effect is uncertain and the requirements for the grafted material are unknown. Additional basic research is needed to answer these questions and to define the ultimate role of grafts in brain injury.

EPILEPSY

Some success has been achieved in using neural grafts to block the occurrence of epileptic seizures in a very specific animal model of epilepsy called the "kindled" model. It is thought that the kindled model of epilepsy is analogous to temporal lobe epilepsy (68), which is the most frequent form of the disease in adult humans. In this model, an area of the brain called the locus ceruleus (LC), which inhibits the ability to induce seizures, is destroyed in rats. Investigators can therefore induce seizures in the hippocampus of these animals more easily than in normal, intact rats.[6] A graft of fetal rat LC tissue placed in the hippocampus, however, can form connections with the cells in the hippocampus and inhibit the induction of seizures (12,98). Thus, the LC grafts mimic, to a certain degree, the normal action of the intact LC in this model. LC tissue grafts have also been shown to inhibit seizures in another rat model of epilepsy that uses a combination of surgery and drugs to induce seizures (28).

While these studies show that LC grafts can inhibit the *induction* of seizures in these models, the relationship to *naturally occurring seizures in* persons with epilepsy is unclear. There is no evidence to date that LC grafts can inhibitor otherwise affect naturally occurring seizures.

The ability of grafts of other types of fetal brain tissue to suppress naturally occurring seizures has been examined in rats that have a genetic predisposition to seizures. The severity of seizures in these rats can be decreased if either of the neurotransmitters noradrenaline or gamma-aminobutyric acid (GABA) is injected into certain areas of the brain; however, grafts of tissue rich in these neurotransmitters, implanted into the proper areas of the brain, did not appreciably reduce the intensity of the rats' seizures (138).

Experiments conducted to date indicate that grafts can affect the induction of seizures. However, additional animal research is needed to determine what role grafts could play in reducing naturally occurring epileptic seizures.

NEUROENDOCRINE DEFICITS

The ability of grafts to supply chemicals makes them well suited to reduce deficits caused by a loss or imbalance of normal hormone levels. Neurons in an area of the brain called the hypothalamus regulate the release of hormones from the pituitary gland (which lies under the hypothalamus) into the bloodstream. In addition, some hormones are made by neurons in the hypothalamus itself and are released directly into blood vessels. Once in the blood vessels, the hormones travel throughout the body.

[6] Seizures are induced by electrically stimulating a portion of the brain called the limbic system, which includes the hippocampus. The electrical stimulation is given in small, progressive steps which make the limbic system so sensitive that even a mild electrical shock will induce a generalized seizure. Thus, the seizure is said to have been kindled. The locus ceruleus is thought to inhibit the kindling phenomenon by sending noradrenaline fibers to the hippocampus. Kindling takes place more quickly and easily when these fibers are destroyed.

If the area of the hypothalamus that secretes the hormone vasopressin (VP) directly into the bloodstream is destroyed in rats, the resulting low levels of VP cause water loss in the urine and produce dehydration. The same phenomenon is observed in a mutant strain of rat that has a congenital absence of VP-producing neurons. If VP-producing neurons are grafted into either of these animal models, the grafts become incorporated into the host and secrete VP into the circulatory system (59,105,136). Grafts of VP-producing cells can also ameliorate some of the deficits in fluid regulation seen in these animals (61,106). Finally, these grafts can prevent the death of hypothalamic neurons that normally occurs when a wound is made, perhaps by the release of growth-promoting factors (107).

Another model that has been used in this line of research is a special strain of mice with a genetic abnormality that keeps them from producing the hormone GnRH (gonadotrophin-releasing hormone). GnRH, which is released from cells in the hypothalamus, causes cells in the pituitary gland to release hormones that control sexual maturation. Mice of either sex with this genetic abnormality have immature reproductive organs and are sterile. The implantation of fetal grafts of hypothalamic tissue from normal, GnRH-producing mice into the hypothalamus of adult mice with this dysfunction can correct many of the reproductive deficiencies that occur in these animals (22,29,62-65,90). The grafts result in increased levels of pituitary hormones, maturation of sexual organs, and initiation of sexual behavior.

Neural grafts have been shown to restore sexual potency and sexual behavior in aged, impotent male rats (79). The sexual behavior of such rats before and after fetal hypothalamic tissue was implanted into the hypothalamus was observed. Before the implants, the animals did not engage in sexual behavior when exposed to receptive females. After the grafts, the sexual behavior of most of the rats was restored, resulting in increased sexual activity and impregnation of the females.

The ability of neural grafts to reverse deficits and imbalances in hormone levels due to neurological damage or abnormalities has been repeatedly shown in a number of animal models. Since analogous clinical conditions in humans are rare, and when they occur are treated with drugs, the ultimate role of neural grafts in human clinical neuroendocrine conditions is yet to be elucidated.

Photo credit: C.S. Raine, Neurocellular Anatomy in Basic Neuroohemistry, *4th ed., G. Siegel, B. Agranoff, R. Albers, and P. Molinoff (eds.) (New York, NY: Raven Press, 1989) p. 29.*

A photograph through a microscope showing a Schwann cell (N) and the myelin it produces (black ring) surrounding an axon (A).

DEMYELINATING DISORDERS: MULTIPLE SCLEROSIS

Demyelinating disorders disrupt nervous system activity by causing a breakdown in the insulating sheath that surrounds many axons. Loss of the myelin sheath interferes with the normal transmission of signals between neurons, causing messages to travel more slowly than normal. Specialized glial cells (oligodendrocytes in the CNS, Schwann cells in the PNS) produce the myelin covering of neurons. Within the CNS, demyelinating diseases attack either the oligodendrocytes or the myelin they produce.

A number of disorders can affect myelin in the CNS. While most are rare, one, multiple sclerosis (MS), is more common. MS destroys patches of

myelin in an erratic and random fashion throughout the CNS. The cause of MS is unknown.

Demyelination can also occur in certain types of spinal cord injuries. Injuries caused by a compressive force on the spinal cord often result in an area of demyelinated axons surrounding a core of dead tissue (149). The ability of grafts to restore the myelin covering of the appropriate axons could aid in the recovery of lost functions.

The therapeutic strategy underlying the use of neural grafts in patients with MS or other demyelinating conditions would be to provide a source of myelin that could become incorporated into the affected area and restore the lost myelin sheath. Any graft tied at replenishing lost myelin would have to include either oligodendrocytes or Schwann cells. Since these cells, when implanted into the CNS, can migrate some distance from the site of insertion, it is thought that they may be usable in treating disorders that result in patchy areas of demyelinated axons.

Over the past decade, animal experiments have shown that it is possible to replace lost myelin by injecting the appropriate cells into regions in which experimentally induced demyelinating lesions have been produced. This has been demonstrated using suspensions of Schwann cells from peripheral nerves (21,22,39,76), cell suspensions of CNS tissue (23), and fragments of CNS tissue (73,74). Additional animal experimentation is needed to determine whether these grafting procedures can restore functional deficits caused by demyelination. Also, it is unknown whether implanted myelin-producing cells would be susceptible to the underlying disease process that caused the original demyelination.

SUMMARY AND CONCLUSIONS

The possible therapeutic uses of neural grafting into the brain and spinal cord are varied and diverse, encompassing a wide range of neurological deficits. Of these, the application of neural grafting in persons with Parkinson's disease is the most advanced. But in Parkinson's disease, as well as all other applications, no definitive statement about the actual usefulness of neural grafting as a therapeutic procedure can be made at this time. The data from the basic research that has been conducted thus far provide tantalizing hints of the potential usefulness of neural grafting procedures, but additional animal experimentation needs to be conducted to clarify that potential. To increase the applicability of animal data to human disorders, animal models of the various neurological disorders under study need to be developed. Neural grafting holds the promise of new therapeutic interventions for neurological disorders, but a final determination of its usefulness must await the accumulation of more information about the mechanisms underlying neurological disease and injury, graft functions, and how those functions relate to various neurological disorders.

CHAPTER 5 REFERENCES

1. Allen, G. S., Burns, R. S., Tulipan, N.B., et al., ' 'Adrenal Medullary Transplantation to the Caudate Nucleus in Parkinson's Disease," ***Archives of Neurology*** 46:487-497, ***1989.***
2. Apuzzo, M.L.J., Neal, J.H., Waters, C.H., et al., ''Utilization of Unilateral and Bilateral Stereotactically Placed Adrenomedullary-Striatal Autografts in Parkinsonian Humans: Rationale, Techniques, and Observations, ' ***Neurosurgery*** 26:746-757, ***1990.***
3. Arbuthnott, G., Dunnett, S.B., and MacLeod, N., ' 'Electrophysiological Properties of Single Units in Dopamine-Rich Mesencephalic Transplants in Rat Brain," ***Neuroscience Letters*** 57:205-210, ***1985.***
4. Arendt, T., Allen, Y., Sinden, J., et al., ''Cholinergic-Rich Brain Transplants Reverse Alcohol-Induced Memory Deficits," ***Nature*** 332:448-450, ***1988.***
5. Backlund, E. O., Granberg, P. O., Hamberger, B., et al., "Transplantation of Adrenal Medullary Tissue to Striatum in Parkinsonism, First Clinical Trials," ***Journal of Neurosurgery*** 62:169-173, ***1985.***
6. Bakay, R.A.E., Allen, G. S., Apuzzo, M.L.J., et al., "Preliminary Report on Adrenal Medullary Grafting From the American Association of Neurological Surgeons GRAFT Project," ***Progress in Brain Research, in*** press.
7. Bakay, R.A.E., Barrow, D. I., Fiandaca, M. S., et al., "Biochemical and Behavioral Correction of MPTP Parkinson-Like Syndrome by Fetal Cell Transplantation,' ***Annals of the New York Academy of Sciences*** 495:623-638, ***1987.***
8. Bakay, R.A.E., Fiandaca, M. S., Barrow, D.L., et al., "Preliminary Report on the Use of Fetal Tissue Transplantation To Correct MPTP-Induced Parkinson-like Syndrome in Primates, ' ***Applied Neurophysiolology*** 48:358-361, ***1985.***
9. Bakay, R.A.E., and Herring, C.J., "Central Nervous System Grafting in the Treatment of Parkinsonism, " ***Stereotactic and Functional Neurosurgery*** 53:1-20, ***1989.***

10. Bankiewicz, K. S., Plunkett, R.J., Jacobowitz, D.M., et al., "TheEffect of Fetal Mesencephalon Implants on Primate MPTP-Induced Parkinsonism,'' *Journal of Neurosurgery* 72:231-244, 1990.
11. Bankiewicz, K.S., Plunkett, R.J., Kopin, I.J., et al., "Transient Behavioral Recovery in Hemiparkinsonian Primates After Adrenal Medullary Allografts," *Progress in Brain Research,* vol. *78, Transplantation Into the Mammalian CNS*, D.M. Gash and J.R. Sladek, Jr. (eds.) (Amsterdam: Elsevier Science Publishers, 1988).
12. Barry, D.I., Kikvadze, I., Brundin, P., et al., "Grafted Noradrenergic Neurons Suppress Seizure Development in Kindling-Induced Epilepsy,' *Proceedings of the National Academy of Sciences, U.S.A.* 84:8712-8715, 1987.
13. Bernstein, J.J., "Successful Spinal Cord Regeneration: Known Biological Strategies,' *Current Issues in Neural Regeneration Research,* P. Reier, R. Bunge, and F. Seil (eds.) (New York, NY: Alan R. Liss, 1988).
14. Bernstein, J.J., and Goldberg, W.J., "Fetal Spinal Cord Homografts Ameliorate the Severity of Lesion-induced Hind Limb Behavioral Deficits," *Experimental Neurology* 98:633-644, *1987.*
15. Bing, G., Netter, M.F.D., Hansen, J.T., et al., "Comparison of Adrenal Medullary, Carotid Body and PC12 Cell Grafts in 6-OHDA Lesioned Rats," *Brain Research Bulletin* 20:399-406, 1988.
16. Bing, G., Netter, M.F.D., Hansen, J.T., et al., "Enhanced Survival and Function of Grafted Adrenal Medullary Cells When Cografted With Trophic Producing Arnitotic C6 Glioma Cells," *Neuroscience, in* press.
17. Björklund, A., Dunnett, S.B., Stenevi, U., et al., "Reinnervation of the Denervated Striatum by Substantial Nigra Transplants: Functional Consequences as Revealed by Pharmacological and Sensorimotor Testing," *Brain Research* 199:307-333, *1980.*
18. Björklund, A., Nomes, H., and Gage, F.H., "Cell Suspension Grafts of Noradrenergic Locus Coeruleus Neurons in Rat Hippocampus and Spinal Cord: Reinnervation and Transmitter Turnover,'' *Neuroscience* 18:685-698, *1986.*
19. Björklund, A., and Stenevi, U., "Reconstruction of the Nigrostriatal Dopamine Pathway by Intracerebral Nigral Transplants,'' *Brain Research 177:555-560,1979.*
20. Björklund, A., Stenevi, U., Schmidt, R.H., et al., ''Intracerebral Grafting of Neuronal Cell Suspensions, II: Survival and Growth of Nigral Cell Suspensions Implanted in Different Brain Sites," *Acta Physiologic Scandinavia 522(supp.):9-18, 1983.*
21. Blakemore, W.F., "Remyelination of CNS Axons by Schwann Cells Transplanted From the Sciatic Nerve," *Nature* 266:68-69, *1977.*
22. Blakemore, W.F., and Crang, A.J., "The Use of Cultured Autologous Schwann Cells to Remyelinate Areas of Persistent Demyelination in the Central Nervous System," *Journal of Neurological Sciences* 70:207-223, *1985.*
23. Blakemore, W.F., and Crang, A.J., "Extensive Oligodendrocyte Remyelination Following Injection of Cultured Central Nervous System Cells Into Demyelinating Lesions in the Adult Central Nervous System," *Developmental Neuroscience* 10:1-11, 1988.
24. Bregman, B. S., "Development of Serotonin Immunoreactivity in the Rat Spinal Cord and Its Plasticity After Neonatal Spinal Cord Lesions," *Developmental Brain Research* 431:245-263, *1987.*
25. Bregman, B. S., "Spinal Cord Transplants Permit the Growth of Serotonergic Axons Across the Site of Neonatal Spinal Cord Transection," *Developmental Brain Research* 431:265-279, *1987.*
26. Bregman, B. S., and Reier, P.J., "Neural Tissue Transplants Rescue Axotomized Rubrospinal Cells From Retrograde Death," *Journal of Comparative Neurology 24486-95, 1986.*
27. Buchanan, J.T., and Nomes, H.O., ''Transplants of Embryonic Brainstem Containing the Locus Coeruleus Into Spinal Cord Enhance the Hindlimb Flexion Reflex in Adults," *Brain Research* 381:225-236, *1986.*
28. Buzsaki, G., Ponomareff, G., Bayardo, F., et al., "Suppression and Induction of Epileptic Activity by Neuronal Grafts," *Proceedings of the National Academy of Sciences, U.S.A.* 85:9327-9330, *1988.*
29. Charlton, H.M., ''Neural Grafts and Restoration of Pituitary and Gonadal Function in Hypogonadal (HPG) Mice," *Annals of Endocrinology 48:378-384,1987.*
30. Collier, T.J., Gash, D.M., and Sladek, J.R., Jr., "Transplantation of Norepinephrine Neurons Into Aged Rats Improves Performance of a Learned Task," *Brain Research* 448:77-87, *1988.*
31. Collier, T.J., Redmond, D.E., Jr., Roth, R.H., et al., "Reversal of Experimental Parkinsonism in African Green Monkeys Following Fetal Dopamine Neuron Transplantation," *Progress in Parkinson's Research,* F.F. Hefti and W.J. Weiner (eds.) (New York, NY: Plenum Press, 1989).
32. Daniloff, J.K., Bodony, R.P., Low, W.C., et al., "Cross-Species Septal Transplants: Restoration of Conditioned Learning Behavior," *Brain Research* 346:176-180, 1985.
33. Das, G.D., Hallas, B.H., and Das, K.G., ''Transplantation of Brain Tissue in the Brain of the Rat, I: Growth Characteristics of Cortical Transplants

From Embryos of Different Ages," *Acta Anatomica* 158:135-145, *1980.*

34. David, S., and Aguayo, A.J., "Axonal Elongation Into Peripheral Nervous System 'Bridges' After Central Nervous System Injury in Adult Rats," *Science* 214:932-933, 1981.
35. Deckel, A.W., Moran, T.H., Coyle, J.Y., et al., "Anatomical predictors of Behavioral Recovery Following Fetal Transplants," *Brain Research 365: 249-258, 1986.*
36. Deckel, A.W., Robinson, R.G., Coyle, J.T., et al., "Reversal of Long-Term Locomotor Abnormalities in the Kainic Acid Model of Huntington's Disease by 18-Day Fetal Striatal Implants," *European Journal of Pharmacology* 93:287-288, *1983.*
37. Demierre, B., Martinou, J.-C., and Kate, A. C., "Embryonic Motoneurons Grafted Into the Adult CNS Can Differentiate and Migrate," *Brain Research* 510:355-359, *1990.*
38. Drucker-Colin, R., Madrazo, I., Ostrosky-Solis, F., et al., "AdrenalMedullaryT issue Transplants in the Caudate Nucleus of Parkinson's Patients," *Progress in Brain Research,* vol. *78, Transplantation Into the Mammalian CNS*, D.M. Gash and J.R. Sladek, Jr. (eds.) (Amsterdam: Elsevier Science Publishers, 1988).
39. Duncan, I.D., Aguayo, A.J., Bunge, R.P., et al., "Transplantation of Rat Schwann Cells Grown in Tissue Culture Into the Mouse Spinal Cord," *Journal of Neurological Science* 49:241-252, 1981.
40. *Dunnett,* S.B., Björklund, A., Schmidt, R.H., et al., "Intracerebral Grafting of Neuronal Cell Suspensions, IV: Behavioral Recovery in Rats With Unilateral 6-OHDA Lesions Following Implantation of Nigral Cell Suspensions in Different Forebrain Sites," *Acta Physiologic Scandinavia 522(supp.):29-37, 1983.*
41. *Dunnett,* S. B., Björklund, A., Stenevi, U., et al., "Grafts of Embryonic Substantial Nigra Reinnervating the Ventrolateral Striatum Ameliorate Sensorimotor Impairments and Akinesia in Rats With 6-OHDA Lesions of the Nigrostriatal Pathway," *Brain Research* 229:209-217, 1981.
42. *Dunnett,* S.B., Hernandez,T.D., Summerfield, A., et al., "Graft-Derived Recovery From 6-OHDA Lesions: Specificity of Ventral Mesencephalic Graft Tissues," *Experimental Brain Research 71:411-424, 1988.*
43. *Dunnett,* S.B., Low, W. C., Iverson, S.D., et al., "SeptalTransplants Restore Maze Learning in Rats With Fornix-Fimbria Lesion," *Brain Research* 251:335-348, *1982.*
44. *Dunnett,* S.B., Ryan, C.N., Levin, P.D., et al., "Functional Consequences of Embryonic Neocortex Transplanted to Rats With Prefrontal Cortex Lesions," *Behavioral Neuroscience* 101:489-503, *1987.*
45. Emfors, P., Ebendal, T., Olson, L., et al., "A Cell Line Producing Recombinant Nerve Growth Factor Evokes Growth Responses in Intrinsic and Grafted Central Cholinergic Neurons," *Proceedings of the National Academy of Sciences, U.S.A. 86:4756-4760,1989.*
46. Escobar, M., Femandez, J., Guevara-Agular, R., et al., "Fetal Brain Grafts Induce Recovery of Learning Deficits and Connectivity in Rats With Gustatory Neocortex Lesion," *Brain Research 478:368-374, 1989.*
47. Fiandaca, M. S., Kordower, J.H., Hansen, J.T., et al., "Adrenal Medullary Autografts Into the Basal Ganglia of Cebus Monkeys: Injury-Related Regeneration," *Experimental Neurology 102:76-91,1988.*
48. Fine, A., Dunnett, S.B., Björklund, A., et al., "Cholinergic Ventral Forebrain Grafts Into the Neocortex Improve Passive Avoidance Memory in a Rat Model of Alzheimer's Disease,' *Proceedings of the National Academy of Sciences, U.S.A.* 82:5227-5230, *1985.*
49 Fine, A., Hunt, S. P., Oertel, W. H., et al., "Transplantation of Embryonic Marmoset Dopaminergic Neurons to the Corpus Striatum of Marmosets Rendered Parkinsonian by 1-Methyl-4-Phenyl-l,2,3,6-Tetrahydropyridine," *Progress in Brain Research* 78:479-489, *1988.*
50. Freed, C.P., Breeze, R.E., Rosenberg, N.L., et al., "Transplantation of Human Fetal Dopamine Cells for Parkinson's Disease: Results at 1 Year," *Archives of Neurology* 47:505-512, 1990.
51. Freed, W.J., Cannon-Spoor, H.E., and Krauthamer, E., "Factors Influencing the Efficacy of Adrenal Medulla and Embryonic Substantial Nigra Grafts," *Neural Grafting in the Mammalian CNS*, A. Björklund and U. Stenevi (eds.) (Amsterdam: Elsevier Science Publishers, 1985).
52. Freed, W.J., Cannon-Spoor, H.E., and Krauthamer, E., "Intrastriatal Adrenal Medulla Grafts in Rats, Long-Term Survival and Behavioral Effects," *Journal of Neurosurgery* 65:664-670, *1986.*
53. Freed, W.J., Morihisa, J.M., Spoor, E., et al., "Transplanted Adrenal Chromaffin Cells in Rat Brain Reduce Lesion-Induced Rotational Behavior," *Nature* 292:351-352, 1981.
54. Freed, W.J., Perlow, M.J., Karoum, F., et al., "Restoration of Dopaminergic Function by Grafting of Fetal Substantial Nigra to the Caudate Nucleus: Long-Term Behavioral, Biochemical, and Histochemical Studies," *Annals of* Neurology 8:510-519, 1980.
55. Freund, T.F., Bolam, J.P., Björklund, A., et al., "Efferent Synaptic Connections of Grafted Dopam-

inergic Neurons Reinnervating the Host Neostriatum: A Tyrosine Hydroxylase Immunocytochemical Study," ***Journal of Neuroscience*** 5:603-616, *1985.*

56. Gage, F.H., and Björklund, A., "Cholinergic Septal Grafts Into the Hippocampal Formation Improve Spatial Learning and Memory in Aged Rats by Atropine-Sensitive Mechanism, " ***Journal of Neuroscience*** 6:2837-2847, *1986.*

57. Gage, F.H., Björklund, A., Stenevi, U., et al., "Intra-Hippocampal Septal Grafts Ameliorate Learning Impairments in Aged Rats," ***Science 225: 533-536,*** 1984.

58. Gage, F.H., Wollf, J.A., Rosenberg, M. B., et al., "Implantation of Genetically Engineered Cells to the Brain," ***Progress in Brain Research 78:651-658,1988.***

59. Gash, D. M., and Sladek, J.R., Jr., "Functional and Non-Functional Transplants: Studies With Grafted Hypothalamic and Preoptic Neurons," ***Trends in Neuroscience*** 76:391-394, *1984.*

60. Gash, D. M., and Sladek, J. R., Jr., "Neural Transplantation: Problems and Prospects-Where Do We Go From Here?' Mayo ***Clinic Proceedings*** 64:363-367, *1989.*

61. Gash, D.M., Sladek, J.R., Jr., and Sladek, C.D., "Functional Development of Grafted Vasopressin Neurons," ***Science*** 210:1367-1369, 1980.

62. Gibson, M.J., Charlton, H.M., Perlow, E.A., et al., "Preoptic Area Brain Grafts in Hypogonadal (HPG) Female Mice Abolish Effects of Congenital Hypothalamic Gonadotropin-Releasing Hormone (GnRH) Deficiency," ***Endocrinology*** 114:949-951, *1984.*

63. Gibson, M.J., Krieger, D.T., and Charlton, H.M., et al., "Mating and Pregnancy Can Occur in Genetically Hypogonadal Mice With Preoptic Area Brain Grafts," ***Science*** 225:949-951, *1984.*

64. Gibson, M.J., Moscovitz, H. C., Kokoris, G.J., et al., "Female Sexual Behavior in Hypogonadal Mice With GnRH-Containing Brain Grafts," ***Hormones and Behavior*** 21:211-222, *1987.*

65. Gibson, M.J., Silverman, A.J., Kokoris, G.J., et al., "GnRH Cell Brain Grafts. Correction of Hypogonadism in Mutant Mice," ***Annals of the New York Academy of Sciences*** 495:296-305, *1988.*

66. Giordano, M., Houser, S.H., and Sanberg, P.R., "Intraparenchymal Fetal Striatal Transplants and Recovery in Kainic Acid Lesioned Rats," ***Brain Research*** 446:183-188, *1988.*

67. Girault, J.A., Raisman-Vozari, R., Agid, Y., et al., "Striatal Phosphoproteins in Parkinson's Disease and Progressive Supranuclear Palsy," ***Proceedings of the National Academy of Sciences, U.S.A.*** 86:2493-2497, *1989.*

68. Girgis, M., "Kindling as a Model of Limbic Epilepsy," ***Neuroscience*** 6:1695-1706, *1981.*

69. ***Goetz, C.G.,*** Olanow, C.W., Keller, W.C., et al., "Multicenter Study of Autologous Adrenal Medullary Transplantation to the Corpus Striatum in Patients With Advanced Parkinson's Disease," New ***England Journal of Medicine*** 320:337-341, *1989.*

70. ***Goetz, C. G.,*** Stebbins, G.T., Klawans, H.L., et al., "United Parkinson Foundation Neurotransplantation Registry Multicenter United States and Canada Database Presurgical and 12-Month Followup," ***Proceedings of the Third International Congress of Neurotransplantation: Cambridge*** (Amsterdam: Elsevier Science Publishers, 1989).

71. Goetz, C.G., Tanner, C.M., Pem, M.D., et al., "Adrenal Medullary Transplant to the Striatum of Patients With Advanced Parkinson's Disease: 1 Year Motor and Psychomotor Data," ***Neurology*** 40:273-276, *1990.*

72. ***Gonzalez,*** M.F., and Sharp, F.R., "Fetal Frontal Cortex Transplanted to Injured Motor/Sensory Cortex of Adult Rats," ***Journal of Neuroscience*** 7:2991-3001, *1987.*

73. Gout, O., Gansmuller, A., Baumann, N., et al., "Remyelination by Transplanted Oligodendrocytes of a Demyelinated Lesion in the Spinal Cord of the Adult Shiverer Mouse," ***Neuroscience titters*** 87: *195-199, 1988.*

74. Gumpel, M., Baumann, N., Raoul, M., et al., "Survival and Differentiation of Oligodendrocytes From Neural Tissue Transplanted in New-Born Mouse Brain," ***Neuroscience Letters*** 37:307-311, *1983.*

75. Hansen, J.T., Kordower, J.H., Fiandaca, M. S., et al., "Adrenal Medullary Autografts Into the Basal Ganglia of Cebus Monkeys: Graft Viability and Fine Structure," ***Experimental Neurology 102:65-75, 1988.***

76. Harrison, B.M., "Remyelination by Cells Introduced Into a Stable Demyelinating Lesion in the Central Nervous System,' ***Journal of Neurological Science*** 46:63-81, *1980.*

77. Houle, J.D., and Reier, P. J., "Transplantation of Fetal Spinal Cord Tissue Into the Chronically Injured Adult Rat Spinal Cord," ***Journal of Comparative Neurology*** 269:535-547, *1988.*

78. Houle, J.D., and Reier, P.J., "Regrowth of Calcitonin Gene-Related Peptide (CGRP) Immunoreactive Axons From the Chronically Injured Rat Spinal Cord Into Fetal Spinal Cord Tissue Transplants," ***Neuroscience titters*** 103:253-258, *1989.*

79. Huang, H. H., Kissane, J. Q., and Hawarylewicz, E.J., "Restoration of Sexual Function and Fertility by Fetal Hypothalamic Transplants in Impotent

Aged Male Rats," *Neurobiology of Aging 8:465-472,1987,*

80. Hurtig, H., Joyce, J., Sladek, J.R., Jr., et al., "Postmortem Analysis of Adrenal-Medulla-to-Caudate Autograft in a Patient With Parkinson's Disease," *Annals of Neurology* 25:607-614, *1989.*

81. Isacson, O., Brundin, P., andKelly, P., "Functional Neuronal Replacement by Grafted Striatal Neurons in the Ibotenic Acid-Lesioned Rat Striatum," *Nature* 311:458-460, 1984.

82. Isacson, O., Dunnett, S.B., and Björklund, A., "Graft Induced Behavioral Recovery in an Animal Model of Huntington's Disease," *Proceedings of the National Academy of Sciences, U.S.A. 83:2728-2732,* 1986.

83. Itakura, T., Kamei, I., Nakai, K., et al., "Autotransplantation of the Superior Cervical Ganglion Into the Brain," *Journal of Neurosurgery* 68:955-959, *1988.*

84. Jiao, S., Ding, Y., Zhang, W., et al., letter, New *England Journal of Medicine* 321:325, *1989*

85. Kesslak, J.P., Nieto-Sampedro, M., Globus, J., etal., "Transplants of Purified Astrocytes Promote Behavioral Recovery After Frontal Cortex Ablation," *Experimental Neurology* 92:377-390, *1986.*

86. Kimble, D.P., Bremiller, R., and Stichrod, G., "Fetal Brain Implants Improve Maze Performance in Hippocampal-Lesioned Rats," *Brain Research* 363:358-363, *1986.*

87. Keller, W. C., Morantz, R., Veter-Overfield, B., et al., "Autologous Adrenal Medullary Transplant in Progressive Supranuclear Palsy," *Neurology* 39:1066-1068, *1989.*

88. Kordower, J.H., Fiandaca, M. S., Netter, M.F.D., et al., "Peripheral Nerve Provides NGF-like Trophic Support for Grafted Rhesus Adrenal Chromaffin Cells," *Journal of Neurosurgery, in* press.

89. Kordower, J.H., Netter, M.F., and Gash, D.M., "Neuroblastoma Cells in Neural Transplants: A Neuroanatomical and Behavioral Analysis," *Brain Research* 417:85-98, 1987.

90. Krieger, D.T., Perlow, M.J., Gibson, M.J., et al., "Brain Grafts Reverse Hypogonadism of Gonadotropin-Releasing Hormone Deficiency,' *Nature* 298:468-471, *1982.*

91. Kunkel-Bagden, E., and Bregman, B. S., "Spinal Cord Transplants Enhance the Development and Recovery of Reflex and Locomotor Function After Neonatal Spinal Cord Lesions," *Experimental Brain Research, in* press.

92. Labbe, R., Firl, A., Mufson, E.J., et al., "FetalB rain Transplant Reduction of Cognitive Deficit in Rats With Frontal Cortex Lesion," *Science 221:470-472, 1983.*

93. Landau, W.M., "Clinical Neuromythology VII—Artificial Intelligence: The Brain Transplant Cure for Parkinsonism," *Neurology* 40:733-740, 1990.

94. Lieberman, A.N., Ransohoff, J., Berczeller, P., et al., "Adrenal Medullary Transplants as a Treatment for Advanced Parkinson's Disease," *Acta Neurologica Scandinavia* 126:189-196, *1989.*

95. Lieberman, A.N., Ransohoff, J., and Koslow, M., "Adrenal Medullary to Caudate Nucleus Transplant as an Effective Treatment for Advanced Parkinson's Disease," *Neurology 38(supp.* 1):142, *1988.*

96. Lindvall, O., "Transplantation Into the Human Brain: Present Status and Future Possibilities," *Journal of Neurology, Neurosurgery and Psychiatry supp.:39-54, 1989.*

97. Lindvall, O., Backlund, E.O., and Farde, L., "Transplantation in Parkinson's Disease: Two Cases of Adrenal Medullary Grafts to the Putamen," *Annals of Neurology* 22:457-468, *1987.*

98. Lindvall, O., Barry, D.I., Kikvadze, L, et al., "Intracerebral Grafting of Fetal Noradrenergic Locus Coeruleus Neurons: Evidence for Seizure Suppression in the Kindling Model of Epilepsy," *Progress in Brain Research* 78:79-86, *1988.*

99. Lindvall, O., Brundin, P., Widner, H., eta.l., "Grafts of Fetal Dopamine Neurons Survive and Improve Motor Function in Parkinson's Disease," *Science* 247:574-577, 1990.

100. Lindvall, O., Rechncrona, S., Brundin, P., et al., "Human Fetal Dopamine Neurons Grafted Into the Striatum in Two Patients With Severe Parkinson's Disease: A Detailed Account of Methodology and a 6-Month Followup," *Archives of Neurology* 46:615-631, *1989.*

101. McAllister, J.P., Kaplan, L., and Reynolds, M.A., "Morphology and Connectivity of Fetal Neostriatal Tissue Transplanted Into the Neostriatum of Adult Host," *Anatomical Record, 1984,* p. 107A.

102. Madrazo, I., Drucker-Colin, R., Diaz, V., et al., "Open Microsurgical Autograft of Adrenal Medulla to the Right Caudate Nucleus in Two Patients With Intractable Parkinson's Disease," *New England Journal of Medicine* 316:831-834, *1987.*

103. Mahalik, T.J., Finger, T.E., Stromberg, I., et al., "Substantial Nigra Transplants Into Denervated Striatum of the Rat: Ultrastructure of Graft and Host Interconnections," *Journal of Comparative Neurology* 240:60-70, *1985.*

104. Mampalam, T.J., Gonzalez, M. F., and Weinstein, P., "Neuronal Changes in Fetal Cortex Transplanted to Ischemic Adult Rat Cortex," *Journal of Neurosurgery* 69:904-912, 1988.

105. Marciano, F.F., and Gash, D.M., "Structural and Functional Relationships of Grafted Vasopressin Neurons," *Brain Research* 370:338-342, *1986.*

106. Marciano, F.F., Gash, D.M., and Sladek, J.R., Jr., "Transplanted Vasopressin Neurons: Structural

and Functional Correlates," ***Neural Grafting in the Mammalian CNS***, A. Björklund and U. Stenevi (eds.) (Amsterdam: Elsevier Science Publishers, 1985).

107. Marciano, F.F., Wiegard, S.J., Sladek, J. R., Jr., et al., 'Fetal Hypothalamic Transplants Promote Survival and Functional Regeneration of Axotomized Adult Supraoptic Magnocellular Neurons," ***Brain Research*** 483:135-142, ***1989.***
108. Morihisa, J.M., Nakamura, R.K., Freed, W.J., et al., "Adrenal Medulla Grafts Survive and Exhibit Catecholamine-Specific Fluorescence in the Primate Brain,' ***Experimental Neurology*** 84:643-653, ***1984.***
109. Mudrick, L.A., Leung, P.P., Baimbridge, K.G., et al., "Neuronal Transplants Used in the Repair of Acute Ischemic Injury in the Central Nervous System," ***Progress in Brain Research*** 78:87-93, ***1988.***
110. Mufson, E.J., Labbe, R., and Stein, D. G., "Morphologic Features of Embryonic Neocortex Grafts in Adult Rats Following Frontal Cortical Ablation," ***Brain Research*** 401:162-167, ***1987.***
111. Nash, D.R., Kaplan, S.M., Norman, A.B., et al., "An Evaluation of the Possible Protective Effects of Neonatal Striatal Transplants on Kainic Acid-Induced Lesions,'' paper presented at the annual meeting of the Society for Neuroscience, Toronto, Nov. 18, 1988.
112. Nishino, H., One, T., Shibata, R., et al., "Adrenal Medullary Cells Transmute Into Dopaminergic Neurons in Dopamine-Depleted Rat Caudate and Ameliorate Motor Disturbances," ***Brain Research*** 445:325-337, ***1988.***
113. Norman, A. B., Calderon, S.F., Giordano, M., et al., ''Striatal Tissue Transplants Attenuate Apomorphine-Induced Rotational Behavior in Rats With Unilateral Kainic Acid Lesions," *Neuropharmacology* 27:333-336, ***1988.***
114. Norman, A. B., Lehman, M.N., and Sanberg, P.R., ''Functional Effects of Fetal Striatal Transplants," ***Brain Research Bulletin*** 22:163-172, ***1989.***
115. ***Nornes,*** H., Björklund, A., and Stenevi, U., "Reinnervation of the Denervated Adult Spinal Cord of Rats by Intraspinal Transplants of Embryonic Brain Stem Neurons," Cell ***and Tissue Research 230:15-35, 1983.***
116. Nygren, L. G., Olson, L., and Seiger, A., ''Monoaminergic Reinnervation of the Transected Spinal Cord by Homologous Fetal Brain Grafts," ***Brain Research*** 129:227-235, ***1977.***
117. Olanow, C.W., Cahill, D., and Cox, C., ''Autologous Transplantation of Adrenal Medulla to Caudate Nucleus in Parkinson's Disease," ***Neurology*** 38(supp.1):142, ***1988.***
118. Penn, R.D., Goetz, C.G., Tanner, C.M., et al., "The Adrenal Medullary Transplant Operation for Parkinson's Disease: Clinical Observations in Five Patients," ***Neurosurgery*** 22:999-1004, ***1988.***
119. Perlow, M.J., Freed, W.J., Hoffer, B.J., et al., "Brain Grafts Reduce Motor Abnormalities Produced by Destruction of the Nigrostriatal Doparnine System, " ***Science 204%43-647, 1979.***
120. Peterson, D.I., Price, M.L., and Small, C. S., "Autopsy Findings in a Patient That Had an Adrenal-to-Brain Transplant for Parkinson's Disease,' ***Neurology*** 39:235-238, 1989.
121. Pezzoli, G., Fahn, S., Dwork, A., et al., ''Non-Chromaffin Tissue Plus Nerve Growth Factor Reduces Experimental Parkinsonism in Aged Rats," ***Brain Research*** 459:398-403, ***1988.***
122. ***Price,*** D.L., Troncoso, J. C., Whitehouse, P.J., et al., "Approaches to Neurodegenerative Diseases," ***Diseases of the Nervous System: Clinical Neurobiology,*** A.K. Asbury, G.M. McKhann, and W.I. McDonald (eds.) (Philadelphia, PA: W.B. Saunders, 1986).
123. Privat, A., Mansour, H., Pavy, A., et al., "Transplantation of Dissociated Fetal Serotonin Neurons Into the Transected Spinal Cord of Adult Rats," ***Neuroscience Letters*** 66:61-66, ***1986.***
124. Redmond, D.E., Sladek, J.R., Jr., Roth, R.H., et al., ''Fetal Neuronal Grafts in Monkeys Given Methylphenyl-tetrahydropyridine," *Lancet* 1:1125-1127, 1986.
125. Reier, P.J., Bregman, B. S., and Wujek, J.R., ''Intraspinal Transplantation of Embryonic Spinal Cord Tissue in Neonatal and Adult Rats," ***Journal of Comparative Neurology*** 247:275-296, ***1986.***
126. Richardson, P. M., McGuiness, U. M., and Aguayo, A.J., "PeripheralNerve Autografts to the Rat Spinal Cord: Studies With Axonal Tracing Methods," ***Brain Research*** 237:147-162, ***1982.***
127. Rosenberg, M. B., Friedmann, T., Robertson, R. C., et al., "Grafting Genetically Modified Cells to the Darnaged Brain: Restorative Effects of NGF Expression," ***Science*** 242:1575-1578, ***1988.***
128. Rutherford, A., Garcia-Munoz, M., Dunnett, S. B., et al., ''Electrophysiological Demonstration of Host Cortical Inputs to Striatal Grafts," ***Neuroscience Letters*** 83:275-281, ***1987.***
129. Sanberg, P.R., Henault, M.A., and Deckel, A.W., "Locomotor Hyperactivity: Effects of Multiple Striatal Transplants in an Animal Model of Huntington's Disease,' ***Pharmacology, Biochemistry, and Behavior*** 25:297-300, ***1986.***
130. Sceats, D.J., Friedman, W.A., Sypert, G.W., et al., ''Regeneration in Peripheral Nerve Grafts to the Cat Spinal Cord,'' ***Brain Research*** 362:149-156, ***1986.***
131. Schmidt, R.H., Ingvar, M., Lindvall, O., et al., "Functional Activity of Substantial Nigra Grafts

Reinnervating the Striatum: Neuro-transmitter Metabolism and C-2-deoxy-D-Glucose Autoradiography,'' *Journal of Neurochemistry* 38:737-748, *1982.*

132. Science News, "Experimental Cell Grafts for Huntington's," *Science News* 133:268, *1988.*
133. Siegal, J.D., Kliot, M., Smith, G.M., et al., "Induced Regeneration of Cur Dorsal Root Fibers Into Adult Rat Spinal Cord," paper presented at the annual meeting of the Society for Neuroscience, Toronto, Nov. 18, 1988.
134. Sieradzan, K., and Vrbova, G., "Replacement of Missing Motoneurons by Embryonic Grafts in the Rat Spinal Cord,' *Neuroscience* 31:1 *15-136,1989.*
135. Sladek, J. R., Jr., Redmond, D.E., Jr., Collier, T. J., et al., "Fetal Dopamine Neural Grafts: Extended Reversal of Methyl-phenyl-tetrahydropyridine-Induced Parkinsonism in Monkeys," *Progress in Brain Research* 78:497-506, *1988.*
136. Sladek, J.R., Jr., Scholer, M.F.D., Netter, D. M., et al., ''Immuno-histochemical Analysis of Vasopressin Neurons Transplanted Into the Brattleboro Rat,' *Annals of the New York Academy of Sciences* 394:102-114, *1982.*
137. Sladek, J.R., Jr., and Sholson, I., "Neural Transplantation: A Call for Patience Rather Than Patients," *Science* 240:1386-1388, *1988.*
138. Stevens, J.R., Phillips, I., and Freed, W.J., ''CerebralTransplants for Seizures: preliminary Results," *Epilepsia* 29:731-737, *1988.*
139. Strecker, R.E., Sharp, T., Brundin, P.; et al., ''Autoregulation of Dopamine Release and Metabolism by Intrastriatal Nigral Grafts as Revealed by Intracerebral Dialysis,' *Neuroscience* 22:169-178, *1987.*
140. Stromberg, I., Herrera-Marschitz, M., Ungerstedt, U., et al., "Chronic Implants of Chromaffin Tissue Into the Doparnine-Denervated Striatum: Effects of NGF on Graft Survival, Fiber Outgrowth and Rotational Behavior," *Experimental Brain Research* 60:335-349, *1985.*
141. Stromberg, I., Johnson, S., Hoffer, B., et al., ''Reinnervation of Doparnine-Denervated Striatum by Substantial Nigra Transplants: Immunohistochemical and Electrophysiological Correlates, " *Neuroscience* 14:981-990, *1985.*
142. Tang, Y., and Bernstein, J. J., "Rapid Rejection of Fetal Chick Neocortical Xenografts Into the Spinal Cord of Adult Rats," *Neuroscience Letters 36:389-*392, 1986.
143. Tanner, C.M., Watts, R.L., Bakay, R.A.R., et al., letter, New *England Journal of Medicine* 321:325, *1989.*
144. Tessler, A., Himes, B.T., Houle, J., et al., "Regeneration of Adult Dorsal Roots Into Transplants of Embryonic Spinal Cord," *Journal of Comparative Neurology* 270:537-548, *1988.*
145. Tulipan, N., Huang, S., Whetsell, W.O., et al., "Neonatal Striatal Grafts Prevent Lethal Syndrome Produced by Bilateral Intra-Striatal Injection of Kainic Acid," *Brain Research* 377:163-167, *1986.*
146. Walker, P.D., and McAllister, J.P., "Minimal Connectivity Between Neostriatal Transplants and the Host Brain," *Brain Research* 425:34-44, *1987.*
147. Walsh, J.P., Zhou, F. C., Hull, C.D., et al., "Physiological and Morphological Characterization of Striatal Neurons Transplanted Into the Adult Rat Striatum," *Synapse* 2:37-44, *1988.*
148. Watts, R.L., Balmy, R.A.E., Iuvone, P.M., et al., "Autologous Adrenal-Caudate Transplantation in Patients With Parkinson's Disease," Neurology 38(supp.1):143, 1988.
149. Waxman, S.G., "Demyelination in Spinal Cord Injuries," *Journal of Neurological Sciences 91:1-14, 1989.*
150. Weiner, S.A., Dunnett, S. B., Salamone, J.D., et al., "Transplantation of Embryonic Ventral Forebrain Grafts to the Neocortex of Rats With Bilateral Lesions of Nucleus Basalis Magnocellularis Ameliorates a Lesion-Induced Deficit in Spatial Memory," *Brain Research* 463:192-197, *1988.*
151. Wolff, J.A., Fisher, L. J., Xu, L.T., et al., "Grafting Fibroblasts Genetically Modified To Produce L-dopa in a Rat Model of Parkinson's Disease," *Proceedings of the National Academy of Sciences, U.S.A.* 86:9011-9014, *1989.*
152. Yirmiya, R., Zhou, F. C., and Holder, M.D., "Partial Recovery of Gustatory Function After Neural Tissue Transplantation to the Lesioned Gustatory Neocortex,'' *Brain Research Bulletin* 20:619-625, *1988.*
153. Zetterstrom, T., Brundin, P., Gage, F.H., et al., "In Vivo Measurement of Spontaneous Release Metabolism of Dopamine From Intrastriatal Nigral Grafts Using Intracerebral Dialysis," *Brain Research 362: 344-349, 1986.*

Chapter 6
Relevant Neurological Disorders

CONTENTS

Boxes

Figures

Tables

Chapter 6
Relevant Neurological Disorders

Reports of neural grafts relieving symptoms of Parkinson's disease have captured the attention of the medical profession and public policymakers. Much of their excitement derives from the somber fact that Parkinson's disease is a progressively debilitating illness, the symptoms of which can be only imperfectly controlled. In fact, many central nervous system (CNS) injuries and diseases are marked by severe, unrelenting symptoms that defy cure and exact a great toll in personal suffering and societal costs. Since current animal research intimates that neural grafting may be applicable to the study and treatment of diverse neurological disorders, this technology may ultimately have a significant impact on medicine and society.

Exactly how far-reaching a therapeutic intervention is neural grafting likely to become? Its use as a medical treatment is most advanced in Parkinson's disease, but even there its ultimate therapeutic value is far from established. The study of neural grafting for the treatment of other neurological disorders is faced with important barriers, including inadequate animal models and incomplete knowledge about the basic mechanisms underlying many CNS diseases and injuries. (See ch. 5 for details.) Despite these reasons for caution, it is notable that animal research employing neural grafting has in many cases improved structural or functional deficits in the CNS. These results are preliminary and their ultimate application is unknown, but the amount and diversity of neural grafting research suggests wide-ranging potential applications.

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 (tables 6-1 and 6-2; figure 6-l). Not all neurological disorders are amenable to treatment by neural grafting. In this chapter, the Office of Technology Assessment (OTA) identifies those disorders that may one day be treatable with grafting technology. The criteria for selection were:

- current understanding of the nature and cause of the condition suggests that neural grafting may be a beneficial treatment approach, and
- results from animal experiments indicate the possibility of therapeutic value.

Table 6-1—incidence of Neurological Disorders in the United States

Neurological disorder	Incidence
Stroke	500,000
Brain injury	500,000
Alzheimer's disease	130,000
Epilepsy	125,000
Parkinson's disease	50,000
Spinal cord injury	10,000
Multiple sclerosis	8,800
Amyotrophic lateral sclerosis	5,000
Huntington's disease	850

NOTE: Incidence is defined as the number of new cases of a disease estimated to occur each year in the United States. Sources for estimates are the same as those in the text.

SOURCE: Office of Technology Assessment, 1990.

Table 6-2—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

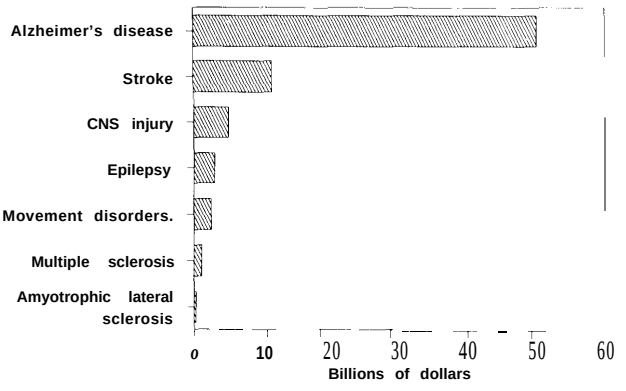
a Estimate of persons permanently disabled from head injury.

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. Sources for estimates are the same as those in the text.

SOURCE: Office of Technology Assessment, 1990.

Although it is reasonable to underscore the potential of neural grafting for the treatment of patients suffering from the neurological disorders chosen, neural grafting as a general therapeutic approach is in the very early stages of development, and predictions of its ultimate utility are speculative at best. Furthermore, only a subset of patients suffering from a particular disorder may benefit from neural grafting. For example, in experiments, grafting with adrenal medulla tissue appears to be more successful if the tissue is derived from a younger rather than an older animal (15). A brief review of the current understanding of, treatment

Figure 8-I-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, 1990.

approaches to, and epidemiological data[1] on each of the designated disorders is presented, exemplifying some of the factors that drive neural grafting research. (A detailed description of the neural grafting research related to each of the listed disorders is presented in ch. 5.)

The epidemiology of the neurological disorders included in this chapter warrants special discussion. In some instances, epidemiological data are inadequate, despite the extensive national health and mortality data collected by the Federal Government (16). This lack of data may reflect several factors. Some disorders are difficult to diagnose. Some are rare and thus elude medical data collection systems. Epidemiological studies can also be confounded by ambiguous criteria for diagnosing a disorder or variations in health care among communities. Many studies were conducted using populations that are not necessarily representative of the United States; for example, information has been derived from local community studies or surveys in which institutionalized persons were not included. Despite these concerns and others, the epidemiological data used in this chapter testify to the significant impact these neurological disorders have on society.

NEURODEGENERATIVE DISORDERS

Parkinson's Disease

In 1817 Dr. James Parkinson described six patients with marked shaking and impaired mobility (46). He called this condition "shaking palsy." Other physicians noted similar cases and named the disease after Parkinson. The predominant pathological change observed in persons with Parkinson's disease is death of nerve cells in a region of the brain called the substantial nigra. In the healthy brain, nerve cells in the substantial nigra communicate with nerve cells located in the striatum, using the chemical transmitter dopamine. Death of substantial nigra nerve cells and the resulting dopamine depletion lead to the symptoms characteristic of the disease--tremor, slowing of movement, and rigidity.

Parkinsonism represents not just one disease, but a collection of illnesses. Some manifestations of parkinsonism are secondary to known causes (e.g., drugs and other toxic chemicals, rare brain tumors, and recurrent head injuries, such as those sustained by professional boxers) (32). The most common form of parkinsonism, however, is that marked by a progressive loss of nerve cells in the substantial nigra due to unknown causes. This subgroup of parkinsonism is called idiopathic Parkinson's disease, or just Parkinson's disease, and it accounts for 80 to 90 percent of parkinsonism cases. In the following section, when discussing the scope of parkinsonism, all forms of the disease will be considered; when examining potential causes of the disorder, the focus will be on Parkinson's disease.

While it is not known what causes the nerve cell death in Parkinson's disease, there is now considerable evidence that the disease process begins a number of years before the clinical features become visible (33, 39, 41). Nerve cell death in the substantial nigra proceeds slowly and does not produce any symptoms until a critical number of cells (80 percent or more) has died.

The onset of symptoms of Parkinson's disease is so imperceptible that patients usually require assis-

[1]Epidemiological data are presented as *incidence,* the number of new cases occurring during a specified period of time (usually 1 year) within a designated area; *incidence rate,* incidence per unit of Population *prevalence, the* total number of cases in existence at a specified time in a designated *area; prevalence rate,* prevalence per unit of population; and *mortality rate, the* number of deaths attributable to a disorder during a specified period of time within a designated area per unit of population.

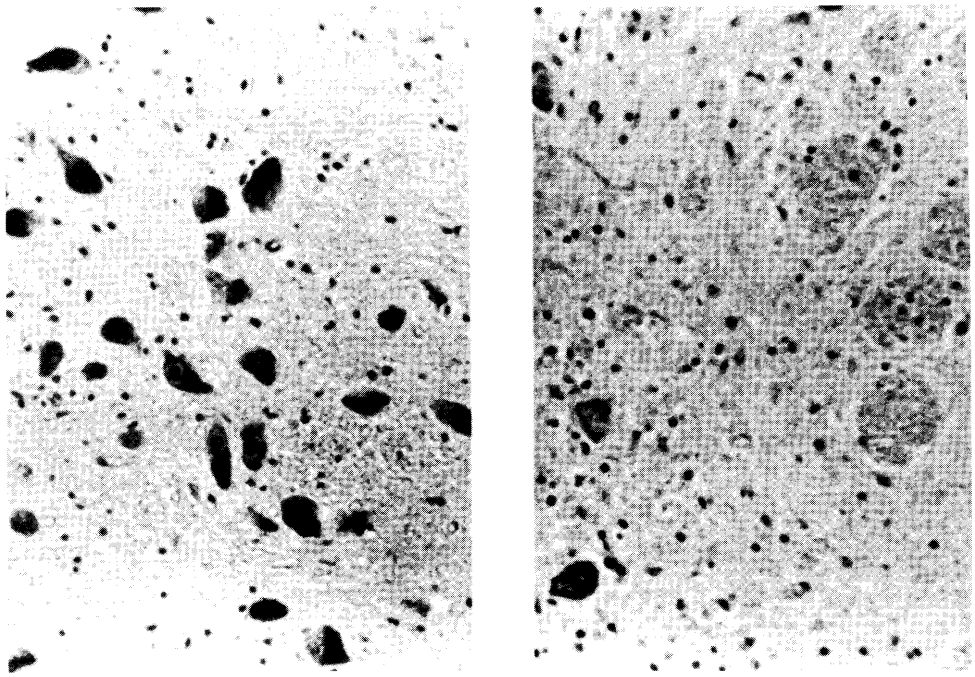


Photo credit: B. Pansky, Medical College of Ohio

Right: picture of the brain of a Parkinson's disease patient showing significant reduction in nerve cells as compared to the adjacent picture, showing the same region of the brain in a normal individual.

tance from friends and relatives to recall its first manifestation. Parkinson's disease is extremely rare in persons under age 20, but the incidence and prevalence rates increase with age. In a study of 806 Parkinson's patients, the median age of onset was found to be 63 (i.e., half the patients had symptoms by their 63rd birthday), and the majority (56 percent) of patients evidenced symptoms before age 65. The mean duration of illness (onset to death) varied from 8 to 14 years (40).

The most crucial element in determiningg the cause of Parkinson's disease is identifying the source of the nerve cell damage. Although the disease is more common among older persons, there is little evidence that it is related to arteriosclerosis, tumor, brain injury, or nutritional problems often associated with aging. Other possible causes may be genetic factors, altered immune system function, or infection. In general, however, there is a lack of evidence that any of these factors plays a role in Parkinson's disease.

Since it is known that certain toxic substances in the environment can produce parkinsonism, there is great interest in examining the role of exogenous toxins in Parkinson's disease (box 6-A). Because of the ubiquitous nature of Parkinson's disease, many substances have been suggested as possible causative agents. For example, nine metals-aluminum, arsenic, calcium, copper, iron, manganese, magnesium, mercury, and zinc-have been correlated with Parkinson's disease (10). As yet, however, metal toxicity as a cause of Parkinson's disease does not have a sound scientific basis.

In 1979, it was discovered that a synthetic narcotic, l-methyl-4-phenyl-l,2,3,6-tetrahydropyridine (MPTP), can cause parkinsonism in humans (9) (see box 5-A). Subsequent observations suggested that Parkinson's disease may be caused by a toxic substance related to MPTP (14). Drugs that inhibit MPTP's toxic effect are currently under investigation for treating Parkinson's disease.

The standard treatment for Parkinson's disease has been drug therapy aimed at increasing dopamine in the brain (50). Dopamine is not readily absorbed into the brain, so administration of dopamine itself is not efficacious. However, levodopa (L-dopa), the precursor of dopamine, is a very effective treatment. When L-dopa is taken, it is absorbed into the brain from the blood and is converted into dopamine by the remaining substantial nigra nerve cells, amelio-

Box 6-A--Cycads and Amyotrophic Lateral Sclerosis, Parkinson's Disease, and Dementia

Amyotrophic lateral sclerosis-Parkinson's disease-dementia (ALS-P-D) syndrome has been known among the Chamorro natives of the Mariana Islands in the Pacific Ocean for more than 150 years and came to the attention of U.S. scientists soon after World War II. It is characterized by parkinsonism and prominent dementia, or amyotrophic lateral sclerosis (Lou Gehrig's disease), or a combination of the three. Gradually, the incidence of the disorder declined, and that decline coincided with a change in lifestyle of the native population, including reduced ingestion of the seed from the endogenous plant known as Cycas ***circinalis. The cycad*** seed is known to contain highly potent neurotoxic substances. During World War II, cycad seeds were the major source of flour and medicine in certain parts of the MarianaIslands. The subsequent high incidence of ALS-P-D syndrome has been attributed to the increased use of cycad for food or medicine.

Monkeys fed the amino acid derived from the cycad seed (known as Beta-N-methyl amino-L-alanine, BMAA) develop motor neuron and parkinsonian symptoms and behavioral changes. Another neurotoxic syndrome in man, lathyrism, is known to be caused by an amino acid that is structurally similar to BMAA. These observations are strong indications that a cycad neurotoxic substance acting like BMAA is the cause of ALS-P-D syndrome, Although this syndrome is distinct from Parkinson's disease, studies of ALS-P-D syndrome provide valuable clues to the etiology of amyotrophic lateral sclerosis, Parkinson's disease, and Alzheimer's disease.

SOURCES: P.S. Spencer, P.B. Nunn, and J. Hugon, "Guam Amyotrophic Lateral Sclerosis-Parkinsonism-Dementia Linked to a Plant Excitant Neurotoxin," *Science* 237: 517-522, 1987; J.C. Steele and T. Guzman, "Observations About Amyotrophic Lateral Sclerosis and the Parkinso nism-Dementia Complex of Guam With Regard to Epidemiology and Etiology," *Canadian Journal of Neurological Sciences* 14:358-362, 1987.

rating many of the motor symptoms of the disease. Usually L-dopa is given in conjunction with another drug, carbidopa, which increases the amount of L-dopa that can enter the brain, thus making the drug even more effective. **Unfortunately L-dopa, the standard therapy for Parkinson's disease, does not have any effect on the progression of the disease, and nerve cell death continues unabated. As a result, in most patients L-dopa therapy loses its effectiveness as the disease progresses, and symptoms become more and more difficult to control.**

Other drugs are used to treat persons with Parkinson's disease as well (table 6-3). All of these work by counteracting the effects of decreased dopamine in the striatum (50). Like L-dopa, these drugs lessen the symptoms of Parkinson's disease without affecting the underlying mechanism that causes the nerve cell death. They, too, tend to lose their effectiveness as the disease progresses. **Neural grafting as a treatment in Parkinson's disease is currently under investigation in animals and humans. Strategies for the use of neural grafting include the replacement of degenerating neurons and the provision of dopamine.**

Recently, a drug that actually slows the progression of Parkinson's disease has been developed (47). In a group of patients with early, untreated Parkinson's disease, administration of the drug deprenyl delayed the onset of serious disability and treatment, compared to a group of patients who did not receive the drug. This finding is not only extremely important for the treatment of Parkinson's disease, it also represents the first time a drug has been shown to have a retarding effect on any neurodegenerative disorder. As more is learned about how deprenyl works, it may shed new light on the mechanisms that produce other progressive degenerative disorders such as Alzheimer's disease and Huntington's disease.

Currently, data on the national prevalence and incidence of parkinsonism are limited. Available data are based on community studies and researchers' estimates. The reported prevalence rates of parkinsonism vary widely, from 4 to 187 cases per 100,000 persons (40). This vast difference undoubtedly reflects the variability in the completeness of case findings and the varying standards of health care indifferent areas, which determine survival and hence prevalence rate. **The number of persons with parkinsonism in the United States has been estimated at 500,000 to 650,000** (37).

The reported annual incidence rates of parkinsonism also vary widely, from 5 to 24 cases per 100,000 persons (40). Data collected from a survey conducted in Rochester, Minnesota, indicated that the annual incidence rate of parkinsonism is 20.5 cases per 100,000 population (adjusted to the 1970 U.S.

Table 6-3-Drugs Used for the Treatment of Parkinson's Disease

Drug	Action
Levodopa (L-dopa)	Increases dopamine levels
Amantadine	Increases release of dopamine
Bromocriptine	Stimulates dopamine receptors
Trihexyphenidyl	Decreases acetylcholine activity
Benztropine	Decreases acetylcholine activity
Deprenyl	Slows progression of cell death[a]

[a]Under investigation.

SOURCE: Office of Technology Assessment, 1990.

population) (51). Study of the same community indicates that Parkinson's disease accounts for 85.5 percent of all cases of parkinsonism and that drug-induced cases (due to antipsychotic drugs used to treat certain mental disorders, and generally reversible) are now the second most common form of parkinsonism (51). The number of persons diagnosed with parkinsonism before age 50 seems to be increasing (2).

Huntington's Disease

Huntington's disease (HD) is an incurable, inherited disorder. Onset is commonly between the ages of 30 and 50 (7). It is heralded by personality and behavioral changes and involuntary movements (12). As HD progresses, the involuntary movements, consisting of uncontrollable writhing and jerking, or chorea, become more frequent and exaggerated, eventually rendering the patient bedridden and incapable of per-forming everyday activities. Some patients, especially with the juvenile form of the disease, also experience slowed movement and rigidity. As the disease progresses, the patient's memory and mental abilities decline. Patients may become emotionally deranged; all eventually lapse into dementia. HD leads to a steady decline in health, and death usually occurs 14 to 19 years after onset of the disease.

The brains of persons with HD appear shrunken at autopsy (12). There is extensive nerve cell death in certain regions of the brain, including the striatum and the cerebral cortex. The abnormal movement associated with HD is attributed to loss of nerve cells in the striatum; dementia is attributed to loss in other regions. The nerve cell loss associated with HD results in a profound decrease in certain brain chemicals, including GABA (gamma-aminobutyric acid) and acetylcholine. How nerve cell death is produced in HD remains a mystery.

A single defective gene appears to be responsible for HD (29). Because HD is an autosomal dominant condition, any child of a parent with HD has a 50 percent risk of inheriting the gene and succumbing to the disease. Advances in molecular genetics have pinpointed the location of the HD gene to chromosome 4 (23, 29). Although the gene itself has not been identified, knowledge of its location has important practical implications-a person or fetus carrying the HD gene may be identified prior to onset of the disease. Researchers are attempting to determine the gene's function and eventually to develop an effective treatment for HD.

There is at present no cure for HD (12). Attempts to replace deficient brain chemicals have been unsuccessful. Treatment is aimed at minimizing the abnormal movements and mental problems associated with the disease. In their normal state, nerve cells that degenerate in HD may suppress the activity of other, dopamine-producing nerve cells. Destruction of the former may lead to excessive and uncontrolled dopamine production, causing the involuntary movements typical of HD. Drug therapy aimed at blocking the action of dopamine is employed to suppress the involuntary movements. This therapy produces undesirable side-effects, however, including sedation, depression, and severe limitation of movement. Drugs are also used to help control the mental changes associated with HD. None of these drug therapies is adequate for the treatment of HD, and none prevents the progression of the disease. Since the symptoms of HD are produced by the death of specific groups of nerve cells, the limited animal research into the treatment of HD by neural grafting is based on the possibility of replacing degenerated cells or replenishing certain brain chemicals.

Huntington's disease is a relatively rare disorder. Epidemiological assessment is complicated by the fact that it is extremely rare in many regions but unusually frequent in others (37). Its worldwide prevalence rate is estimated to be five cases per 100,000 persons (37). Its incidence rate is estimated to be 3.4 cases per 1 million persons each year. In certain regions of the world, notably the Lake Maracaibo region of Venezuela, the prevalence rate is extremely high, affecting up to 700 people per 100,000 persons. Between 1968 and 1974, it was estimated that HD accounted for 1.15 deaths per 1 million persons in the United States per year (37). Although there are no reliable national data on

the prevalence of HD, it is estimated that 25,000 Americans now suffer from this disorder (7, 29, 52). Another 125,000 Americans are thought to be at risk of developing the disease.

Alzheimer's Disease

Alzheimer's disease (AD) is an incurable disorder that robs its victims of their intellect and eventually of their physical health. Its onset is insidious. Typically, its first symptom-loss of memory for recent events—is ignored or attributed to other causes, such as stress, a drug side-effect, or the general forgetfulness of old age. As the disease progresses, memory loss worsens and can no longer be ignored or dismissed. A cascade of other behavioral symptoms ensues, including confusion, irritability, combativeness, restlessness, and fearfulness. Problems with language occur, as do difficulties in executing purposeful movements. Ultimately, the AD patient will be completely helpless—incontinent, bedridden, and unable to speak or eat. Postmortem examination of the brains of AD patients reveals a loss of nerve cells in specific regions, including the basal forebrain, amygdala, hippocampus, locus ceruleus, and parts of the cerebral cortex. The nerve cell loss is associated with reduced quantities of certain brain chemicals, particularly acetylcholine. Reduced noradrenaline and other chemicals in the brain have also been reported (8, 19, 24).

At the present time, a definitive diagnosis of AD is achieved only after the patient's death; it is based on the presence of abnormal structures in the brain: neurofibrillary tangles and neuritic plaques. Neurofibrillary tangles are accumulations of twisted protein filaments inside nerve cells, and neuritic plaques are abnormal clusters of degenerating nerve cell fibers, other brain cells, and amyloid protein (see later discussion) found in the areas between neurons (49). More recent developments have linked the detection of a protein, called Alzheimer's disease-associated protein (ADAP), in postmortem brain tissue with AD (17). Chemical tests for ADAP may lead to the development of a diagnostic test for AD.

The cause or causes of Alzheimer's disease are not known. Genetic effects, environmental effects, and disrupted chemical processes in the brain have all been examined as possible factors in the disease (30, 62, 69). Recently, attention has been focused on a protein *called* beta-amyloid, which is a **key**

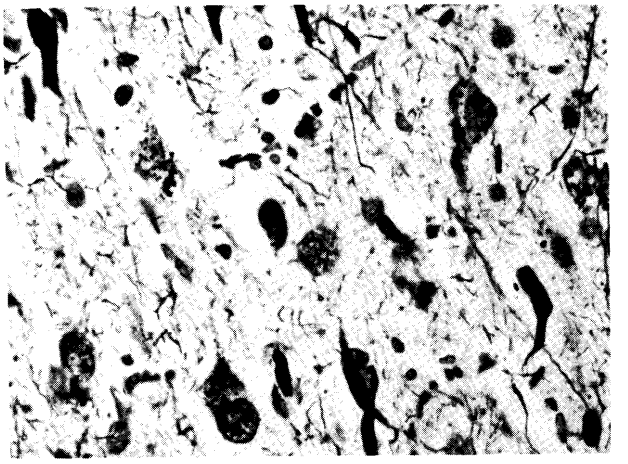


Photo credit: R. Restak, The Mind (New *York, NY: Bantam Books, 1988)*

Picture of microscopic changes, including neurofibrillary tangles and neuritic plaques, that occur in the brain when afflicted with Alzheimer's disease.

component of neuritic plaques (56). It may be that some defect in beta-amyloid synthesis leads to the formation of neuritic plaques and nerve cell degeneration seen in AD (58). Aluminum or aluminum binding is also under consideration as a possible cause of AD (69). Growth factors, specifically nerve growth factor (NGF), may also play a role in the development of AD. NGF has been shown to protect acetylcholine-producing nerve cells from experimentally induced damage in laboratory animals (27, 67).

Pharmacological treatment of AD has met with little success, and there is no cure for AD (table 6-4). As discussed earlier, AD patients suffer from a deficit of several brain chemicals, particularly acetylcholine. Since acetylcholine has been demonstrated to be involved in learning and memory, restoration or augmentation of acetylcholine in AD victims may lead to improvements in their memory and other cognitive abilities. In addition, drugs that act on other chemical systems implicated in AD may also lead to fictional improvements. None of these drugs would have an effect on the cause of the disease, and none would halt its progression. As a result of this fact and the lack of uniform success in alleviating AD symptoms with such drugs, other treatments for AD are being explored.

As mentioned earlier, NGF has been shown to prevent the degeneration of acetylcholine-producing nerve cells after injury, and it appears to improve memory in a rat model of cognitive impairment with age (13). These and other findings have led research-

Table 6-4-Drugs Being Developed for the Treatment of Alzheimer's Disease

Drug	Action
Velnacrine maleate	Inhibits cholinesterase
Physostigmine	Inhibits cholinesterase
Tetrahydroaminoacridine (THA)	Inhibits cholinesterase
Suronacrine maleate	Amplifies noradrenaline action
Milacemide	Stimulates glycine activity
Captopril	Inhibits angiotensin activity
Acetyl-L-carnitine	Enhances activity of nerve growth factor
Nimodipine	Blocks calcium channel
Idebenone	Enhances cerebral metabolism

SOURCE: J.F. Beary, "Alzheimer's Medicines: Sixteen Medicines in Testing," *American Journal of Alzheimer's Care and Related Disorders & Research* (January/February): 4-6, 1990.

ers to suggest that administration of NGF may slow the progression of the major symptoms of AD and could be efficacious in treating persons with the disease (48). The potential use of neural grafts to treat AD has been explored mainly in experiments involving rodents and is based largely on the ability of neural grafts to provide growth factors, such as NGF.

The collection of accurate statistics on the incidence and prevalence of AD is hampered by the inability to diagnose AD definitively during a patient's lifetime. AD is given as the clinical diagnosis when other causes of a progressive dementia have been eliminated (e.g., cardiovascular disease, stroke, head injury, or adverse reaction to drugs). Although improvements have been made in the ability to diagnose AD clinically (30), it remains extremely difficult to diagnose the disease definitively early in its course.

Alzheimer's disease is the primary cause of dementia in the United States. Few national statistics are available on the prevalence and incidence of AD per se; most available data relate to dementing disorders as a whole. A 1987 OTA report (62) estimated that the prevalence of severe dementia in the United States is 1.5 million persons. Mild or moderate dementia was estimated to occur in another 1 to 5 million persons. AD is estimated to account for about 66 percent of all cases of dementia.

Much of the incidence and prevalence data available specifically for AD are based on studies that differ from each other in diagnostic criteria and procedures and in the populations analyzed. Incidence rates per year have been estimated at 123.3 cases per 100,000 persons over the age 29; the age-adjusted rate was calculated to be 51.6 persons per 100,000 persons per year (54). Prevalence rates of AD have been estimated from recent community studies; AD was found among 2.0 to 10.3 percent of those over the age of 65, with an estimated 3 to 5 million persons in the United States afflicted with AD (11, 31). Estimates of the total yearly costs of AD range from $30 billion to $80 billion (28, 62).

Motor Neuron Disease: Amyotrophic Lateral Sclerosis

Motor neuron diseases destroy the nerve cells that control muscle movement, resulting in impaired muscle function. The most well-known motor neuron disease is amyotrophic lateral sclerosis (ALS), or Lou Gehrig's disease. ALS is an incurable neurological disease. The average age of patients at the time of diagnosis is 56 (44). Initial symptoms can include difficulty in performing fine tasks, weakened leg muscles, or difficulty in speech and swallowing. There is progressive loss of muscle control, and ultimately patients are unable to move, except to blink; they cannot speak, eat, or breathe without assistance, yet the mind and senses are left intact. The median survival time following onset of ALS is 23.8 months (37). Fewer than 20 percent of ALS patients survive 5 years or more.

Paralysis in ALS is produced by the selective death of nerve cells in the brain and spinal cord that control muscle movement (43, 72). No single cause of ALS has been widely accepted. Five to 10 percent of ALS is familial, and research is being directed toward uncovering its genetic underpinnings. Genetic factors were initially thought to be responsible for the high incidence of ALS observed in Guam. More recent studies, however, indicate that an environmental factor may have produced the high incidence of ALS in Guam (box 6-A) and may be responsible for the increase in ALS mortality rate in the United States (38). An infectious cause of ALS has also been considered (43). Disrupted immune system function, leading to autoimmunity, is another suspected cause of ALS, and clinical trials are now under way to evaluate the effectiveness of immunosuppression in treating the disease.

Early diagnosis of ALS can be difficult, since it is not associated with any specific chemical marker (44). Abnormal muscle function is generally detect-

able at the time of diagnosis, however, and concentrations of a chemical associated with muscle atrophy may be elevated in the blood. At present, there is no treatment or cure for ALS. Medical intervention is directed at the management of symptoms. Drugs may be employed to limit muscle spasticity and cramping and hypersalivation. Counseling and rehabilitation services are employed to help ALS patients adapt to their disability. In the final stages of the disease, a feeding tube or respirator may be used to maintain the patient. Neural grafting with motor neurons has been reported in a few animal experiments, although many difficulties characterize this approach to the treatment of ALS.

Difficulty in early diagnosis of ALS and some disagreement over nomenclature have complicated epidemiological studies of this disease (37). A recent study indicates that the mortality rate from motor neuron disease increased among the elderly between 1962 and 1984 (38). In 1987, 3,381 deaths in the United States were attributed to motor neuron disease (64). The number of people suffering from ALS in the United States can only be estimated, since there are no national data on the incidence and prevalence of this disease. The incidence of ALS is estimated from medical records in Rochester, Minnesota, between the years of 1925 and 1977; on average, two cases per 100,000 persons were diagnosed each year (37, 72). Extrapolation from these data indicates that 5,000 new cases of ALS are diagnosed in the United States each year. It is estimated that approximately 15,000 Americans suffer from ALS at any given time. Since the incidence of ALS increases with age, the number of cases is expected to increase as the population ages.

CENTRAL NERVOUS SYSTEM INJURY

Spinal Cord Injury

Spinal cord injury is any damage to the spinal cord that results in paralysis or loss of sensation in various parts of the body, or both. The magnitude of fictional loss following injury to the spinal cord is directly related to the extent of the damage and where in the spinal cord the injury occurs. Damage to the spinal cord can be caused by a sudden impact (from a motor vehicle collision or sporting injury), gradual compression of the spinal cord tissue (from a tumor, blood clot, or herniated disk), or an interruption in the blood supply to the spinal cord.

Spinal cord injury caused by sudden impact usually results from a forceful blow on the bones of the spine, causing them to strike the soft nervous system tissue of the spinal cord and injure it. The victim exhibits loss of movement and sensation below the level of the injury. This is partly due to the initial shock of the injury. The injury also sets in motion a chain of microscopic events that leads to degenerative changes. This secondary response may be the most important cause of the permanent damage associated with spinal cord injury.

Unlike sudden-onset trauma, injury due to gradual compression is the result of a relatively slow deformation of the tissue by an intruding body. While permanent loss of function can result from spinal cord compression, the functional loss is often reversed once the compressing body is removed.

Disruption of the blood supply to the spinal cord for a prolonged period of time can result in cell death and permanent damage. Any sort of blockage of blood vessels, such as a blood clot, or damage to the major arteries supplying the spinal cord can cut off the blood supply.

Whatever the cause, damage to the spinal cord disrupts the nerve cell networks and the brain's control over body functions. Injuries to the upper regions of the spinal cord affect most of the body and are often life-threatening because control of breathing may be disrupted. Patients with an injury to the upper portion of the spinal cord generally must be maintained on a respirator for the rest of their lives. Quadriplegic, or paralysis and loss of sensation from the shoulders down, results from damage to the upper spinal cord. Paraplegia, or loss of movement and sensation from the waist down, results from damage to the middle or lower portions of the spinal cord. Other results of injury to the spinal cord include muscle problems such as spasticity; sensory conditions where the patient can experience pain from the slightest touch; abnormal blood pressure and temperature regulation; disturbances of sexual function; loss of voluntary bladder control, which can lead to bladder infections; and loss of voluntary bowel function.

As many as 30 percent of persons die within 24 hours of a spinal cord injury (36). The nature of the traumatic event and the amount of force that caused

the injury are important factors related to survival during the first 24 hours. For example, one study showed that the 24-hour survival rate was 97 percent for recreational injuries and 60 percent for motor vehicle crashes (36). If a patient survives the initial spinal cord trauma, his or her chance of long-term survival is high. It has been estimated that 86 percent of patients who survive the first 24 hours following a spinal cord injury are still alive 10 years later (60).

In the event of an injury to the spinal cord, there are two phases at which therapeutic interventions can be directed-the acute phase and the chronic phase. Interventions during the acute phase are aimed at prevention of damage, while treatment during the chronic phase is directed toward improvement of function.

During the acute phase, 8 to 12 hours immediately following a spinal cord injury, surgical intervention may be necessary to prevent further damage to the spinal cord. In addition, attempts may be made to slow or confine further nerve cell death and degeneration in response to the spinal cord injury. Since it has been shown in animal experiments that only a small fraction of nerve cells has to be saved to retain some degree of function, any tissue spared could significantly improve subsequent rehabilitation. A number of drugs are being considered for use in this situation, including antioxidants, calcium channel antagonists, naloxone, thyrotropin-releasing hormone, and corticosteroids. Dramatic results have been reported when the corticosteroid methylprednisolone was administered shortly after an injury to the spinal cord (42). This treatment significantly decreases the ultimate extent of injury in patients and lessens the disability they exhibit following the injury. The continued development of drugs and procedures that prevent, or at least contain, this acute degenerative process is an important and promising area of research.

The chronic phase of treatment, aimed at rehabilitation and improving function, continues throughout the life of the patient. Some newer techniques include electrical stimulation of muscles and various biofeedback procedures. Advances in microelectronics have paved the way for the development of neural prosthetic devices to activate and coordinate activity in the injured spinal cord. All of these therapies are aimed at maximizing the rehabilitation process following an injury to the spinal cord: None is directed at repairing the damaged spinal cord. Several strategies for the use of neural grafts to repair spinal cord injury have been proposed and tested in animal experiments, including the promotion of regrowth, the bridging of the injured region, and the replacement of nerve cells in the spinal cord.

Since the vast majority of spinal cord injuries is caused by trauma, prevention is an important strategy in reducing incidence. Motor vehicle crashes have been reported to account for 48 percent of spinal cord injuries, followed by falls (20 percent), acts of violence (15 percent), and sports injuries (14 percent) (60). Older adolescents and young adults have the highest rate of spinal cord injury, both in the United States and in other countries (34).

The incidence of spinal cord injury may be underestimated because injuries resulting in immediate death may not be reported. The average age-adjusted mortality rate for spinal cord injury was estimated at 2.9 per 100,000 persons in Olmsted County, Minnesota, from 1935 to 1981 (20). The incidence rate in that population was 8.34 per 100,000 males, and 2.77 per 100,000 females (21). The estimated prevalence rate was 47.3 per 100,000 persons (20). A recent survey of a nationwide sample of institutionalized and noninstitutionalized persons estimated the prevalence rate of spinal cord injury to be 72.1 cases per 100,000 persons or a prevalence of approximately 180,000 persons in the United States (25) (box 6-B). Medical intervention, rehabilitation services, and lost income due to spinal cord injury have been estimated to cost more than $2 to $8 billion annually.

Brain Injury

Traumatic brain injury has been labeled the silent epidemic (66); brain injury is the major cause of death and disability among children and young adults in the United States (66). Since so many of the people who sustain brain injury are young, the cost to society, including medical and rehabilitation expenses, support services, and lost income, is great, estimated at nearly $25 billion each year (66).

Motor vehicle collisions, violent assaults, and falls are the main causes of head trauma and brain injury. The consequences of head trauma depend upon the amount and type of damage sustained by the brain (53). When head injury produces a mild concussion, there are usually few overt symptoms, although the brain may sustain structural damage

Box 6-13-Neurological Disorders and the Veteran

There are approximately 27 million veterans in the United States. Their medical needs are handled through the 172 medical centers and 227 outpatient clinics of the Department of Veterans Affairs (VA). In fiscal year 1989, 71,995 patients were discharged from the medical centers after having been treated for a variety of neurological disorders. These included cerebrovascular disease (18,850 patients), dementia and organic brain syndrome (13,406), epilepsy (13,950), neuromuscular diseases (7,&17), diseases of the basal ganglia (3,096), and demyelinating diseases and diseases of the spinal cord (2,755).

Spinal cord injury (SCI), caused principally by battlefield trauma during wartime and vehicular and diving injuries during peacetime, is of special concern to the VA, which maintains 20 SCI centers throughout the United States (table 6-5). The number of veterans with an SCI has been put at 45,000. During fiscal year 1987,18,300 such patients were treated at VA centers; 64 percent of their injuries were service-related. Among this patient population, 50 percent were over the age of 55, and just about all (98.9 percent) were men. Forty-one percent of the men served during World War II, veterans from the Korean conflict made up 22 percent of the patient population, and 30 percent were from the Vietnam and post-Vietnam eras. Within this VA population of SCI patients, 53 percent were paraplegic and 47 percent were quadriplegic. For fiscal year 1988, $90.8 million was allocated for direct medical care by these SCI centers.

SOURCES: L. Lehman, acting director, Neurology, Department of Veterans Affairs, Washington, DC, personal communication% April 1990; T. Stripling, Paralyzed Veterans of America, personal communication, July 1990; Department of Veterans Affairs, Spinal **Cord** Injury Service, Washington DC, 1990.

Table 6-5-Department of Veterans Affairs, Spinal Cord Injury Centers, Fiscal Year 1989

	Operating beds	Inpatients treated	Outpatient visits
Augusta, GA.	60	546	342
Brockton/ West Roxbury, MA	**115**	**548**	**201**
Bronx, NY.	**80**	**182**	**1,766**
Castle Point, NY	**43**	**259**	**972**
Cleveland, OH	**80**	**271**	**338**
East Orange, NJ	**25**	**135**	**191**
Hampton, NY	**64**	**134**	**94**
Hines, IL	**135**	**522**	**1,660**
Houston, TX	**26**	**159**	**1,327**
Long Beach, CA.	**197**	**980**	**15,316**
Memphis, TN	**120**	**690**	**3,381**
Miami, FL	**36**	**207**	**375**
Milwaukee, WI	**56**	**506**	**2,205**
Palo Alto, CA	**30**	**277**	**1,378**
Richmond, VA	**120**	**785**	**996**
San Diego, CA.	**5**	**89**	**4,195**
San Juan, PR	**20**	**197**	**1,086**
Seattle, WA	**37**	**330**	**1,613**
Sepulveda, CA[a]	**NA**	**NA**	**1,096**
St. Louis, MO	**42**	**351**	**496**
Tampa, FL	**70**	**448**	**2,588**
Total	**1,361**	**7,616**	**41,184**

Outpatient **center.**

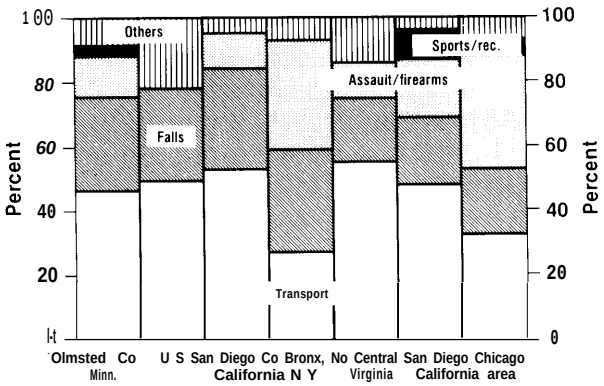
SOURCE: Department of Veterans Affairs, Spinal Cord Injury Service, Washington, DC, 1990.

with long-lasting effects. More serious head trauma can lead to diffuse injury throughout the brain, brain swelling, extensive bleeding, or direct damage of nerve cells. The sequelae of such damage depend on which areas of the brain are injured and may include temporary loss of consciousness, seizures, paralysis, loss of memory, permanent loss of responsiveness, or death.

Immediate and expert medical attention may be able to prevent death and limit complications that follow serious injury of the brain; rehabilitation may enhance and foster intact neurological functions. The death of nerve cells in the brain, however, cannot be reversed by any medical intervention at this time. The irreversible nature of brain injury emphasizes the importance of strategies aimed at preventing and reducing the severity of traumatic brain injury. **The basis for neural grafting as a therapeutic approach in brain injury is the possible replacement of degenerated nerve cells. This strategy has been examined in animal experiments.**

The system for determining the incidence and prevalence of brain injury in the United States has been decried as inadequate (35, 59). Many factors contribute to the difficulty of tracking such injuries. There is no single registry of all victims of brain injuries. Sufferers of brain injury are widely dispersed throughout the health care system; for example, 50 percent of the fatal cases of brain injury never enter the hospital, where many statistics are collected. And universal nomenclature for defining head and brain injuries is lacking. The Interagency Head Injury Task Force (66), convened in response

Figure 6-2-Types of Head Injury Causing Death



Graph illustrates regional differences in death rates following head injury due to transport (vehicle collisions), assault and use of firearms, falls, and sporting injuries.

SOURCE: J.F.Kraus, "Epidemiology of Head Injury," *Head Injury,* P.R. Cooper (cd.) (Baltimore, MD: Williams & Wilkins, 1987).

to congressional concerns about the seriousness of traumatic brain injury, affirmed the need for epidemiologica1 investigation.

Each year in the United States, 75,000 to 100,000 persons die from head injuries (66) (figure 6-2). A study of deaths associated with brain injury in the United States between 1979 and 1986, based on data from the National Center for Health Statistics, found an annual rate of 16.9 deaths per 100,000 persons, or approximately 42,250 people each year (59). A community-based study in Olmsted County, Minnesota, between 1965 and 1974, estimated that brain injuries are responsible for 32 deaths per 100,000 persons among males and 9 deaths per 100,000 persons among females (3; see also 35). Currently, there are no national data on the prevalence of brain injury. Estimates of the incidence rate of brain injury, mostly derived from community studies, indicate that 200 persons per 100,000 population per year, or 500,000 persons per year in all, suffer from injury to the brain that is serious enough to require hospital admission (35). There are no data on how many people sustain permanent loss of function due to head injuries. It has been calculated that 70,000 to 90,000 people each year are permanently disabled as a result of head injury (35).

Stroke

Most strokes are caused by cerebrovascular disease. They result in a sudden, specific neurological deficit, the severity of which varies depending on

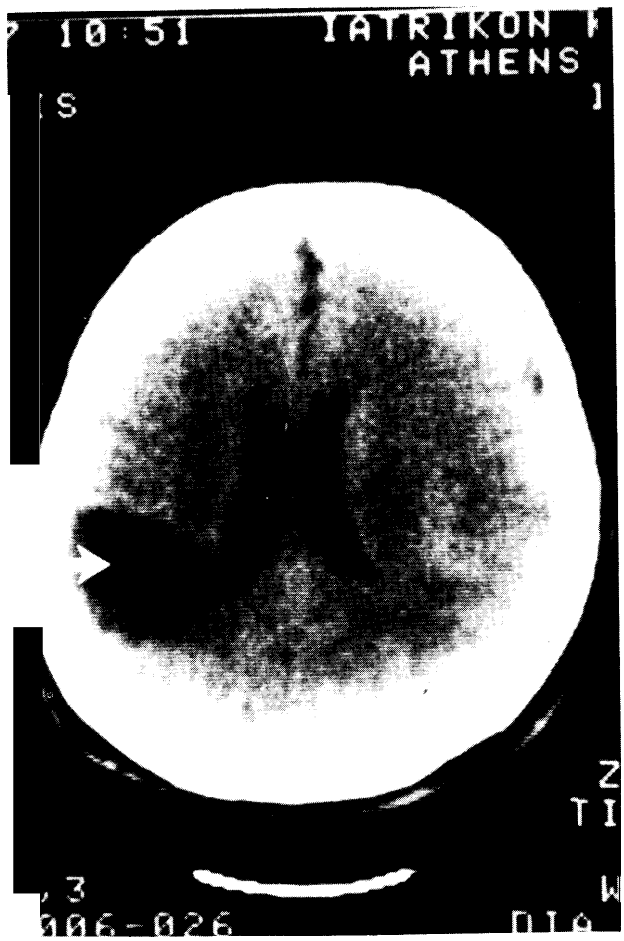


Photo credit: R. Restak,* The Mind (New *York,* NY: *Bantam Books, 1988)

Picture of CAT scan of brain following a stroke. Arrow indicates region of damage.

where in the brain the lesion occurred. Functional problems can include coma, paralysis, or inability to speak. A severe stroke can result in death.

There are two broad categories of conditions under the heading of stroke. Ischemia, or decreased blood flow, is most commonly caused by blockage of a blood vessel in the brain and produces 82 percent of strokes (45, 61). Bleeding into the brain tissue or spaces around the brain causes 18 percent of strokes and is largely attributable to rupture of blood vessels and less often to high blood pressure. Both ischemic stroke and intracranial hemorrhage interrupt normal blood flow to brain tissue and cause a shortage of oxygen and nutrients.

Currently, the brain damage produced by a stroke cannot be reversed. Therapeutic interventions are aimed at reducing any further damage in the brain and preventing a reoccurrence (71). Medical

therapy to reverse and prevent blood vessel blockage includes aspirin and other drugs that prevent or disrupt the formation of blood clots. Drugs that inhibit blood vessel spasm may also be useful. Drugs or surgery may be necessary to reduce bleeding or excess fluid in the brain. Rehabilitation therapy is advised in order to maximize functional recovery following a stroke. Recovery depends on many factors, including the site and size of the stroke and the degree of brain damage incurred.

Recent experimental data suggest that much of the brain damage induced by strokes may ultimately be preventable. The immediate nerve cell death produced by an interrupted blood supply appears to be rather modest; subsequent changes in the brain, such as changes in the blood vessels and the release of excess excitatory chemicals, may be more destructive. Experiments in animal models of stroke indicate that blocking the action of excess excitatory chemicals in the brain can reduce nerve cell death (45). Since nerve cell death causes the disability that follows stroke, replacement of the nerve cells with a neural graft is considered a potential medical therapy in some cases. Some animal experimentation has been carried out investigating this possibility.

The nomenclature for stroke has varied considerably during the last century, complicating epidemiological analysis. Furthermore, stroke is sometimes overdiagnosed (37). Despite these problems, it is apparent that stroke is the third leading cause of death in the United States, after heart disease and cancer. It is estimated that stroke costs $10 billion each year in direct medical expenses and lost income. In 1987, approximately 150,000 deaths nationwide were due to stroke, representing an age-adjusted mortality rate of 30.0 per 100,000 persons, or 7.1 percent of all deaths (66). With increasing age, the incidence of stroke, as well as death due to stroke, increases; however, the nationwide incidence of and mortality rate from stroke are declining, perhaps due to improved control of hypertension, diabetes, and cardiac disease, as well as a reduction in cigarette smoking (61, 71).

Mortality statistics do not present the entire medical picture of stroke, since strokes are not always fatal. There are 500,000 new stroke victims in the United States annually (45). Among persons under age 54, the yearly incidence rate of stroke is 17 per 100,000 persons (37). Among persons over age 65, the annual incidence of stroke is more than 500 per 100,000 persons.

A national survey conducted by the National Institutes of Health found that as of 1976,1.7 million people still living had a history of hospitalization for stroke (65). The most recent national data available from the National Health Interview Survey indicated a prevalence rate in the United States of 1,120 cases per 100,000 persons (66).

EPILEPSY

An epileptic seizure may suddenly render an individual unconscious and lead to violent body movements, or it may simply cause a brief loss of consciousness or repetitive and sometimes subtle movements such as chewing. The occurrence of a seizure does not necessarily lead to a diagnosis of epilepsy, since seizures may result from infections, head injury, and tumors. In general, a diagnosis of epilepsy is made if repeated seizures occur in a patient due to CNS dysfunction.

Approximately one-half of those who suffer from epilepsy experience their first seizure before age 20 (18). Seizures are classified as generalized or partial, depending on the nature of the onset of abnormal brain function (table 6-6). Electrical recording of brain activity during a seizure and clinical symptoms are used to delineate the different classes of seizure. Generalized seizures involve large regions of the brain and are often characterized by loss of consciousness and symmetrical involvement of the muscles of the body. A partial seizure reflects abnormal activity beginning in a single area of the brain and usually results in more restricted disturbances.

The electrical impulses that are normally used by nerve cells to communicate and to send information throughout the body go awry in epilepsy. Nerve cells display excessive excitability and dispatch electrical impulses at a manic rate. At the same time, metabolism in the brain is profoundly altered. Nerve cells may be unable to regulate properly the entry of charged molecules, thus rendering them more excitable. In addition, research indicates that abnormal input from other nerve cells may lead to enhanced excitability.

Management of epileptic disorders is complex (18). The first step involves accurate diagnosis and determination of the cause of the seizures. A careful

Table 6-6—Types of Epileptic Seizures

- Partial (seizures that begin in a discrete region of the brain)
  - simple partial (no loss of consciousness)
  - complex partial (impaired consciousness)
  - partial seizures that spread throughout the brain
- Generalized (seizures that begin throughout the brain)
- Unclassified

SOURCE: Office of Technology Assessment, 1990.

medical history and sometimes intensive monitoring are necessary to diagnose the origin of seizures; in most cases, however, the cause of seizures is not found. The second step is to design a drug therapy. Anticonvulsant drugs can completely eliminate or at least significantly curtail the occurrence of seizures among 75 percent of persons with epilepsy; however, none of the drugs currently available can cure epilepsy, and all have side-effects. Anticonvulsant drugs may act by blocking the entry of charged molecules into nerve cells or by increasing the action of the inhibitory brain neurotransmitter GABA. Constant assessment and monitoring of the dosage and combination of drugs to control a patient's epilepsy are generally necessary. Another treatment for some cases of epilepsy involves surgical removal of the hyperexcitable nerve cells. Initial animal experiments have shown that neural grafting can inhibit seizures, suggesting that this approach may one day provide a useful therapy for some cases of epilepsy (5).

There are a number of sources of epidemiologica1 data about epilepsy. Estimates of the prevalence and incidence of epilepsy vary with the definition of the disorder (a single seizure v. chronic seizures). The source of the data, whether from medical records or surveys, also adds variability to the estimates. There is no doubt, however, that epilepsy is a common disorder. Five to 10 percent of the population will suffer at least one epileptic seizure (26). The prevalence rate of epilepsy in 1974 in Rochester, Minnesota, was 650 cases per 100,000 persons; when extrapolated nationwide, these data indicate that there are approximately 1.5 million cases of epilepsy in the United States (37). Approximately 40 to 60 new cases per 100,000 persons are diagnosed each year (37).

DEMYELINATING DISORDERS: MULTIPLE SCLEROSIS

Multiple sclerosis (MS) is a chronic neurological disease characterized by an array of symptoms,

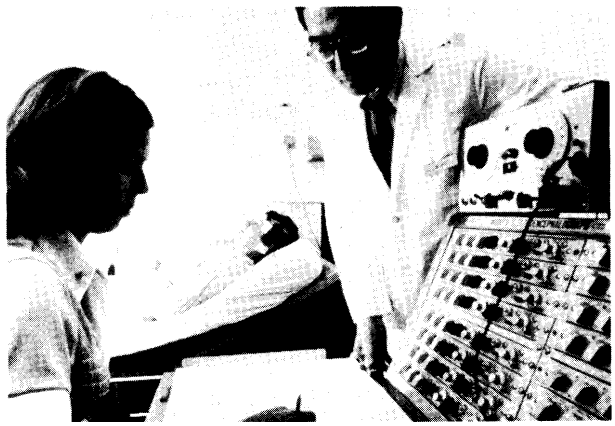


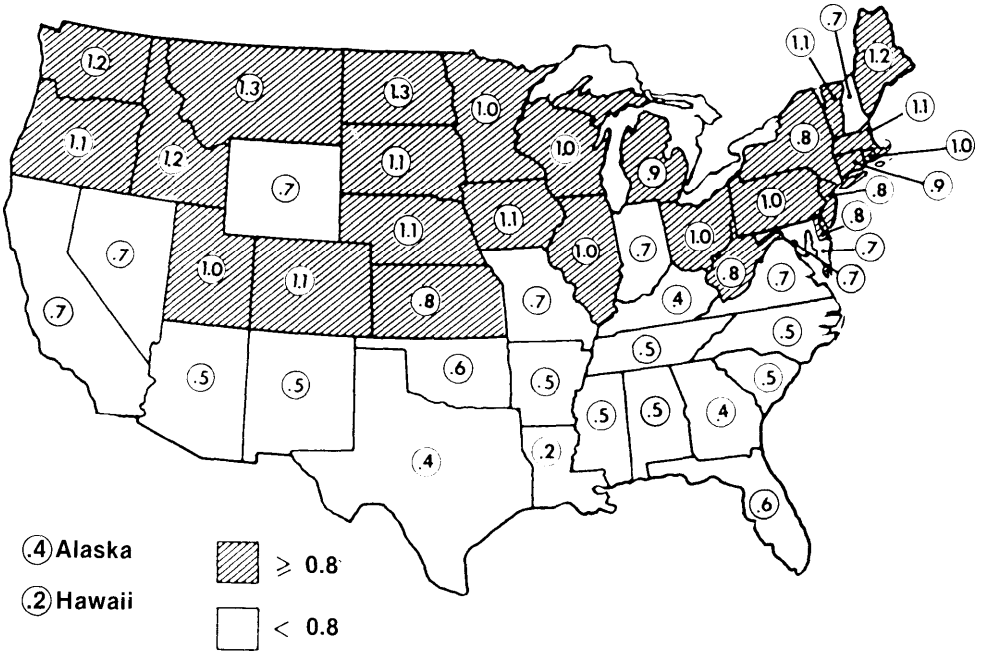
Photo credit: National Institutes of Health

Picture of measurement of brain activity using an electroencephalograph, or EEG. Measurement is used to detect epilepsy.

depending on wherein the CNS lesions occur (57). Initial symptoms of MS may include muscle weakness; numbness and tingling, especially in the arms and legs; loss of coordination and balance; dizziness; slurred speech; fatigue; and loss of bowel or bladder control. Optic neuritis, which can result in blurred or double vision or disturbances of color vision, may bean early symptom of the disease. The onset of MS usually occurs between the ages of 20 and 40 (70). The course of the disease is unpredictable; typically, symptoms emerge, go away completely, and then reemerge. Less frequently, symptoms worsen steadily without remission.

The relapsing-remitting symptoms of MS are associated with widespread lesions of myelin sheaths in the CNS. Myelin surrounds many nerve fibers in the nervous system, insulating them and thus permitting the rapid conduction of electrical impulses. When the myelin sheath is destroyed, the conduction of electrical nerve impulses is retarded, producing the characteristic symptoms of MS. It is not known what causes the destruction of myelin in MS. Some data suggest that an infectious agent, particularly a virus, acquired between the ages of 5 and 15 maybe involved, although no such agent has been isolated, despite extensive research (6, 70). Unequal geographic distribution of MS seems to support the idea of an infectious or environmental cause (37). The disease rarely occurs near the equator, and its incidence increases with latitude in the Northern and Southern hemispheres (figure 6-3). Furthermore, migration before the age of 15 to a geographic area with a different incidence of MS

Figure 6-3-Geographical Differences in Death Rate Due to Multiple Sclerosis



Deaths per 100,000 persons, by state of residence at death. Death rates are significantly higher in the northern versus the southern regions of the United States.

SOURCE: J.F. Kurtzke and L.T. Kurland, "The Epidemiology of Necrologic Disease," *Clinical* Neurology, R.J. Joynt (cd.) (Philadelphia, PA: J.B. Lippincott, 1989).

changes an individual's risk of MS to that of the native population. While the immediate cause of MS is likely to be found in the environment, susceptibility is probably genetically determined.

Other data indicate that disrupted immune function may underlie MS. Some genes related to immune system function are associated with MS (55). Furthermore, immune system cells that respond to components of myelin have been identified in individuals with MS (1, 68). It is postulated that a virus may initiate this immune response in genetically susceptible individuals.

Diagnosis of MS presents some difficulties; it rests upon the characteristic symptoms, direct viewing of demyelination within the CNS using MRI (magnetic resonance imaging), and the absence of any other explanation. There is no cure for MS at present. Therapy is directed at shortening the time during which symptoms are present and alleviating disabling symptoms such as muscle spasms or pain. When symptoms of MS flare up, ACTH (adrenocorticotropic hormone) or methylprednisolone is often administered. Such long-term measures, which inhibit immune system function, have not proven to prevent new or more disabling bouts with MS, and they cause serious side-effects. A few animal experiments have suggested that myelin-producing cells can be introduced into the CNS to seek out and myelinate nerve fibers; this research suggests a potential role for neural grafting in MS (22).

A national survey conducted in the 1970s indicated that approximately 10,000 persons are diagnosed with MS annually (4). According to that survey, there were 123,000 MS patients in the United States in 1976, a prevalence rate of 58 cases per 100,000 persons. More current national prevalence data, from the National Health Interview Survey, estimate that 151,000 persons suffer from MS, a prevalence rate of 70 cases per 100,000 persons (63). The incidence and prevalence of MS were also estimated from medical records in Olmsted County, Minnesota, between 1905 and 1984 (70). The prevalence rate of MS increased during the last 10 years of the study, averaging 175 cases per 100,000 persons. Extrapolated nationwide and accounting for the geographical gradient of MS, these data suggest that approximately 250,000 people in the United States suffer from MS. This observed

increase in MS was attributed largely to improved diagnosis, although an increase in survival or occurrence of the disease may have also contributed. Two-thirds of the MS patients were ambulatory and able to work.

SUMMARY AND CONCLUSIONS

Neurological disorders that may one day prove amenable to treatment with neural grafting are listed in this chapter. It is impossible to assert definitively the future applications of neural grafting at this early stage in its development. However, the wide array of animal research currently probing the many different uses and actions of neural grafting suggests that this technology may ultimately have several applications. Furthermore, as new discoveries unveil the chemical and structural alterations associated with other brain disorders, additional applications of neural grafting may become apparent.

While precise epidemiological data are often unavailable, it is clear that the neurological disorders listed in this chapter area significant cause of illness, disability, and death in the United States. For many of these disorders, there is no known cause and no adequate therapy. For none is there a cure for the nerve ceil death or other underlying pathology that causes mortality and morbidity. Research efforts involving genetic analysis, molecular biology, and new drugs, as well as neural grafting, continue to improve investigators' understanding of the disorders and to suggest treatments.

CHAPTER 6 REFERENCES

1. Allegretto, M., Nicklas, J.A., Srirarn, S., et al., "T-Cells Responsive to Myelin Basic Protein in Patients With Multiple Sclerosis," *Science 247:718-721, 1990.*
2. American Parkinson's Disease Association, quarterly newsletter, winter 1989-90.
3. Annegers, J.F., Grabow, J.D., Kurland, L.T., et al., "The Incidence, Causes, and Secular Trends of Head Trauma in Olmsted County, MN, 1935-1974," *Neurology* 30:912-919, *1980.*
4. Baum, H.M., and Rothschild, B.B., "The Incidence and Prevalence of Reported Multiple Sclerosis," *Annals of Neurology* 10:420-428,1981.
5. Buzsaki, G., Ponomareff, G., Bayardo, F., et al., "Suppression and Induction of Epileptic Activity by Neuronal Grafts," *Proceedings of the National Academy of Sciences, U.S.A.* 85:9327-9330, *1988.*
6. Calder, V., Owen, S., Watson, C., et al., "MS: A Localized Immune Disease of the Central Nervous System," *Immunology Today* 10:99-103, *1989.*
7. Conneally, P.M., "Huntington's Disease: Genetics and Epidemiology," *American Journal of Human Genetics* 36:506-526, *1984.*
8. Davies, P., Katzman, R., and Terry, R.D., "Reduced Somatostatin-like Immunoreactivity in Cerebral Cortex From Cases of Alzheimer's Disease Senile Dementia," *Nature* 288:279-180, *1980.*
9. Davis, G. C., Williams, A. C., Markey, S.P., et al., "Chronic Parkinsonism Secondary to Intravenous Injection of Meperidine-analog Synthesis," *Psychiatric Research* 1:249-254, *1979.*
10. Dreosti, I.E., and Smith, R.M., *Neurobiology of Trace Elements* (Clifton, NJ: Humana Press, 1983), vols. 1 and 2.
11. Evans, D.A., Funkenstein, H.H., Albert, M. S., et al., "Prevalence of Alzheimer's Disease in a Community Population of Older Persons Higher Than Previously Reported,' *Journal of the American Medical Association* 262:2551-2556, *1989.*
12. Fahn, S., "Huntington's Disease and Other Forms of Chorea," *Merritt's Textbook of Neurology,* L.P. Rowland (ed.) (Philadelphia, PA: Lea & Febiger, 1989).
13. Fischer, W., Wictorin, K., Björklund, A., et al., "Amelioration of Cholinergic Neuron Atrophy and Spatial Memory Impairment in Aged Rats by Nerve Growth Factor," *Nature* 329:65-68, *1987.*
14. Fomo, L. S., Langston, J.W., DeLanney, L.E., et al., ''Locus Ceruleus Lesions and Eosinophilic Inclusions in MPTP-Treated Monkeys," *Annals of Neurology* 20:449-455, *1986.*
15. Freed, W.J., Cannon-Spoor, H.E., and Krautharner, E., "Factors Influencing the Efficacy of Adrenal Medulla and Embryonic Substantial Nigra Grafts," *Neural Grafting in the Mammalian CNS*, A. Björklund and U. Stenevi (eds.) (Amsterdam: Elsevier Science Publishers, 1985).
16. Gable, C. B., "A Compendium of Public Health Data Sources,' *American Journal of Epidemiology* 131:381-394, *1990.*
17. Ghanbari, H.A., Miller, B.E., Haigler, H.J., et al., "Biochemical Assay of Alzheimer's Disease-Associated Protein(s) in Human Brain Tissue," *Journal of the American Medical Association* 263:2907-2910, *1990.*
18. Goldensohn, E.S., Glaser, G.H., and Goldberg, M.A., "Epilepsy," *Merritt's Textbook of Neurology,* L.P. Rowland (cd.) (Philadelphia, PA: Lea & Febiger, 1989).
19. Greenwald, B.S., and Davis, K.L., "Experimental Pharmacology of Alzheimer's Disease," *The Dementias*, R. Mayeux and W.G. Rosen (eds.) (New York, NY: Raven Press, 1983).
20. Griffii, M.R., O'Fallen, W.M., Opitz, J.L., et al., "Mortality, Survival and Prevalence: Traumatic

Spinal Cord Injury in Olmsted County, MN, 1935-1981," ***Journal of Chronic Disorders*** 38:643-653, ***1985.***

21. ***Griffin,*** M.R., Opitz, J.L., Kurland, L.T., et al., "Traumatic Spinal Cord Injury in Olmsted County, MN, 1935 -1981," ***American Journal of Epidemiology*** 121:884-895, 1985.
22. Gumpel, M., Baumann, N., Raoul, M., et al., "Survival and Differentiation of Oligodendrocytes From Neural Tissue Transplanted in New-Born Mouse Brain," ***Neuroscience Letters*** 37:307-311, ***1983.***
23. Gusella, J.F., Wexler, N. S., Conneally, M.P., et al., "A Polymorphic DNA Marker Linked to Huntington's Disease," ***Nature*** 306:234-238, ***1983.***
24. Haroutunian, V., Kanof, P.D., Tsuboyama, G.A., et al., "Animal Models of Alzheimer's Disease: Behavior, Pharmacology, Transplants,' ***Canadian Journal of Neurological Science*** 13:385-393, ***1986.***
25. ***Harvey, C.,*** Rothschild, B., Asmann, A.J., et al., "Estimates of Spinal Cord Injury Prevalence: A Survey-based Approach," paper presented at the annual meeting of the American Spinal Cord Injury Association, Orlando, FL, May 1990.
26. Hauser, W. A., and Hesdorffer, D. C., ***Epilepsy: Frequency, Causes, and Consequences*** (Landover, MD: Epilepsy Foundation of America, 1990).
27. Hefti, F., "Nerve Growth Factor Promotes Survival of Septal Cholinergic Neurons After Fimbrial Transections,' ***Journal of Neuroscience 6:2155-2161, 1986.***
28. Huang, L.F., and Hu, T.W., "Economic Costs of Senile Dementia in the United States," paper prepared for the National Institute on Aging, Washington, DC, 1984.
29. Jenkins, J.B., and Conneally, P.M., "The Paradigm of Huntington's Disease," ***American Journal of Human Genetics*** 45:169-175, ***1989.***
30. Katzman, R., ''Alzheimer's Disease," New ***England Journal of Medicine*** 314:964-973, ***1986.***
31. Kokmen, E., Chandra, V., and Schoenberg, B.S., "Trends in Incidence of Dementing Illness in Rochester, MN, in Three Quinquennial Periods, 1960-1974," ***Neurology*** 38:975-980, ***1989.***
32. Keller, W.C. (cd.), "Classification of Parkinsonism,'' ***Handbook of Parkinson's Disease (New*** York, NY: Marcel Dekker, 1987).
33. Keller, W., O'Hara, R., Weiner, W., et al., "Relationship of Aging to Parkinson's Disease,' ***Advances in Neurology,*** M.D. Yahr and K.J. Bergmann (eds.) (New York, NY: Raven Press, 1987).
34. Kraus, J.F., "Epidemiologic Aspects of Acute Spinal Cord Injury: A Review of Incidence, Prevalence, Causes, and Outcome," ***Central Nervous System Trauma Status Report 1985,*** D.P. Becker and J.T. Povlishock (eds.) (Bethesda, MD: National Institutes of Health, 1985).
35. Kraus, J.F., "Epidemiology of Head Injury," ***Head Injury,*** P.R. Cooper (cd.) (Baltimore, MD: Williams & Wilkins, 1987).
36. Kraus, J.F., Franti, C.E., Borhani, N.O., et al., "Survival With an Acute Spinal-Cord Injury," ***Journal of Chronic Disorders*** 32:269-283, ***1979.***
37. Kurtzke, J.F., and Kurland, L.T., "TheEpidemiology of Necrologic Disease," ***Clinical Neurology,*** R.J. Joynt (cd.) (Philadelphia, PA: J.B. Lippincott, 1989).
38. Lilienfeld, D.E., Chan, E., Ehland, J., et al., "Increasing Mortality From Motor Neuron Disease in the United States During the Past Two Decades, ''***Lancet*** 1:710-713, 1989.
39. Marsden, C.D., "Basal Ganglia Disease," ***Lancet*** 2:1141-1146, 1982.
40. Marttila, R.J., "Epidemiology," ***Handbook of Parkinson's Disease,*** W.C. Keller (cd.) (New York, NY: Marcel Dekker, 1987).
41. Marttila, R.J., and Rinne, U.K., "Clues From Epidemiology of Parkinson's Disease," ***Advances in Neurology,*** M.D. Yahr and K.J. Bergmann (eds.) (New York, NY: Raven Press, 1986).
42. Marwick, C., "Administering Methylprednisolone Promptly Appears To Mitigate Cord-Injury Paralysis," ***Journal of the American Medical Association*** 263:2150-2151, ***1990.***
43. Mitsumoto, H., Hanson, M.R., and Chad, D.A., ''Amyotrophic Lateral Sclerosis; Recent Advances in Pathogenesis and Therapeutic Trials,' ***Archives of Neurology*** 45:189-202, ***1988.***
44. Munsat, T.L., "Adult Motor Neuron Diseases," ***Merritt's Textbook of Neurology,*** L.P. Rowland (cd.) (Philadelphia, PA: Lea & Febiger, 1989).
45. Nadeau, S. E., "Stroke," ***Medical Clinics North America*** 73:1351-1369, ***1989.***
46. Parkinson, J., "An Essay on the Shaking Palsy," ***James Parkinson (1755-1824): A Bicentenary Volume of Papers Dealing With Parkinson's Disease,*** W.H. McMenemey, F.M.R. Walshe, and J.G. Greenfield (eds.) (London: Sherwood Neely & Jones, 1817; reprinted London: MacMillan, 1955).
47. Parkinson Study Group, "Effect of Deprenyl on the Progression of Disability in Early Parkinson's Disease,' New ***England Journal of Medicine 321:1364-1371, 1989.***
48. Phelps, C.H., Gage, F.H., Growdon, J.H., et al., "Potential Use of Nerve Growth Factor To Treat Alzheimer's Disease," ***Neurobiology of Aging*** 10:205-207, ***1989.***
49. ***Price,*** D.L., "New Perspectives on Alzheimer's Disease," ***Annual Review of Neuroscience 9:489-512, 1986.***
50. ***Price,*** D.L., Troncoso, J. C., Whitehouse, P.J., et al., "Approaches to Neurodegenerative Disease," ***Diseases of the Nervous System, Clinical Neurobiology,***

A.K. Asbury, G.M. McKhann, and W.I. McDonald (eds.) (Philadelphia, PA: W.B. Saunders, 1986).

51. Rajput, A.H., Offord, K.P., Beard, C.M., et al., "Epidemiology of Parkinsonism: Incidence, Classification and Mortality," ***Annals of Neurology*** 16:278-282, *1984.*
52. Roberts, L., "Huntington's Gene: So Near, Yet So Far," ***Science*** 247:624-627, *1990.*
53. Rowland, L.P., and Sciarra, D., "Head Injury," ***Merritt's Textbook of Neurology***, L.P. Rowland (cd.) (Philadelphia, PA: Lea & Febiger, 1989).
54. Schoenberg, B. S., Kokeman, E., and Okazaki, H., ''Alzheimer's Disease and Other Illnesses in a Defined United States Population: Incidence Rates and Clinical Features,' ***Annals of Neurology 22:724-729, 1987.***
55. Seboun, E., Robinson, M.A., Doolittle, T.H., et al., "A Susceptibility Locus for Multiple Sclerosis Is Linked to the T-Cell Receptor Beta Chain Complex, " Cell 57:1095-1100, 1989.
56. Selkoe, D.J., "Deciphering Alzheimer's Disease: The Amyloid precursor Protein Yields New Clues," ***Science*** 248:1058-1060, *1990.*
57. Sibley, W.A., Poser, C.M., and Alter, M., "Multiple Sclerosis," ***Merritt's Textbook of Neurology,*** L.P. Rowland (cd.) (Philadelphia, PA: Lea & Febiger, 1989).
58. Sisodia, S. S., Koo, E.H., Beyreuther, K., et al., "Evidence That Beta-Amyloid Protein in Alzheimer's Disease Is Not Derived by Normal Processing," ***Science*** 248:492-495, *1990.*
59. ***Sosin,*** D.M., Sacks, J.J., and Smith, S.M., "Head Injury-Associated Deaths in the United States From 1979 to 1986,'' ***Journal of the American Medical Association*** 262:2251-2255, *1989.*
60. Stover, S.L., and Fine, P.R. (eds.), ***Spinal Cord Injury and Facts*** (Birmingham, AL: University of Alabama at Birmingham, Spinal Rehabilitation Center, 1986).
61. Toole, J.F., "Etiology and Pathogenesis," ***Merritt's Textbook of Neurology,*** L.P. Rowland (cd.) (Philadelphia, PA: Lea & Febiger, 1989).
62. U.S. Congress, Office of Technology Assessment, ***Losing a Million Minds: Confronting the Tragedy of Alzheimer's Disease and Other Dementias***, OTA-BA-323 (Washington, DC: U.S. Government Printing Office, April 1987).
63. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Center for Health Statistics' computer database (Hyattsville, MD: National Center for Health Statistics, 1988).
64. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Center for Health Statistics' computer database (Hyattsville, MD: National Center for Health Statistics, 1990).
65. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Institute of Neurological and Communicative Disorders and Stroke, ***National Survey of Stroke,*** NIH-83-2069 ***(Bethesda, MD:*** National Institutes of Health, 1983).
66. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Institute of Neurological Disorders and Stroke, ***Interagency Head Injury Task Force Report*** (Bethesda, MD: National Institutes of Health, 1989).
67. Williams, L.R., Varon, S., Peterson, G.M., et al., "Continuous Infusion of Nerve Growth Factor Prevents Basal Forebrain Neuronal Death After Fimbria Fornix Transection," ***Proceedings of the National Academy of Sciences, U.S.A.*** 83:9231-9235, *1986.*
68. Wucherpfennig, K.W., Ota, K, Endo, N., et al., "Shared Human T-Cell Receptor V-Beta Usage to Irnmunodominant Regions of Myelin Basic Protein," ***Science*** 248:1016-1019, *1990.*
69. Wurtman, R.J., "Alzheimer's Disease," ***Scientific American*** 252(January):62-74, 120, 1985.
70. Wynn, D.R., Rodriguez, M., O'Fallen, W.M., et al., "Update on the Epidemiology of Multiple Sclerosis," ***Mayo Clinic Proceedings*** 64:808-817, *1989.*
71. Yatsu, F.M., "Treatment and Prevention of Stroke," ***Merritt's Textbook of Neurology***, L.P. Rowland (cd.) (Philadelphia, PA: Lea & Febiger, 1989).
72. Yoshida, S., Mulder, D.W., Kurland, L.T., et al., "Followup Study on Amyotrophic Lateral Sclerosis in Rochester, MN, 1925 Through 1984," ***Neuroepidemiology*** 5:61-70, *1986.*

Chapter 7
Legal and Regulatory Issues

CONTENTS

Box

Figure

Tables

Chapter 7
Legal and Regulatory Issues

Basic legal tenets govern experimentation and biomedical research on human beings (see box 7-A). This chapter addresses the legal issues raised by neural grafting, including protection of recipients, protection of donors, informed consent, and Federal and State regulation.

PROTECTION OF NEURAL GRAFT RECIPIENTS

Recipients of neural grafts may often be individuals needing special protection. Both the Federal and State Governments have recognized this need and have sought to provide protection through statutes and regulations. The relevant Federal and State legislation is outlined below.

Coverage by Department of Health and Human Services Regulations Governing Research

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]. These Federal regulations have potentially widespread application. The Federal budget for the National Institutes of Health (NIH) alone represents over one-third of all money spent on health-related research in the United States (63). In addition, the reach of these Federal regulations extends well beyond federally funded research, since the regulations are used widely as guidelines in institutions that do not receive Federal funding (19).

The DHHS regulations apply to both therapeutic and nontherapeutic research and define research as "a systematic investigation designed to develop or contribute to generalizable knowledge" [45 CFR 46.101-46.409; 21 CFR 50.1-50.48; 45 CFR 46.102 (e)]. Some types of research are exempt from Federal regulations under certain conditions, for example educational research and research involving survey or interview procedures [45 CFR 46.10 l(b)(l) and (3)].

All Federally funded human research projects must be reviewed and approved by an Institutional Review Board (IRB) [45 CFR 46.103(b)]. IRBs are required to conduct continuing review, which can include third-party observation [45 CFR 46.109(e)]. The intervals of continuing review are contingent on the degree of risk involved in the experiment but must not be less than once per year. The regulations also provide that risks of the proposed research must be minimized and must be reasonable in relation to anticipated benefits [45 CFR 46.ill(a)(l), (2)], and they provide for expedited review of research that involves minimal risk [45 CFR 46.1 IO@)]. "Minimal risk" means that the risks of harm anticipated in the proposed research are not greater than those encountered in daily life or during the performance of routine physical or psychological tests [45 CFR 46.102(g)]. Research activities involving no more than minimal risk include, for example, collection of hair and nail clippings, recording of data that do not involve invasion of the subject's privacy [46 FR 8392], and minor changes in approved procedures [45 CFR 46.110(b)].

Federal regulations require that selection of subjects be equitable [45 CFR 46.ill(a)(3)] and that informed consent be obtained from each subject [45 CFR 46.116]. The regulations stipulate the basic elements that must be included in informed consent and require that such consent be documented and provided in language the subject can understand. They further provide that neither the researcher, the institution, nor the sponsor may be released from liability through the subject's oral or written consent. DHHS regulations specifically address research involving fetuses, pregnant women, and human *in vitro* fertilization [45 CFR 46.201]. Moreover, separate provisions are included for research with children [45 CFR 46.401 (a)].

Coverage by State Laws and Regulations

In research programs where there is no Federal involvement or influence, government oversight will depend on whether there are State statutes. Where DHHS and Food and Drug Administration (FDA) regulations overlap State statutes, the Federal regulations are not intended to preempt applicable State or local laws [45 CFR 46.10 l(g); 21 CFR 50.25(c)]. Few States have statutes that address human experimentation specifically. At least six address human research as part of patients' rights

Box 7-A—The Genesis of Medical Research Ethics

Many legal principles in the area of medical research ethics have been developed in response to abuses of research subjects in Nazi Germany. Examples of unethical research in the United States further stimulated public discussion and policy considerations. The most well-known examples of research abuses in the United States are the Willowbrook hepatitis study and the Tuskegee syphilis study. In the 1960s, institutionalized mentally disabled children at Willowbrook Institution were infected with live hepatitis virus in an effort to develop a vaccine. The scientists justified their procedures by noting that hepatitis ran rampant through the institution and that all of the children would eventually contract the disease. From 1932 to 1972, scientists conducting a U.S. Public Health Service study of 400 black men suffering from syphilis deliberately withheld treatment from them in order to study the effects of allowing the disease to take its course, even though penicillin had been found to be an effective treatment. At least *28* of perhaps as many as 107 men died as a result of this study.

In the trials of Nazi physicians, the court set forth standards that should be met before and during research. The Nazi physicians tried to defend themselves by pointing out abuses in research that had occurred elsewhere, including those in the United States, However, this defense did not succeed, and 15 of the 23 physicians were found guilty of war crimes and crimes against humanity. Those standards, subsequently adopted by the United Nations General Assembly, are known as the Nuremberg Code. The tenets of the code significantly influenced subsequent State laws. For example, the preamble to the California human experimentation law states that the law was necessary since the Nuremberg Code was not codified and thus is unenforceable [Cal. Health & Safety Code 24171(b)]. Federal regulations in the United States dealing with research were likewise influenced.

The Nuremberg Code provides guidelines for ensuring that participation in research is voluntary and that the risks of research are minimized It provides that:

- certain basic research and animal research must be done before human research is undertaken;
- the research must be well designed;
- the research must be undertaken only by scientifically qualified individuals;
- the potential results must justify the risk involved in the performance of the research; and
- those results must not be procurable by other means of study.

The central principle of the Nuremberg Code is that participation in research must be voluntary, informed, and uncoerced and that subjects have the right to bring the experimentation to an end. The code also requires that risks be minimized through appropriate design and conduct of the research as well as adequate preparation and facilities to protect the subjects. Research is forbidden if there is an ***a priori*** reason to believe that death or disabling injury will occur (although the code does allow an exception if the scientists also serve as subjects), and ongoing research must be stopped if there is reason to believe that its continuation will lead to the injury, disability, or death of the subjects.

In applying the ethical principles enunciated in the Nuremberg Code to the issue of neural grafting, the question of whether there has been sufficient animal research may arise. Fetal grafts in rodents and in monkeys have been studied, but some experts in the field believe that more animal research is necessary. They also believe that certain additional information is needed about the nervous system. They argue that eventually, however, human subjects must be involved.

SOURCES: Office of Technology Assessment, 1990; based on L. Andrews, *Medical Genetics: A Legal Frontier (Chicago, IL: American* Bar Foundation, **1987); B. Barber, "The Ethcis** of Experimentation with Human Subjects," *Scientific American 234(February):* 25-31, 1976; A.M. Capron,"Human Experimentation," BioLaw l0:217-229, 1986; T. Gill and R Lund., "Implantation of Tissue into the Brain: An Immunologic Perspective, '' *Journal of the American Medical Association* 261 **:2674-2676, 1989; S. Golby, "Experiments at the** Willowbrook State School,' *Lancet 1:749,* 1971; R. Greenwald, M. Ryan, and J. Mulvihill, *Human Subjects Research: A Handbook for Institutional Review Boards (New York, NY:* Plenum Press, 1982); J. Jones, *Bad Blood: The Tuskegee Syphilis Experiment (New York, NY: Free Press, 1981).*

statutes. Some States have statutes protecting particular groups of research subjects (e.g., the mentally disabled), while others have a professional ethics statute that mandates obtaining patients' consent to experimentation. The provisions range from a simple statement that individuals have the right to refuse to participate in experimental research to statutes that list the requisite elements of informed consent. Some statutes simply prohibit human experimentation that involves any significant risk of physical or psychological harm. Often, the statutes use the terms "human research" and "human experimentation" interchangeably. Table 7-1 lists State regulations covering human subjects in experimentation.

Table 7-l-State Regulations Pertaining to the Protection of Human Subjects in Experimentation

Alaska regulates human experimentation with the mentally ill; limits experiments to those that pose no hazardous risk.

Arizona requires informed consent before a person may participate in a research project as a human subject. Regulates human experimentation with the developmentally disabled.

Arkansas regulates human experimentation with the mentally ill; provides that patients have the right to refuse to participate.

California has a comprehensive statute regulating experimentation involving novel therapy and research on human subjects. Requires Institutional Review Board (IRB) approval and informed consent for any research involving human subjects; requirements for informed consent include an explanation of procedures, possible side-effects, information about alternative therapy, and subject's right to withdraw consent at any time during the experiment. Regulates human experimentation with the mentally ill; informed consent of the patient or guardian is required, and the research must be intended to benefit the mentally ill subject. A grievance mechanism is provided should the experiment go awry.

Colorado requires informed consent before a person may anticipate in a research project as a human subject. Regulates human experimentation with residents of facilities for the developmentally disabled; informed consent of the patient or guardian is required.

Connecticut provides that prospective subjects in human experimentation have the right to refuse to participate.

District of Columbia requires informed consent before a person may participate in a research project as a human subject. lates h

mentally retarded; informed consent of the patient or guardian and review board approval are required.

Delaware regulates human experimentation with the mentally disabled; informed consent of the patient and IRB approval are required. The requirement for informed consent may be waived in cases where an attempt to obtain informed consent from the patient has failed, no other therapy exists or the patient has not responded to accepted therapies, the research would be in the best interests of the patient, and the waiver has been approved by the IRB and the patient's legal guardian or next of kin.

Florida requires informed consent before a person may participate in a research project as a human subject. Regulates human experimentation with the developmentally disabled; informed consent of the patient or guardian is required. Physician may request court approval when unwilling to act on developmentally disabled patient's consent and the guardian is unknown or cannot be located.

Hawaii regulates human experimentation with the mentally disabled; states that patients have the right to refuse to participate.

Illinois regulates human experimentation with the mentally ill and developmentally disabled; informed consent of the patient or guardian is required.

Kansas requires informed consent for participation in research Projects. Regulates human experimentation with mentally ill inpatients; requires informed consent of the patient and his or her guardian.

Maine requires informed consent before a person may participate in a research project as a human subject. Regulates human experimentation with the mentally retarded; informed consent of the patient or guardian is required.

Massachusetts provides that prospective subjects in human experimentation have the right to refuse to participate.

Michigan provides that respective subjects in human experimentation have the right to refuse to participate.

Minnesota requires informed consent for participation in research projects.

Missouri requires IRB approval for research with the mentally disabled, informed consent of the patient or guardian, and that the research be intended to benefit the mentally ill subject.

Montana requires State review board approval and informed consent for research with the mentally disabled.

Nevada provides that prospective subjects in human experimentation have the right to refuse to participate.

New Hampshire requires IRB approval for any research involving human subjects.

New Jersey regulates experimentation with the mentally ill and mentally retarded; provides that mentally disabled patients have the right to refuse to participate and requires that the research be intended to benefit the mentally ill subject. Court approval is mandatory if the disabled patient is declared incompetent.

New Mexico regulates human experimentation with the developmentally disabled and the mentally ill; requires informed consent of the patient or guardian.

New York has a comprehensive statute regulating experimentation with novel therapy on humans and research on healthy human subjects. Requires IRB approval of any research with human subjects; requirements for informed consent include an explanation of procedures, possible side-effects, alternative therapies, and subject's right to withdraw consent at any time during the experiment. Mal es specific mention of these rights with respect to the mentally ill.

North Carolina regulates human experimentation with the mentally ill, the retarded, and substance abusers; requires informed consent of the patient or guardian.

North Dakota requires informed consent for participation in research projects. Regulates human experimentation with the mentally ill and developmentally disabled; requires informed consent of the patient or guardian and that research be in the best interests of the patient. A court order is mandatory for psychosurgery, sterilization, medical/behavioral research, or pharmaceutical research on resident of a facility for the developmentally disabled.

Ohio regulates human experimentation with the mentally ill; requires informed consent of the patient or guardian. A court or ders r equired for unusually hazardous treatment procedures if the patient is legally incompetent or involuntarily committed to a mental institution.

Oregon requires informed consent for participation in research projects.

Rhode Island requires informed consent for participation in research projects.

South Carolina regulates human experimentation with the mentally ill and the developmentally disabled; states that mentally disabled patients have the right to refuse to participate.

South Dakota requires State review board and informed consent of the patient or guardian before the mentally ill may participate in research.

Texas provides that prospective subjects in human experimentation Rhave the right to refuse to participate.

Vermont provides that prospective subjects in human experimentation have the right to refuse to participate.

Vlrginia has a comprehensive statute regulating experimentation with novel therapy on humans and research on healthy subjects. Requires IRB approval of any research with human subjects; requirements for informed consent include an explanation of procedures, possible side-effects, alternative therapies, and subject's right to withdraw consent at any time during the experiment. Specifically regulates human experimentation with the mentally ill; experiments are limited to those that pose no hazardous risk.

Washington requires informed consent for participation in research projects.

Wisconsin regulates human experimentation with the developmentally disabled, mentally ill, and substance abusers; requires informed consent of the patient and his or her guardian and IRB approval.

Wyoming requires informed consent for participation in research Projects. Regulates human experimentation with the mentally ill; informed consent of the patient or guardian is required.

SOURCE: Office of Technology Assessment, 1990.

Only three States have enacted comprehensive legislation that applies specifically to medical research with human subjects-California, New York, and Virginia [Cal. Health & Safety Code 24170-24179.5; N.Y. Public Health Law 2440-2446; Va. Code 37.1-234-37.1-241]. The statutes of both California and New York affirm that human experimentation is vital for the benefit of humankind but require that it be undertaken with due respect for the rights of individuals to determine what is done with their bodies. The New York and Virginia statutes provide that researchers conducting experimentation in compliance with Federal regulations concerning protection of human subjects are not subject to the State requirement. California provides that researchers conducting investigations within institutions receiving Federal funding and who obtain informed consent as required by Federal regulations are exempt from all State requirements except the provisions requiring that the subject receive a list of subjects' rights and a list of any penalties that may attach for violation. The list of subjects' rights does not include information beyond that required in the Federal regulations. As noted earlier, compliance with Federal regulations does not render State or local laws inapplicable [45 CFR 46.10 l(g)]. Therefore, in States that do not make provisions for the overriding applicability of Federal regulations, researchers must observe both Federal regulations and any State or local statutes or regulations.

All three of the comprehensive State statutes appear to regulate experimentation involving novel therapy on patients as well as research on healthy subjects. Each defines human experimentation (research). Virginia defines "human research" as any medical research that departs from established methods using human subjects who might be exposed to possible injury as a consequence of their participation. This appears to encompass therapeutic experimentation. California and New York define "human experimentation" as experiments that are not necessary for treatment nor of direct benefit to the subject. Although these statutes appear to be aimed primarily at experimentation on healthy subjects, both include as an element of informed consent a requirement that the individual receive information concerning appropriate alternative procedures. As this information would not be relevant to the subject of purely nontherapeutic experimentation, it could be argued that these statutes also apply to therapeutic experimentation.

Although Federal regulations and the statutes of California, New York, and Virginia specifically address the elements of informed consent, some States merely provide that informed consent be obtained. In all, statutes of 24 jurisdictions contain provisions requiring some kind of informed consent before a person may participate in a research project as a human subject. Of these statutes, 11 apply to research with the mentally disabled. Eleven of the informed consent statutes do not specify what information must be provided. Many States have general medical consent statutes that would apply to recipients of neural grafts. Of the remaining statutes, 10 provide only that the prospective subject has a right to refuse to participate in human experimentation. Four of these statutes apply only to research with the mentally disabled.

The California human experimentation statute provides fines and terms of imprisonment for anyone who violates its requirements. Liability extends to persons who are primarily responsible for conducting medical experiments and representatives or employees of pharmaceutical companies who are directly responsible for contracting with the subjects.

Role of Institutional Review Boards

There has been concern that research proposals be reviewed in advance by groups uninvolved with the research project itself. This has led to the formation of IRBs to assess the ethical ramifications of proposed research. IRB approval is necessary before a project can receive Federal funding [45 CFR 46. 103(b)]. Federal regulations and some State laws provide for advance review of research proposals by IRBs. This mechanism arose out of concern for the rights of human subjects who participate in medical research (5,53) and the fear that relying on the investigator's sense of professional responsibility was an insufficient safeguard of the subject's rights (45). There is an inherent conflict between the researcher's goals in undertaking the experiment (which may lead to acquisition of knowledge, enhanced professional status, or commercial gain) and the patient's rights (53). Because of this conflict, it was thought necessary to ensure that proposed research is reviewed by an impartial body. When functioning properly, IRBs prevent premature experimentation with human subjects (by monitoring whether appropriate laboratory and animal research has been con-

Photo credit: Gregory Robertson, Howard University

An Institutional Review Board voting on approval of a protocol involving human subjects in research.

ducted to support the scientific design and safety of the study) and ensure that the subject has given fully informed consent.

Currently, the Federal Government requires that any product for which marketing approval is sought from FDA and all research involving human subjects that is conducted or funded by DHHS be reviewed and approved by an IRB [45 CFR 46.101-46.409; 21 CFR 56.107, 56.108]. Similarly, four States—California, New Hampshire, New York, and Virginia-require IRB review of any research involving human subjects. Seven States and the District of Columbia provide for IRB approval of any research with the mentally disabled.

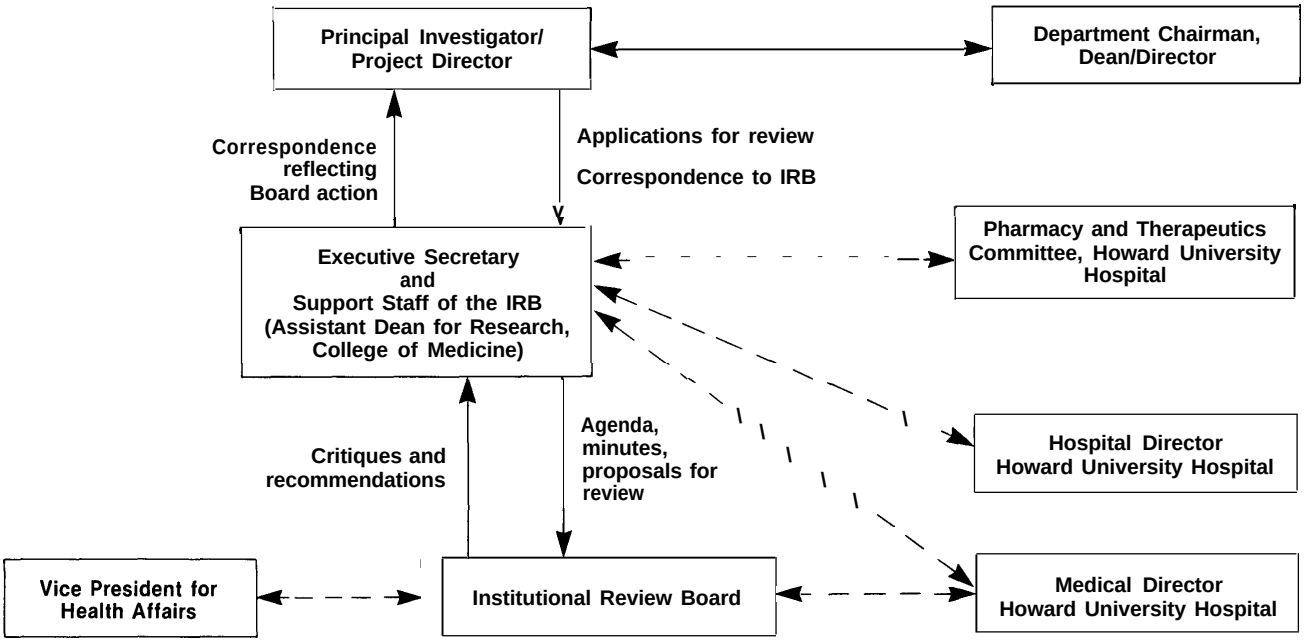
Federal regulations and New York and Virginia statutes set forth duties of an IRB, which include evaluating risks and benefits to the prospective subject and ensuring that risks are outweighed by potential benefits to the subject or by the importance of the knowledge to be gained. An IRB must take the following factors into consideration in deciding whether or not to authorize human research:

- the adequacy of the researcher's description of the potential benefits and risks involved;
- the adequacy of the methodology of the research;
- whether any nontherapeutic research presents a hazardous risk to human subjects;
- whether risks to human subjects are outweighed by potential benefits to the subjects;
- the adequacy of the informed consent form; and
- whether the informed consent is to be obtained by adequate and appropriate methods.

IRBs are also charged with deciding whether the persons proposing to conduct human research are qualified and competent, and they must periodically investigate each project to ensure that it is being carried out according to the original proposal [N.Y. Public Health Law 2444; Va. Code 37.1-236]. Figure 7-1 illustrates the procedure for obtaining IRB approval for projects involving human subjects at one research institution.

In any IRB review, the fundamental ethical guidelines for determining whether a therapy

Figure 7-l—An Institutional Review Board Approval Process



These interactions shall occur as the need arises, such as projects involving drugs (PTC); inpatients ·· Howard University Hospital (Hospital and Medical Directors); adverse reaction (Medical Director, Hospital Director, and Vice President for Health Affairs); annual reports (Vice President for Health Affairs).

Procedure for obtaining Institutional Review Board approval currently in use at one research institution.
SOURCE: Howard University, Institutional Review Board, Washington, DC.

may be experimentally used on humans is to hold each person fundamentally entitled to respect as an individual (70) and to proceed only if there is a favorable ratio of benefits to risks (l). Specifically, this standard requires a thorough assessment of the probable outcome (in both its helpful and harmful aspects), which is weighed against the results of not using the proposed treatment. For example, if **a** patient has a fatal disease and there are no known mitigating treatments, a therapy previously untested in humans that was not likely to cause serious or lethal harm to the patient might be approved for experimental use in the patient.

Only the Federal regulations [45 CFR 46.109; 21 CFR 56.108] and the statutes of Delaware, New York, Missouri, and Virginia **set** forth the composition of an IRB. Under Federal law each IRB must include:

- . at least five members with varying backgrounds (including racial and cultural backgrounds);
- . **a** combination of men and women;
- . a member from a nonscientific discipline, such as a lawyer or an ethicist; and
- . a member who is not otherwise affiliated with the institution [45 CFR 46.107].

Problems may arise if members of the IRB are associated with the institution. Such individuals may not be able to be completely objective because of their identification with the researcher, their loyalty to the institution, and the fact that any possible success may accrue indirectly to associated review board members (45). One way to avoid this problem would be to require that the IRB include as members only individuals who have no connection with the research institution. Some commentators argue that this proposal may promote unwarranted public interference with medical research (45) and that membership on an IRB could become **a political** appointment, which might threaten the academic freedom of researchers (56). However, it has been suggested that the possibility of political interference should be outweighed by the necessity for objective input. The principle underlying IRBs is that protection of the rights of human research subjects overrides the absolute freedom of the

researcher to perform unrestricted experimentation (56).

Requirements for Informed Consent

The doctrine of informed consent is based on the right of every individual to participate in decisions about his or her own medical care (17). Informed consent means the 'knowing" consent of a person or, if the person is not competent to consent, his or her legally authorized representative (24). An individual cannot consent to be an experimental subject without understanding what that may entail. Adequate informed consent requires that the researcher transmit to the prospective subject, in language the subject can understand, any information that might influence the subject's decision to participate or not participate (24).

Potential problems with attempting to convey all updated information to subjects have been noted (69). Studies are statistically designed to have sufficient power to acceptor reject a given hypothesis; however, unplanned interim analyses may be invalid and may not provide sufficient, reliable information. Early disclosure of benefits (or lack of benefits) may be unfair to patients recruited early in the study. Such patients consent to participate without any preliminary data. Patients acquired after the study has been under way may be at a distinct advantage if they are provided with benefits gleaned from data (or lack of data) derived from the earlier patients. However, it would be reasonable to update the informed consent by providing information concerning new risks or alternative therapies (69).

Some of the likely recipients of experimental neural grafts, persons with Alzheimer's disease, for example, may have impaired mental functioning, which may or may not affect their ability to give informed consent. Thus, it is likely that some subjects in this field may be incapable of giving consent for themselves (11,64,65). Various guidelines have been suggested for research on subjects who are incapable of consenting. There is general agreement that such individuals should be allowed to participate in therapeutic research the intent of which is to provide a health benefit to them. With respect to nontherapeutic research, some commentators suggest that it should not be undertaken on people who cannot personally give valid, informed consent (49). Others suggest that it should be permissible to undertake important, nontherapeutic research on incompetent individuals, provided there is proxy consent and there are minimal or no risks (32).

Discussion of research in the four decades since adoption of the Nuremberg Code has highlighted some additional ethical concerns. The concern that selection of subjects for research be equitable has been incorporated into the Federal regulations [45 CFR 46.ill(a)(3)]. For example, a particular class or race of persons should not serve as subjects for research that primarily benefits persons of another class or race. Some commentators suggest that this should be particularly true in the case of subjects incapable of consenting (e.g., research on an incompetent, elderly subject should benefit other elderly people).

The adequacy of consent for experimental therapy raises more questions than that for proven treatment because less is known about the efficacy and risks involved in an experimental procedure. Although no absolute guarantee exists that an established treatment will be effective and will cause no harm, even fewer and possibly no guarantees exist when the proposed therapy is experimental. Therefore, a prospective subject must be made aware that little is known about the possible risks and consequences involved in participation in the experiment (15). As the New York human experimentation law provides, "Every human being has the right to be protected against the possible conduct of medical or psychological research on his body without his voluntary informed consent" [N.Y. Public Health Law 2440].

Federal regulations and laws in California, New York, and Virginia provide that the information given for proper informed consent must include the following:

- an explanation of the procedures, drugs, or devices to be used in the experiment;
- a description of any possible risks and discomforts that might be expected;
- an explanation of possible benefits;
- a disclosure of appropriate alternative procedures, drugs, or devices;
- an offer to answer questions that the prospective subject may have concerning the experiment and its effect; and

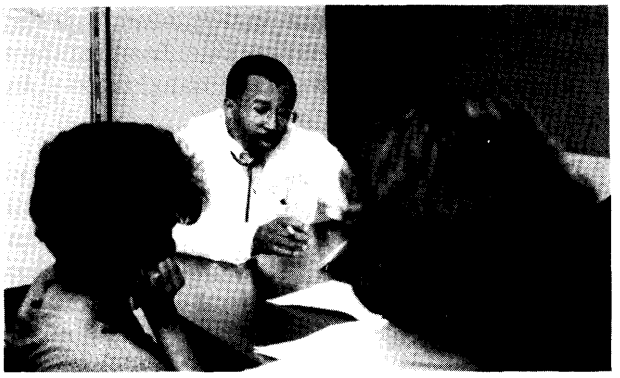


Photo credit: Gregory Robertson, Howard University

Clinical investigator counsels patient prior to obtaining informed consent for her participation in human subjects research protocol.

. an instruction that the individual's consent to participate in the experiment maybe withdrawn at any time, without prejudice [Cal. Health & Safety Code 24172; N.Y. Public Health Law 2441; Va. Code 37.10234; 45 CFR 46.116].

There is virtually no disagreement concerning the requirement of these elements for informed consent. Federal regulations require, in addition, that informed consent include a statement describing the extent to which the confidentiality of the subject will be maintained, the expected duration of the subject's participation, and an explanation as to whether any medical treatments or compensation are available in the event of injury.

When the subject is also a patient, it is important that a realistic assessment of the expected results of the therapy be provided. Patients may tend to overestimate the benefits they will experience with an experimental treatment. To counter that tendency, it may be useful to provide information, when applicable, about the extent of previous research on the experimental treatment in animals and humans.

Informed consent must also include a statement of whether any alternative treatments exist. The subject should be told if the use of the experimental treatment will foreclose any of those alternatives. An example of this would be when the subject's disease will have advanced too far after he or she has received experimental therapy to treat it with traditional therapy (30).

The use of aborted fetal tissue for neural transplantation raises a unique issue about consent. The recipient should be told the source of the tissue-that it was from an aborted fetus-since that information may be material to the recipient's decision whether or not to consent to the transplant (57). Another commentator goes further, stating that disclosure should be made concerning all animals used in preclinical studies (10).

There are concerns about what should happen if the human subject is harmed in the study. According to Federal regulations and California law, the subject should be given an explanation of the availability of medical therapy in case of injury incurred as a result of the experiment [45 CFR 46.116(a)(6); 21 CFR 50.25(a)(6); Cal. Health & Safety Code 24172(f)]. If compensation for research injuries is not provided for, the prospective subject should be so informed. If a subject has not been specifically informed that he or she bears the financial cost of potential physical injury, the informed consent is, arguably, not complete (53).

Research subjects must also be given an assurance that they are free to refuse to participate or to withdraw their consent at any time and to discontinue participation in the project without penalty or loss of benefits to which they are otherwise entitled [45 CFR 46.116(a)(8); 21 CFR 50.25(a)(8)]. All ethical codes stipulate that subjects must be able to withdraw from an experimental project at any time, without prejudice or penalty (30). The right to withdraw is derived from the premise that the subject is doing something for the benefit of others and that such acts are generally not obligatory (30).

If researchers do not provide adequate information to a subject before the study is undertaken, they can be sued for damages if harm results (26). In addition, physician-researchers who do not obtain informed consent may be disciplined for unprofessional conduct. In the Jewish Chronic Disease Hospital case, 22 debilitated patients were injected with live cancer cells without first having given their informed consent (45). The Attorney General of New York brought an action against the principal investigators to the Board of Regents Discipline Committee, which found the doctors guilty of fraud, deceit, and unprofessional conduct. The doctors were punished, not because they performed experiments that resulted in harm to the patients, but because they did not obtain informed consent before proceeding. California law also provides penalties for violation of the informed consent provision, including damages up to $1,000 for

negligent failure to obtain informed consent, damages up to $5,000 for willful failure to obtain informed consent, and damages up to $10,000 and up to 1 year in jail for willful failure to obtain informed consent that exposes the subject to substantial physical or psychological risk. Additional protections are provided regarding drug companies. A representative or employee of a pharmaceutical company who knows of substantial physical or psychological risks of an experiment and does not disclose them can be imprisoned for up to a year and freed up to $10,000 [Cal. Health & Safety Code 24176(a)].

Handling of Grievances and Nonrelease From Liability

The California statute provides a grievance mechanism for patients when an experiment goes awry. It requires that the subject be given the "name, address, and phone number of an impartial third-party, not associated with the experiment, to whom the subject may address complaints about the experiment" [Cal. Health & Safety Code 24173 (c)(lo)].

Like the Federal regulations [45 CFR 46.116; 21 CFR 50.20], the statutes in California, New York, and Virginia provide that any attempted or purported waiver of an individual's legal rights is void. The New York and Virginia statutes state that it is impermissible to release any individual, institution, or agency and any agents thereof from liability for negligence [Cal. Health & Safety Code 24176; N.Y. Public Health Code 2442; Va. Code 37.1-235].

Protections for Particularly Vulnerable Subjects

Some statutes and regulations cover research on particularly vulnerable groups, for example children or the mentally disabled. Statutes concerning research on the mentally disabled may be relevant to experimental neural grafts into subjects with disorders that affect their mental functioning. Federal regulations provide that IRBs shall add appropriate additional safeguards if the potential subjects suffer from acute or severe physical or mental illness [45 CFR 46.ill(b)]. Although the regulations do not describe what these additional protections might be, NIH has introduced guidelines covering intramural research (20). The guidelines include a procedure for obtaining proxy consent as well as additional oversight for research that involves more than minimal risk. The guidelines prohibit research of more than minimal risk if the patient is incapable of choosing a proxy decisionmaker and has no next of kin to seek court-appointed guardianship.

Twenty-five States and the District of Columbia specifically regulate experimentation on the mentally disabled (see table 7-l). Other States regulate experimentation on residents of nursing homes [Mo. Ann. Stat. 198.088(l)(b)(c); Or. Rev. Stat. 441.385]. The abundance of State legislation reflects a general concern that institutionalized persons are frequently used as experimental subjects because they are "administratively convenient" to the researcher (30) and that they are often taken advantage of, either because of their mental deficiencies or their guardians' lack of interest in their welfare (2). That State laws tend to pay close attention to the issue of informed consent for mentally ill patients is due to concerns not only about voluntariness, but also about the capacity of these persons to comprehend information (76).

Of the 25 jurisdictions that provide statutory guidelines for experimentation on the mentally disabled, 14 States and the District of Columbia require that informed consent of the patient or patient's guardian be obtained. Kansas and Wisconsin require informed consent of both the mentally disabled person and the guardian [Kan. Stat. Ann. 59-2929(6); Wise. Stat. Ann. 51.61]. Five States provide only that mentally disabled patients have the right to refuse to participate in experimentation projects.

In some States, the permissibility of research on mentally disabled individuals turns on both its purpose and its level of risk. At least two States, Alaska and Virginia, limit experimentation on the mentally deficient to that which poses no hazardous risks. These statutes authorize an administrator to determine what procedures are both experimental and risky. Four States, California, Missouri, New Jersey, and North Dakota, require that the research be intended to benefit the mentally ill subject. A similar approach, with more stringent provisions, is taken by the Delaware statute, which prohibits the participation in experimental research of mentally ill persons who are incapable of giving voluntary consent-except under the following circumstances [Del. Code Ann. Tit. 16,5172, 5175]:

. an attempt to obtain informed consent from the patient has failed;

- no other therapy exists or the patient has not responded to accepted therapies;
- the research would be in the best interests of the patient; and
- the waiver has been approved by the IRB and the patient's legal guardian or next of kin.

The proposed waiver must then be approved by a court, which may deny approval for any reason it deems appropriate.

Other statutes specify a particular review mechanism that must be followed. Six States require prior review and approval of any research projects by an IRB, while three jurisdictions require review and approval by State boards before experiments are conducted on mentally disabled persons. Florida, New Jersey, North Dakota, and Ohio require some sort of judicial determination of the necessity of an experimental procedure before it maybe used on an incompetent person. Florida, New Jersey, and North Dakota require that the patient be physically present at such a judicial hearing, represented by counsel, and provided the right and opportunity to confront and cross-examine witnesses. These three States also place the burden of proof on the party alleging the necessity of the treatment.

FDA Regulation of Neural Grafting Materials

Neural grafting presents a number of issues for would-be recipients. A potential patient might be concerned about what material is to be grafted into his or her brain and whether that material is safe and effective. These issues are likely to come within the jurisdiction of the FDA. Any description of the FDA's role in regulating the safety and efficacy of 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 (and materials that could potentially be used for neural grafts) represent developing technologies that have not yet been directly addressed by the FDA. A final complicating factor is the developing nature of FDA policies for the regulation of biological products that may be analogous to neural grafting materials and the resulting lack of published regulations or decisions in this area.

The FDA is responsible for regulating the distribution of drugs and devices under the Federal Food, Drug, and Cosmetic Act (FFDCA) [21 U.S.C. 321 *et seq.]* and has been delegated authority to regulate the commercial distribution of biologics under the Public Health Service Act (PHSA) [42 U.S.C. 262]. In addition, the Coordinated Framework for the Regulation of Biotechnology [49 FR 50856; 50 FR 47174; 51 FR 23302] delegated authority for the regulation of human drugs, medical devices, and biologics produced by biotechnology to the FDA. As described in chapter 4, materials used in neural grafting are varied and may come from various sources. Neural grafting ranges from implanting tissue obtained from the patient's own body to implanting genetically engineered cells from a cell line developed and maintained in a laboratory. The risks inherent in using each type of material have yet to be assessed by the FDA, but it is possible to outline the issues that the agency is likely to consider, based on its statutory mandate, existing regulations, and decisions with respect to similar materials.

Neural grafting materials present challenges at the cutting edge of developing FDA policy because these materials are sometimes analogous to tissue transplants and sometimes to products of genetic engineering. The principal questions regarding neural grafting materials are:

- Is the FDA likely to regulate the manufacture and distribution of the product?
- If the answer to the first question is yes, will the product be regulated as a drug, device, or biologic?

FDA jurisdiction with respect to drugs, devices, and biologics is described below. Areas in which the law is unclear as it may apply to neural grafting materials are described, and issues in the potential regulation of specific types of neural grafts are presented.

FDA Jurisdiction

Drug—The FFDCA defines "drug" in part as "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man. . .' and 'articles (other than food) intended to affect the structure or any function of the body of man . . . but does not include devices or their components, parts, or accessories" [21 U.S.C. 321(g)(l)]. The classification of a product is thus based in part on the use intended by the manufacturer. A product may not be classified as both a drug and a device, but it maybe regulated as both a drug and a biologic. The Supreme Court has sustained the

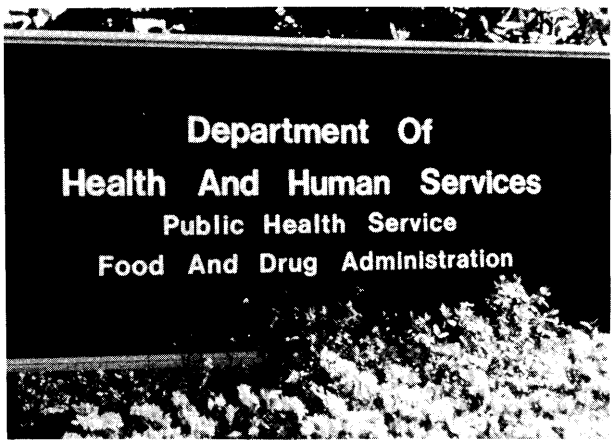


Photo credit: Food and Drug Administration

FDA's authority to interpret the FFDCA'S definitions broadly, in view of the broad public health objectives of the legislation (60).

Device—The term "device" is defined in the FFDCA as "an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article. . . which is . . . intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease" or which is "intended to affect the structure or any function of the body" ***and*** "which does not achieve any of its principal intended purposes through chemical actions within or on the body" *and* "which is not dependent on being metabolized for the achievement of any of its principal intended purposes" [21 U.S.C. 321(h)].

The items listed as devices in the statute imply that Congress intended the term to refer to man-made products. Aside from implants and in vitro reagents, the items in the list are synthetic products that are generally made of materials such as metal or plastic. The legislative intent underlying the definition of device is probably limited to artificial implants (66). Some products that may otherwise fit the definition of drugs or biologics are regulated as devices because they are considered accessories to or components of a device. A product may be classified as both a biologic and a device.

Biologic—The law that authorizes Federal regulation of biological products for human use was enacted in 1902 and was revised in 1944 as part of the recodification of the PHSA, (now codified at 42 U.S.C. 262) (39). The PHSA establishes requirements for "any virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product . . . applicable to the prevention, treatment, or cure of diseases or injuries of man" [42 U.S.C. 262]. At present, the scope of the term "analogous product" is unclear. It has not been extensively reviewed by the courts (71), nor did Congress clarify the term in 1970, when, in response to conflicting positions by the courts on whether blood was an analogous product, it amended the PHSA to specifically include blood, blood components or derivatives, and allergenic products [Public Law 91-515]. It is therefore unclear whether courts would uphold FDA regulation of neural grafting materials under the PHSA without the enactment of specific language to add such materials to the statute.

The initial question, then, in determininggg whether the FDA has jurisdiction to regulate neural grafting materials is whether a particular material meets the definition of a drug, device, or biologic. All biologics are considered either drugs or devices as well as biologics (71). However, an article proposed for use as a neural graft cannot simultaneously be both a drug and a device. The question of how to categorize neural grafting materials will be considered further later in this chapter.

FDA Regulation of Safety and Efficacy

The FDA regulates product safety and efficacy in a number of ways. Under the FFDCA, a drug or device is deemed to be adulterated if it consists of a filthy substance or if it has been prepared under unsanitary conditions such that it may have been contaminated with filth or rendered injurious to health. Drugs and devices are considered adulterated if the methods used in manufacturing, storing, or packing them do not conform to current good manufacturing practice or if the container is made of a substance that may render the contents injurious to health. Drugs are also adulterated if their strength, purity, or quality is less than is represented [21 U.S.C. 351].

A drug or device is misbranded [21 U.S.C. 352] if its labeling is false or misleading or if adequate directions for use or adequate warnings against unsafe use are omitted from the label. Any drug or device is misbranded if it is dangerous to health when used in the dosage or manner or with the frequency or duration described in the labeling.

Owners or operators of establishments for the manufacture, preparation, propagation, compounding, or processing of drugs or devices must register all places of business with the FDA [21 U.S.C. 360] in order to facilitate inspection and enforcement of FDA regulations. Several types of operations are exempted from the registration requirement. These include pharmacies dispensing prescription drugs or devices on prescriptions of licensed practitioners prescribing for patients in the course of professional practice [21 U.S.C. 360(g)(l)], practitioners licensed by law to administer drugs or devices and who manufacture these items solely for use in their professional practices [21 U.S.C. 360 (g)(2)], and persons who make the products solely for use in research, teaching, or chemical analysis and not for sale [21 U.S.C. 360 (g)(3)].

Premarket approval of a new drug application (NDA) is required for new drugs [21 U.S.C. 355]. A "new drug" is one that is not generally recognized by qualified experts as safe and effective for use under the conditions prescribed in the labeling [21 U.S.C. 321(p)(l)]. An application for premarket approval (PMA) is required for some devices [21 U.S.C. 360(e)], but all manufacturers of devices are required to at least notify the FDA 90 days before introducing a device into the market [21 U.S.C. 360 (k)].

An exemption from premarket approval may be obtained for shipment of products intended solely for investigational use by filing an investigational new product application. This submission is either an investigational new drug application (IND) [21 U.S.C. 355(i); 21 CFR Part 312)] or an investigational device exemption [21 U.S.C. 360(j)(g); 21 CFR Part 812]. The FDA reviews the submission to protect the safety of investigational subjects and to ensure that the research design is adequate for the purpose of testing safety and effectiveness in the event that an NDA or PMA is filed. The study must be approved by an IRB in each institution or area in which the drug or device will be tested.

The FDA requires manufacturers of approved drugs and devices to make prompt reports of adverse events and periodic reports on safety and effectiveness [21 CFR 314.80, 314.81, and part 803] after the products have been distributed for use.

Biologics are subject to all of the FFDCA requirements listed above except the premarket approvals. Instead of an NDA or PMA, both biologics and the establishments that produce them must be licensed (product and establishment licenses are required prior to marketing). In addition, biologics are regulated for false labeling under the PHSA [42 U.S.C. 262(b)].

The FDA can enforce its requirements in a variety of ways. Administrative mechanisms include inspections to monitor compliance, revocation of approved marketing applications (NDA, PMA, or product licenses), and recalls. Judicial actions that may be sought by the FDA include seizures of adulterated, misbranded, or unapproved drugs or devices (including biologic), injunctions against shipping, and criminal prosecutions (71).

Possible Limits on the FDA's Regulatory Authority

Two legal concepts, interstate commerce and the practice of medicine, may limit the FDA's jurisdiction over some types of neural grafting materials. Arguments on both sides of each concept are summarized here, although the courts have generally allowed the FDA broad authority to carry out its statutory mandates. The success of the arguments outlined below will depend, however, on the facts and circumstances of the cases in which they may arise.

Interstate Commerce-One argument against Federal regulation is that if the material is produced and distributed within a State, the interstate nexus required for Federal regulation does not exist. For example, cells obtained from one patient that are cultured and then grafted into the brain of another patient within the same hospital do not appear to be involved in interstate commerce.

The FDA has successfully mounted several arguments that enabled it to regulate products that were not shipped interstate. First, some of the statutory requirements for drugs, devices, and biologics do not require the showing of an explicit interstate nexus. Examples of these are registration of producers of drugs and devices [21 U.S.C. 360] and regulation of false labeling of biologics [42 U.S.C. 262(b)] (61). In addition, the Medical Device Amendments of 1976 [Public Law 94-295] authorize seizure of misbranded or adulterated devices without proof of interstate commerce (39).

A second argument used successfully by the FDA has been that if a component of the drug travels in interstate commerce, the interstate nexus has been

satisfied. An analogous argument could be made about the solutions in which tissues are preserved or the petri dishes or media in which cells are cultured.

Finally, section 361 of the PHSA [42 U.S.C. 264] authorizes the Surgeon General, with the approval of the secretary of DHHS, to make and enforce regulations to prevent the transmission or spread of communicable diseases. This authority has been delegated to the Commissioner of the FDA for fictions related to FDA-regulated products [21 CFR 5.10 (a)(4)]. The power of the FDA to ban the *intrastate sale* of small turtles in order to prevent the *interstate* spread of Salmonella was upheld pursuant to this provision in *State of Louisiana v. Mathews (58). The* FDA also relied on section 361 as a primary source of statutory authority to regulate blood in intrastate commerce in order to prevent the spread of syphilis, hepatitis B, and HIV (71).

Practice of Medicine--Traditionally, the FDA has not interfered with the practice of medicine. The FDA does not regulate the use by physicians of approved drugs for unapproved purposes (62,72), and physicians practicing medicine are specifically exempted from the registration requirement imposed by the FFDCA [21 U.S.C. 360(g)(l)(2)]. The new technologies involved in neural grafting present difficult questions of what constitutes the practice of medicine, whether there are circumstances under which the FDA would decide to regulate what might be called the practice of medicine, and the circumstances, if any, under which FDA jurisdiction to do so would be upheld.

The traditional exemptions serve several purposes. Approved drugs are presumably safe when reasonable doses are prescribed and contraindications are observed. In fact, the freedom of physicians to prescribe as they see fit can lead to the discovery of important new uses for existing products. The U.S. District Court in *United States v. Evers*, concerned about regulation of the intrastate practice of medicine, stated that restricting the medical profession (here a licensed physician) from using a drug for a purpose not contraindicated on the label would exceed the powers of Congress (62). The court opined that malpractice claims provide appropriate protection for the patient. Another reason for the traditional exemption of the practice of medicine might be the difficulty of trying to regulate the practices of individuals relative to the ease of regulating manufacturers, who are likely to be shipping large quantities of products in interstate commerce. Finally, the fact that the practice of medicine usually overlaps the issue of intrastate commerce (because physicians have generally practiced on patients within their States) may have influenced the position of the FDA with respect to individual practitioners.

Neural grafting materials and other tissues or products of biotechnology raise new questions about FDA regulation and the boundaries of the practice of medicine. What is the boundary between product and process? For example, should the safety and efficacy of neural grafting be seen as a function of the quality of the grafting material, the storage of the material (e.g., tissue banking), or the grafting process? Is the grafting process the practice of medicine? If so, will the FDA regulate the process?

In practice, the decision to regulate will probably depend on the perceived dangers of the product. For example, concern about HIV infection through blood products led to an innovative process for the regulation of blood banks. At the Federal level, blood is regulated as a service rather than a product. This has the effect of decreasing the liability of blood banks and hospitals from strict liability for a dangerous material to malpractice liability for negligence. Some persons believe that tissue banks should be similarly regulated.

Genetically engineered materials present the option of customized biologics, or therapeutics tailored to each individual patient (34). This is a very different situation from that of traditional biologics, such as vaccines, which were produced in large quantities and distributed to large portions of the healthy population in order to prevent disease. Cells, for example, might be genetically engineered in a laboratory at the same hospital where they will be grafted into the patient. Is this the practice of medicine? The label "practice of medicine" does not necessarily preclude FDA regulation. Rather, it indicates a gray area in which the FDA may find enforcement difficult and physicians may protest regulation. Products of biotechnology such as genetically engineered cells present safety hazards unlike those of traditional drugs or biologics. Manufacturing problems include difficulty in product characterization and potency, nonreproducible products, difficulty with product stability, and the presence of adventitious agents and contaminants (intrinsic and

acquired). Scientific problems include the absence of feasible animal models for preclinical testing for safety, efficacy, or both (38).

The problems outlined above present both a reason for the FDA to be concerned about the safety of neural grafting materials derived from biotechnology and a challenge to its present regulatory scheme. The development of these products and their use by physicians may present a challenge to the traditional exemption of the practice of medicine from FDA regulation.

Regulation of Neural Grafting Materials

The principal questions with respect to FDA regulation of materials used in neural grafting are:

- Will FDA regulate the material?
- If so, how will the material be categorized (drug, device, or biologic)?

The decision as to whether the FDA will regulate neural grafting materials depends largely on whether the FDA determines that the product fits within the statutory definition of drug, device, or biologic. Another consideration is whether the FDA has reason to be concerned about the safety of the material. Finally, the question of whether or not the product is intended for commercial distribution may be relevant. The terms of the PHSA are "sale, barter or exchange" [42 U.S.C. 262], which may allow for regulation even where commerce is not involved. As described earlier, the Commissioner of the FDA is empowered to promulgate regulations to prevent the transmission or spread of communicable diseases, without regard to interstate commerce [21 U.S.C. 264].

The second question is how neural grafting materials will be categorized. At present, there are no published regulations to help answer this question. The FDA has issued "Points to Consider" for manufacturers of exvivo-activated mononuclear leukocytes and for cell lines used to produce biologics. Points to Consider do not have the force of law, nor do they represent formal FDA policy, but they do indicate the current thinking of scientists at the FDA. Points to Consider for somatic cell therapy are likely to be relevant to neural grafting materials, but they have not yet been approved for distribution by the FDA. Tissue products and products of biotechnology are regulated on a case-by-case basis in order to allow flexibility with respect to new technologies.

Decisions about whether a given product is a drug, device, or biologic and which administrative center at the FDA will regulate it depend on the intended use of the product, who in the agency has the requisite expertise, and what analogous products are regulated in each center. This means that the situation will change as similar materials are regulated, making it impossible to predict with confidence how neural grafting materials will be regulated by the time they are actually considered by the FDA. As more tissue and biotechnology products are developed and regulated by the FDA, however, the agency could develop consistent regulations, as it did for blood products. As mentioned earlier, it is unclear whether a court would find neural grafting materials 'analogous' to blood products and therefore subject to regulation under the PHSA without the enactment of more specific statutory language.

There are many different types and sources of neural grafting materials (see ch. 4). The following classification scheme will be used here to describe the issues the FDA is likely to consider in deciding whether and how to regulate these materials:

- autografts of tissue,
- allografts of tissue or cultured cells,
- autografts of genetically engineered cells, and
- genetically engineered cells distributed to patients.

The discussion which follows is subject to the caveat that there are no formal regulations specifically describing the role of the FDA with respect to these materials. Considerations that are salient today could become less important by the time the FDA is actually confronted with the need to regulate neural grafting materials.

Autografts of Tissue—This refers to tissue obtained from the patient's own body (e.g., the adrenal medulla) and grafted into his or her brain. This material is least likely to be regulated by the FDA because there is minimal manipulation of the tissue, there is no increased risk of transmission of communicable disease, and the procedure is within the traditional practice of medicine. The FDA does not, for example, currently regulate bone marrow autografts.

Allografts of Tissue or Cultured Cells—The source of this same-species graft material could be, for example, fetal tissue or cells from another person. This category is a gray area in which it is

unclear what the FDA will decide. The FDA is likely to want to regulate for safety purposes (e.g., to prevent the spread of communicable diseases such as HIV infection). The considerations here could be analogous to those surrounding blood banks, leading to regulation of tissue banking and distribution.

The FDA has recently decided to regulate implants of dura mater, the tough, outer membrane covering the brain and spinal cord, because of concern about the possible transfer of Creutzfeldt-Jacob disease or human retroviruses. Dura mater is regulated as a device because it does not achieve any of its principal intended purposes through chemical actions within or on the body or through metabolism. To the extent that tissue grafts for mitigation of Parkinson's disease are intended to act by releasing dopamine, they are more likely to be regulated as drugs than as devices. Tissue grafts used to patch injured neural systems may be more analogous to dura mater and therefore regulated as devices. Similarly, certain cell lines that are cultured in vitro and used for skin transplantation and in wound and burn therapy are regulated as medical devices (74). This suggests that cell lines used as neural grafting material for the purpose of mechanically bridging the traumatized or injured central nervous system could be regulated as devices. It is most likely, however, that such cell lines would be considered biologics, because the neural bridging function is dependent on the biological activity of the cells (75).

Cells that are cultured, modified, or otherwise expanded in vitro are regarded by the FDA as biological drugs and are believed to be subject to regulation under the PHSA (74). The regulatory status of in vitro-cultured cells that are not shipped in interstate commerce is not clear, but in most instances such cells are administered with investigational biologics, necessitating an IND application (74). If an investigator were to produce cells without additional investigational agents, the role of the FDA in regulating the therapy under the IND regulations would be less clear (73).

Autografts of Genetically Engineered Cells—Cells that are prepared by a patient's personal physician for infusion back into the same patient may be considered "practice of medicine" and therefore may not be subject to FDA regulation (74). However, safety issues arise in therapies that make use of genetically engineered cells because of the unknown effects of the foreign genetic material on the patient and persons in contact with the patient (74). In addition, cells may synthesize a drug or biologic. The FDA might therefore choose to assert jurisdiction despite the practice of medicine issue. A clinical trial begun under an IND at NIH recently set a precedent for FDA regulation of an autograft of genetically engineered cells. The FDA is concerned that when using a virus there is a small chance of recombination with a virus already existing in the body (25).

Genetically Engineered Cells Distributed to Patients-This category includes cells from animals or humans other than the patient which are engineered and then grafted into the patient. Given the safety considerations and the precedent established for autologous grafts of engineered cells described above, it is likely that the FDA would seek to regulate engineered cells in wider distribution.

Regulation of New Surgical Procedures

The previous section described briefly the complex regulatory scheme developed by Congress and the FDA as it might apply to neural grafting materials. That 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 contrasts sharply with the absence of any direct Federal regulation of new surgical procedures developed for the same purposes.[1] Whether considering biomedical articles or procedures, the problem is whereto draw the line between safety and efficacy, on the one hand, and encouragement of biomedical innovation, on the other.

This section describes the implications of the absence of direct Federal oversight for the development of neural grafting procedures. Indirect mechanisms for regulating new surgical procedures are outlined, and a mechanism for potential Federal involvement in the assessment of safety and efficacy of new surgical procedures is described. The intent is to describe the current situation and ways in which it could be modified, if that is deemed desirable.

While Congress and the FDA have recognized the need for careful consideration before moving from animal studies to controlled clinical trials

[1]This section is concerned with new surgical procedures that are not part of federally funded research.

involving gradually increasing numbers of patients for assessment of new products, there is no analogous regulation of the move from animal studies to human trials for surgical procedures. An IRB will only approve protocols that demonstrate some hope of benefit to the subject and the absence of long-term negative effects, but there are no specific criteria for moving from animal studies to human research.

Of the neural grafting procedures, only techniques meant to alleviate the symptoms of Parkinson's disease have progressed to human trials. Grafts of tissue from a patient's adrenal medulla have been performed for Parkinson's disease patients in Sweden, Mexico, China, Canada, England, Spain, Portugal, Cuba, Colombia, Chile, and the United States. Implants of human fetal tissue have been per-formed in Sweden, Mexico, England, Spain, Cuba, China, and the United States (18). A few studies have been done privately in the United States despite the ban on federally funded transplantation research that uses fetal tissue obtained from induced abortions. Although these trials are already under way, debate continues as to whether the results of animal studies justify them. Some believe that animal research has already produced sufficient information to justify limited human trials. In the words of one scientist, "animal research is the key to initial understanding and refining techniques, but never solves all the problems" (4).

Persons who question the wisdom of advancing to human neural grafting trials at this stage of research question whether the animal (and the few human) trials that have been done provide evidence of the absence of long-term adverse immunological effects or the presence of beneficial effects. Others argue against progressing with human trials on the grounds that no one has been able to identify the etiology of Parkinson's disease and it is therefore not known whether the same disease processes that caused the initial neuron degeneration could also produce degeneration of grafted neurons (23). A neurologist who has used the procedure and identified adverse side-effects stated: "This is an area in which we've done too much too fast" (40). A neurobiologist advised even greater caution: "I'm not convinced the procedure is ready for humans. . . if we move ahead too soon, the results can be overinterpreted" (40).

While well-controlled human research using methods such as randomized clinical trials is essential to the development of new drugs, the feasibility and utility of such methods for evaluating the efficacy of new surgical procedures is controversial. Some surgeons argue that surgical procedures differ from drugs in ways that render the results of randomized clinical trials of surgical procedures useless, if not harmful, to the development of surgical treatments (8, 9, 68). The outcomes of surgical procedures, according to this view, are so dependent on the skill and experience of the individual surgeon and the circumstances of the individual patient that research which generalizes across patients and physicians will be meaningless. Other physicians and surgeons believe that controlled clinical trials are important for determining whether an innovative surgical therapy is of value (6, 31) and when an accepted surgical procedure of unproved value should be discontinued (21).

The absence of well-controlled clinical studies and of standards for deciding when to move from animal to clinical studies may lead to several problems. First, physician-investigators may be encouraged to take large risks in order to be among the first to perform new surgical procedures. This encouragement takes the form of publicity, funding, and professional attention for bold new efforts to save lives. While the surgeon may risk his or her professional reputation, the greater risks are to the patient, who may not be able to give truly informed consent because of the combination of chronic or terminal illness and lack of information about benefits and risks of the new surgical procedure. The physician and patient may believe that any procedure is better than certain death or prolonged, severe disability, even if the benefits and risks of the procedure are unknown. This logic was used to justify liver transplantation in 1983, before there were adequate data supporting its efficacy (51). In the absence of well-controlled clinical trials, procedures may be widely accepted clinically even if they are not actually effective.

A study of the introduction of four new surgical procedures found that, with the exception of one procedure which was evaluated through the FDA drug approval process, the procedures were introduced without controlled clinical trials or well-designed observational studies (12). This means that the procedures which were performed did not contribute to an overall evaluation of their efficacy

and that future patients will not have adequate information on which to base their decisions about treatment. In addition, when effectiveness is still in question, tension is likely to develop about the extremely high costs of some new surgical procedures (51).

A three-stage procedure for the evaluation of new surgical procedures has been suggested (12). First, the physician-investigator should develop the new procedure and define diagnostic criteria to evaluate it. The second stage would be collaborative clinical trials in which formal research protocols are followed and quantitative evidence is collected and analyzed according to predetermined statistical criteria. Finally, after efficacy is established, the procedure could be released for more general use.

Indirect Regulation of New Surgical Procedures

New surgical procedures are regulated indirectly by third-party payers, which decide whether or not to reimburse for them. The number of patients who undergo a procedure is determined in part by the extent to which coverage is provided by insurers. Federal insurers of medical care include the Health Care Financing Administration, Department of Veterans Affairs, and the Department of Defense. Safety and efficacy determinations are sometimes part of the process by which insurers decide whether a surgical procedure is experimental or accepted treatment and, ultimately, whether they will cover the procedure. Discussion of the means by which each Federal and private insurer assesses safety and efficacy in the course of deciding the status and coverage of procedures is beyond the scope of this report. The very different processes by which decisions were made about the status of liver, kidney, and heart transplantation have been described (51).

Other forms of indirect regulation of surgical practice include hospital standards set by the Joint Commission on Accreditation of Healthcare Organizations, professional standards of practice from specialty societies, State licensing laws, and medical malpractice claims. IRBs exert the most direct control over research on new surgical procedures. While research protocols are often submitted to local IRBs, there is no Federal requirement that this be done unless the research receives Federal funding or takes place as part of an FDA application. In addition, IRBs will have difficulty evaluating a protocol in the absence of risk-benefit information.

Potential Federal Role

Concern about rising health-care costs and the safety and efficacy of new medical procedures has led to increasing congressional interest in the evaluation of such procedures. While direct regulation of the practice of medicine may strain the regulatory authority of the FDA, the Federal Government could play a role in the evaluation of new procedures and could promulgate standards of practice for purposes of consumer information and decisionmaking by physicians and third-party payers.

Neural grafting may eventually be considered as a treatment for some debilitating neurological disorders that affect large numbers of vulnerable patients with chronic or terminal illnesses. It is essential, therefore, that the clinical development and use of the procedures be based on well-controlled research on safety and efficacy rather than on desperate hopes of cures for these patients. The methods of assessing the safety and efficacy of liver transplants prior to 1984 (51) are a model of what to avoid in assessing new surgical procedures.

The newly created Agency for Health Care Policy and Research [Budget Reconciliation Act of 1989, Public Law 101-239, sec. 6103] is charged with promoting research on selected surgical procedures in order to assess their appropriateness, necessity, and effectiveness. This agency could be charged with assessing the development of clinical neural grafting procedures, still in their infancy, to ensure that the use of these procedures develops in accordance with data from well-controlled studies, rather than in response to factors external to the actual efficacy of the procedures.

PROTECTION OF DONORS OF FETAL TISSUE

Since embryos and fetuses are among the proposed sources of tissue for neural grafts (23), Federal regulations and State laws governing embryo and fetal research may apply. Some of these laws appear to be sufficiently restrictive to forbid experimental transplants using fetal tissue in certain States. However, if neural grafting becomes standard medical therapy, current embryo and fetal research laws would no longer prohibit the procedure. In legal

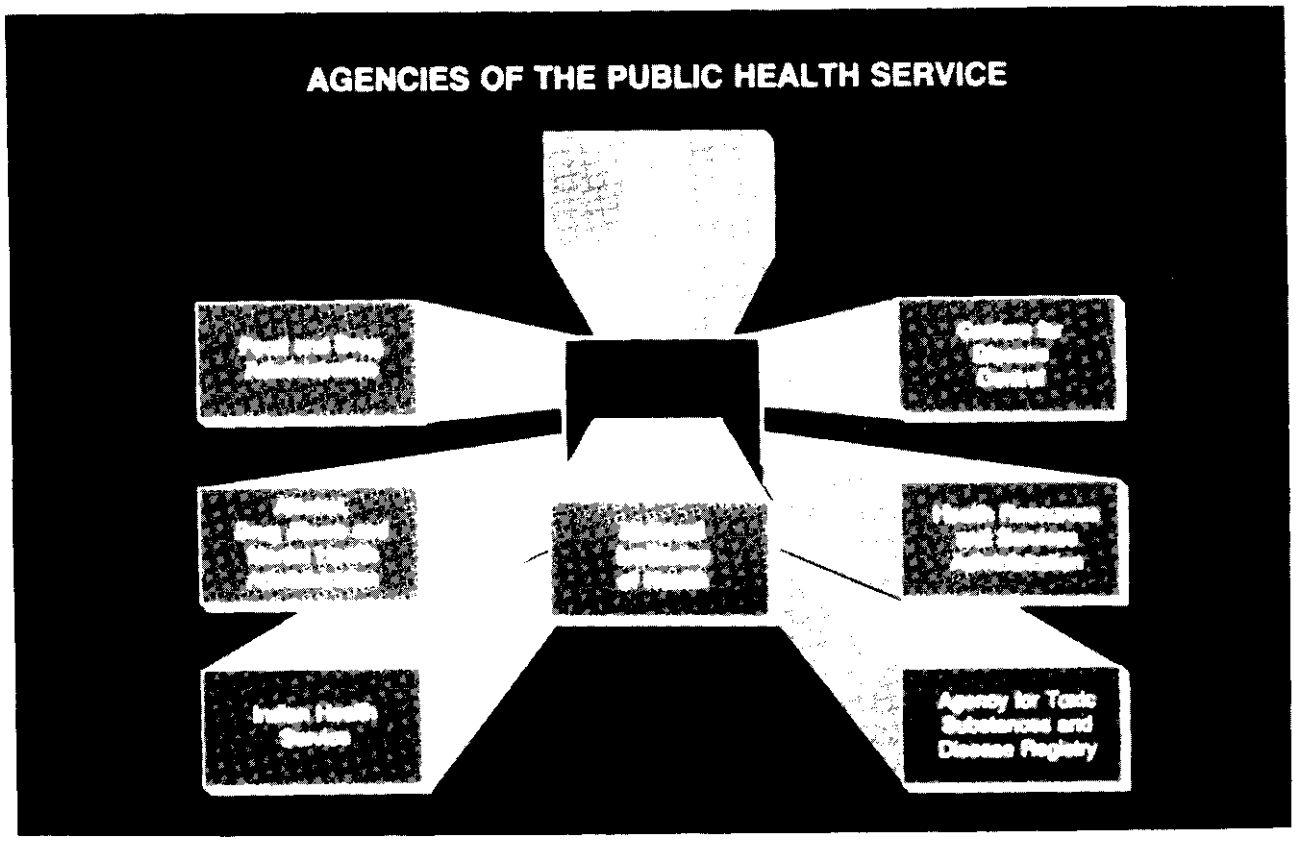


Photo credit: National Institutes of Health

contexts, the term "embryo' has been used to refer to the conceptus from fertilization until the end of the eighth week, and the term 'fetus" has been used to refer to the conceptus in all stages of development.

The use of fetuses as a source of tissue for neural grafts raises complicated issues. In most instances, the tissue will come from fetal cadavers, although the tissue itself may still be living. Abortuses of between 8 and 12 weeks' gestation are presently considered appropriate sources of tissue for grafting. However, there may also be instances in which physicians intend to remove tissue from live, nonviable fetuses (fetuses incapable of surviving outside the womb). Moreover, some experimental interventions might involve the pregnant woman and her living, in utero fetus; for example, a woman might be asked to undergo an alternative abortion procedure in order to better preserve fetal tissue or to postpone the abortion until the fetus is more developed (36). Different laws will apply, depending on whether the fetus is dead, alive ex utero, or alive in utero and depending on whether the experiment presents risks to the pregnant woman as well.

Further issues are raised regarding maternal consent. These center on whether a pregnant woman should have the right to prohibit or authorize the use of her fetus for experimentation. Some laws address this issue, as well as the role of the father in the consent process. An additional issue addressed by fetal research laws is whether women should be allowed to receive payment for fetal tissue. Some laws banning compensation would extend to payment of third-party intermediaries as well.

Development of Federal Policy on Fetal Research

Federal activity with respect to the issue of fetal research has been extensive. In 1974 Congress passed the National Research Act [Public Law 93-348]. This legislation established the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, whose first charge was to investigate the scientific, legal, and ethical aspects of fetal research. The statute prohibited all federally funded nontherapeutic research on fetuses prior or subsequent to an abortion until the

Commission made its recommendations and regulations were adopted. In 1975 the Commission made its recommendations (46), and in 1976 the Department of Health, Education, and Welfare (now the Department of Health and Human Services) adopted regulations for the Federal funding of fetal research [45 CFR 46.201-211]. Under these regulations, which for the most part comport with the recommendations of the Commission, certain types of fetal research are allowed, with constraints based on obtaining parental consent and minimizing risk to the pregnant woman and the fetus.

In 1985, Congress again acted on the issue of fetal research. It passed a law forbidding Federal conduct or finding of research on viable ex utero fetuses [42 U.S.C. 289]; however, there is an exception for therapeutic research and for research that 'will pose no added risk of suffering, injury, or death to the fetus and the purpose of which is the development of important biomedical knowledge which cannot be obtained by other means" [42 U.S.C. 289g(a)]. It also provides that, for research on living fetuses in utero, Federal regulations must require the standard of risk to be the same for fetuses that will be aborted as for fetuses that will be carried to term. Simultaneously, Congress passed legislation creating a Biomedical Ethics Board, composed of six members of the Senate and six members of the House of Representatives, with an outside advisory committee [42 U.S.C. 275]. Fetal research was the first order of business for the group. Under existing Federal regulations, the Secretary of DHHS may authorize research that does not comply with the regulations in instances of great need and great potential benefit [45 CFR 46.211]. A recent statute, however, suspends that authority until the Biomedical Ethics Advisory Committee (BEAC) conducts a study of the "nature, advisability, and biomedical and ethical implications of exercising any waiver of the risk provisions of the existing Federal regulations on fetal research" [42 U.S.C. 289g(c)]. As of autumn 1989, the activities of the BEAC had been suspended, and it seems that no report on fetal research will be undertaken.

Federal attention again turned to the issue of fetal tissue transplantation research in 1988. The Director of NIH requested permission to fund projects using fetal tissue for transplantation. On March 22, 1988, the Assistant Secretary for Health denied the request on the grounds that the use of fetal grafts raised ethical and legal issues that should be addressed by an advisory panel and imposed a moratorium on Federal funding of human fetal tissue transplantation research using tissue from induced abortions. Such an advisory panel was convened and subsequently published its recommendations in the *Report of the Human Fetal Tissue Transplantation Research Panel (67). The* panel recommended lifting the moratorium and emphasized that commercialization should be prohibited and that the abortion procedure should be separated from the procedure using fetal tissue. (See app. A for a discussion of the DHHS moratorium on fetal tissue transplantation research.)

Federal Regulations Governing Fetal Research

Federal regulations define the term "fetus" as a conceptus after implantation. They defer to State and local laws on the subject of research with fetal cadavers [45 CFR 46.210]; however, there is some dispute about whether another section of the statute, which does not specifically apply to dead fetuses, should be read to apply in the context of research (3). That section provides that "[n]o inducements, monetary or otherwise, may be offered to terminate pregnancy for purposes of the [research] activity" [45 CFR 46.206(b)]. Even if this section on inducements were read into the Federal law about research on fetal cadavers, it would not necessarily preclude experimentation involving neural grafts from abortuses. Although some commentators have alleged that the possibility of donating fetal tissue for experimental transplantation might lead women to undergo abortion (3) and thus is an inducement, others have suggested that there is little evidence that women would do so if there were prohibitions on payment for fetal tissue and on donation of tissue to a relative (54). These persons have noted that informing women who are ambivalent concerning abortion about the chance to donate tissue would not be an inducement unless it were specifically aimed at convincing the woman to abort, particularly if no valuable consideration is offered (54). Moreover, there is support for the position that the term "inducement" means valuable consideration and that the possibility of participating in research, without compensation, would not be considered valuable consideration (54).

With respect to research on live fetuses, Federal regulations provide that appropriate studies must be done on animal fetuses before human studies are

carried out [45 CFR 46.206(a)(2)]. When research involving live human fetuses is undertaken, the consent of the pregnant woman and prospective father are required (unless the prospective father's identity or whereabouts are not reasonably ascertainable, he is not reasonably available, or the pregnancy resulted from rape) [45 CFR 46.208(b), 46.209(d)]. Some persons criticize the requirement that the prospective father's consent be obtained (54). To protect the pregnant woman and the fetus, the research must not alter a pregnancy termination procedure in a way that would cause greater than minimal risk to either [45 CFR 46.206(a)(3) (4)].

To protect the fetus, the researchers must not have a role in either the determination of what procedure is used to terminate the pregnancy or the assessment of whether the fetus is viable [45 CFR 46.206(a)(3)]. In utero fetal research may be undertaken if the research is designed to be therapeutic to the particular fetus and places the fetus at the minimum risk necessary to meet its health needs [45 CFR 46.208(a)(l)]. It may also be undertaken if the research imposes minimal risks and 'the purpose of the activity is the development of important knowledge which cannot be obtained by other means" [45 CFR 46.208(a)(2)].

Where it is unclear whether an ex utero fetus is viable, that fetus may not be the subject of research unless the purpose of the research is to enhance its chances of survival or the research subjects the fetus to no additional risk and its purpose is to develop important, otherwise unobtainable biomedical knowledge. Research on a living, nonviable, ex utero fetus may be undertaken if the vital functions of the fetus will not be artificially maintained, experimental activities terminating the heartbeat or respiration will not be employed, and the purpose of the research is the development of important, otherwise unobtainable biomedical knowledge [45 CFR 46.209(b)].

State Laws Governing Embryonic and Fetal Research

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 at fetal tissue transplants. The Missouri law makes it a crime for any physician to perform an abortion knowing that the woman is seeking it for the purpose of donating the fetal tissue for implantation, or for anyone to offer consideration for the conception of a fetus which will be aborted and used for transplantation. In Pennsylvania no fetal tissue or organs maybe obtained for transplant purposes without the written consent of the pregnant woman. No payment of any kind maybe offered, and consent is valid only if obtained after the decision to abort has been made. All persons who participate in the procurement, use, or transplantation of fetal tissue or organs, including the recipients, must be informed of the source of the tissue or organs (e.g., stillbirth, miscarriage, ectopic pregnancy, abortion, or other means). The person giving consent to the procurement or use of fetal tissue or organs may not designate the recipient. Violation of these provisions may result in civil penalties.

A proposed law in California takes a similar approach (59). While allowing the donation of a fetus for "medical research or therapeutic application," this law incorporates many guidelines first suggested in 1987 in a forum on fetal tissue transplants convened by Case Western Reserve University School of Medicine (35) and suggested by the Human Fetal Tissue Transplantation Research Panel in its report (67). The proposed law prohibits consideration as an inducement to undergo an abortion for the purpose of donating the tissue, the naming of a specific recipient, and doctors "participating in the procedures resulting in the loss of a fetus" from participating in any research using tissue from that fetus.

Although other States have not specifically addressed the question of neural tissue grafts from fetuses, the general fetal research laws in effect in 25 States may bear on it. Table 7-2 lists and describes State regulations. State laws governing fetal research are not as precise as Federal law. Some contain no definition of fetus, death, or research. Indeed, "the uncertainties surrounding the reach of such State regulatory regimes may both create a dangerous chilling effect on even peripheral research, and leave the regimes exposed to constitutional attack" (59).

Only one State, New Mexico, has adopted a law patterned on Federal regulations pertaining to fetal research. Other States have enacted a variety of regulatory approaches, with the permissibility of fetal research depending, in part, on the following factors:

Table 7-2-State Regulations Pertaining to the Use and Procurement of Fetal Tissue for Grafting Research

Arizona regulates research using fetal cadavers and live ex utero fetuses; prohibits research with fetal cadavers (except for pathological examinations and autopsies) obtained through a planned abortion; prohibits experimentation on live ex utero fetuses.

Arkansas requires maternal consent for research using fetal cadavers obtained through planned abortions; bans nontherapeutic research involving live ex utero fetuses. Prohibits the sale of tissue from fetal cadavers.

California regulates research using live ex utero fetuses and fetal cadavers obtained through planned abortions; prohibits nontherapeutic research with live ex utero fetuses. Prohibits contribution of organs for valuable consideration, but excludes from "valuable consideration" the costs of removing, transporting, inspecting, preserving, and reimplanting the organ or tissue; prohibits sales and purchases of an organ or tissue when the organ or tissue is to be removed after the death, as well as the use of an organ known to have been transferred for valuable consideration; prohibits the sale of unclaimed bodies.

Connecticut has no regulations directly addressing experimentation with fetal tissue. Prohibits contribution of organs for valuable consideration, but excludes from "valuable consideration" the costs of removing, transporting, inspecting, preserving, and reimplanting the organ or tissue, as well as the donor's expenses of travel, housing, and lost wages; prohibits trafficking in dead bodies.

District of Columbia has no regulations directly addressing use of fetal tissue. Prohibits offering valuable consideration for organs; nothing is excluded from definition of valuable consideration.

Delaware has no regulations directly addressing experimentation with fetal tissue. Prohibits organ donor from receiving compensation for disposition of his or her own body; however, payment to mother for fetal tissue is not prohibited.

Florida bans nontherapeutic research on live in utero and live ex utero fetuses when done in connection with a planned abortion. Bans the selling, purchasing, or transferring of a human embryo for valuable consideration. Prohibits the offering of valuable consideration for organs, but excludes from "valuable consideration" the expenses of removal and use of organ (this statute would require regulatory action to cover brain tissue); prohibits the purchase and sale of unclaimed bodies.

Georgia has no regulations directly addressing experimentation with fetal tissue. Prohibits buying or selling a human fetus or fetal part; this prohibition does not apply to donations under the Uniform Anatomical Gift Act (UAGA), reimbursement of a living donor's actual expenses, or payment of costs associated with collecting, storing, and implanting a donated part; prohibits the purchase and sale of bodies.

Hawaii has no regulations directly addressing experimentation with fetal tissue. Prohibits contribution of organs for valuable consideration, but excludes from "valuable consideration" the costs of removing, transporting, inspecting, preserving, and reimplanting the organ or tissue; prohibits sales and purchases of an organ or tissue when the organ or tissue is to be removed after the death; prohibits sale of dead bodies.

Idaho has no regulations directly addressing experimentation with fetal tissue. Prohibits contribution of organs for valuable consideration, but excludes from "valuable consideration" the costs of removing, transporting, inspecting, preserving, and reimplanting the organ or tissue; prohibits sales and purchases of an organ or tissue when the organ or tissue is to be removed after the death.

Illinois prohibits research with fetal cadavers except for autopsies and pathological examinations) obtained through planned abortions [the Federal District Court recently ruled that this law is unconstitutional]; with fetus not obtained from a planned abortion, research can be undertaken on its tissues or cells with the consent of one parent. Prohibits sale of fetal tissue for any purpose; prohibits contribution of organs for valuable consideration, but excludes from "valuable consideration" the costs of removing, transporting, inspecting, preserving, and reimplanting the organ or tissue.

Indiana regulates research with fetal cadavers and live ex utero fetuses; prohibits research with fetal cadavers (except for autopsies and pathological examinations) obtained through a planned abortion; with fetal cadavers not obtained from a planned abortion, research can be undertaken on tissues or cells with the consent of one parent; prohibits research with live ex utero fetuses.

Kentucky bans research using live ex utero fetuses. Prohibits donation of live fetus for experimentation; prohibits sale of tissue from live or viable fetuses for research purposes. Prohibits sale or purchase of a child for adoption or any other

Louisiana prohibits farming in vitro fertilized fetuses for research or for any use other than to create a pregnancy. Prohibits sale of in vitro fertilized embryos prior to implantation; prohibits purchases and sales of all bodies and parts for valuable consideration.

Maine prohibits research on live ex utero and live in utero fetuses. Prohibits sale or donation of fetal tissue from live fetuses for research.

Massachusetts regulates research using fetal cadavers, live ex utero fetuses, and live in utero fetuses; requires mother's consent for research with fetal cadavers; bans research on live ex utero fetuses and live in utero fetuses which is nontherapeutic for the fetus when the fetus is to be the subject of a planned abortion except for diagnostic and remedial measures to preserve the life or health of the mother) ;when fetus is not to be the subject of a planned abortion, study of in utero fetuses is allowed, providing the procedures do not substantially jeopardize the life or health of the fetus. Prohibits donation of a fetus for experimentation; prohibits the performance of an abortion in cases where "part or all of the consideration for said performance is that fetal remains may be used for experimentation"; prohibits sale of fetal tissue for research; prohibits purchase and sale of bodies.

Michigan regulates research using fetal cadavers, live ex utero fetuses, and live in utero fetuses; requires mother's consent for research with fetal cadavers; bans research on live ex utero fetuses and live in utero fetuses which is nontherapeutic for the fetus when the fetus is to be the subject of a planned abortion (except for diagnostic and remedial measures to protect the life of the mother); when fetus is not to be the subject of a planned abortion, study of in utero fetuses is allowed, providing the procedures do not substantially "jeopardize the life or health of the fetus. Prohibits donation of a fetus for experimentation; prohibits the performance of an abortion in cases where" art or ail of the consideration for said performance is that fetal remains may be used for experimentation"; prohibits contribution of organs for valuable consideration, but excludes from "valuable consideration" the expenses of removal of the organ, use of the organ, and donor's losses and expenses (this statute would require regulatory action to cover brain tissue).

Minnesota prohibits nontherapeutic research using live ex utero and live in utero fetuses. Prohibits sale of tissue from live fetuses for any purpose. Prohibits sale of living conceptuses or nonrenewable organs, but allows the buying and selling of a cell culture line from a nonliving conceptus.

Missouri prohibits nontherapeutic research using live ex utero or live in utero fetuses obtained through a planned abortion. Prohibits physicians from performing an abortion knowing that the woman will donate tissue for implantation; prohibits monetary inducement to conceive with the intention of aborting the pregnancy and using the tissue for experimentation or tissue implantation; prohibits knowingly offering or receiving valuable consideration for organs or tissues of an aborted fetus other than payments for burial, other final dispositions, and pathological examination.

Montana bans nontherapeutic research on live ex utero fetuses.

Nebraska bans research using live ex utero fetuses obtained through a planned abortion (except for diagnostic and remedial measures to preserve the health of the mother). Prohibits sale of tissue from live or viable fetuses for research when fetal tissue is obtained through a planned abortion.

Continued on next page

Table 7-2—State Regulations Pertaining to the Use and Procurement of Fetal Tissue for Grafting Research-Continued

Nevada prohibits anyone from using or making available the remains of an aborted embryo or fetus for commercial purposes; prohibits contribution of organs for valuable consideration, but excludes from "valuable consideration" expenses associated with removal and use of donated organ as well as expenses incurred by the donor.

New Mexico prohibits nontherapeutic research or research that poses a greater than minimal risk to the fetus on live ex utero and live in utero fetuses. Prohibits monetary inducement to conceive in order to subject fetus or live-born infant to clinical research activity; prohibits sale of unclaimed bodies.

New York has no regulations directly addressing experimentation with fetal tissue. Prohibits contribution of organs for valuable consideration but excludes from "valuable consideration" the costs of removing, transporting, inspecting, preserving, and reimplanting the organ or tissue, as well as travel expenses and lost wages of donor (this statute would require regulatory action to cover brain tissue).

North Dakota regulates research with fetal cadavers, live ex utero fetuses, and live in utero fetuses; prohibits research using fetal cadavers obtained through a planned abortion; fetal cadavers not obtained through a planned abortion allowed with maternal consent; bans nontherapeutic research using live ex utero and live in utero fetuses except to preserve mother's health. Prohibits donation of fetus for experimentation; prohibits the performance of abortions done to obtain material for experimentation; prohibits the sale of live fetuses; prohibits the Sale by anyone but the mother of fetal cadavers or research; prohibits the contribution of organs for valuable consideration, but excludes from valuable consideration" the costs of removing, transporting, inspecting, preserving, and reimplanting the organ or tissue; prohibits sales and purchases of an organ or tissue when the organ or tissue is to be removed after death.

Ohio regulates research with fetal cadavers and live ex utero fetuses; prohibits research with fetal cadavers obtained from abortions except for autopsies and pathological examinations; bans research on live ex utero fetuses. Prohibits the sale of fetal tissue.

Oklahoma regulates research with fetal cadavers, live ex utero fetuses, and live in utero fetuses; prohibits research with fetal cadavers obtained from abortions except for autopsies and pathological examinations; bans nontherapeutic research on live ex utero fetuses and live in utero fetuses. Prohibits the sale of fetal tissue for any purpose.

Pennsylvania regulates research with fetal cadavers, live ex utero fetuses, and live in utero fetuses; requires mother's consent for research or human transplantation using fetal cadavers (no payment allowed in return for consent, consent must be obtained after the decision to abort, and the mother may not designate the recipient of any transplanted tissue); bans nontherapeutic research using live ex utero and live in utero fetuses. Prohibits sale of fetal tissue from fetuses obtained through an abortion; prohibits contribution of organs for valuable consideration, but excludes from valuable consideration" the costs of removal and use of organ.

Rhode Island regulates research with fetal cadavers, live ex utero fetuses, and live in utero fetuses; requires mother's consent for research with fetal cadavers; bans research on live ex utero fetuses and live in utero fetuses which is nontherapeutic for the fetus when the fetus is to be the subject of a planned abortion (except for diagnostic and remedial measures to preserve the life or h health of the mother); prohibits abortion if main motivation is procurement of tissue for research; prohibits donation of fetus for experimentation. Prohibits sale of fetal tissue for experimentation.

South Carolina has no regulations directly addressing experimentation with fetal tissue. Prohibits purchase and sale of dead bodies.

South Dakota requires consent for research with fetal cadavers, live ex utero fetuses, and live in utero fetuses.

Tennessee requires mother's consent for research with fetal cadavers obtained through a planned abortion; maternal consent required for research using live ex utero fetuses. Prohibits sale of tissue from live fetuses for any purpose; prohibits receipt of compensation for an aborted fetus by anyone except the mother.

Texas has no regulations directly addressing experimentation with fetal tissue. Prohibits knowing and intentional transfers of fetal tissue for valuable consideration, but excludes from "valuable consideration" fees to physicians, reimbursement to benefit ultimate receiver, and donor's travel, housing, and lost wages; prohibits sale of organs for valuable consideration, but excludes from "valuable consideration" costs for removing, transporting, inspecting, preserving, and reimplanting the or an or tissue and for expenses incurred by the donor; prohibits purchase and sale of bodies.

Utah prohibits research using live in utero fetuses. Prohibits sales and purchases of unborn children.

Virgin a "has no regulations directly addressing experimentation with fetal tissue. Prohibits contribution of organs for valuable consideration, but excludes from "valuable consideration" the costs of removing, transporting, inspecting, preserving, and reimplanting the organ or tissue.

West Virginia has no regulations directly addressing experimentation with fetal tissue, Prohibits contribution of organs for valuable consideration, but excludes from "valuable consideration" the costs of removing, transporting, inspecting, preserving, and reimplanting the organ or tissue, as well as the donor's travel expenses and lost wages.

Wisconsin has no regulations directly addressing experimentation with fetal tissue. Prohibits contribution of organs for valuable consideration, but excludes from "valuable consideration" the costs of removing, transporting, inspecting, preserving, and reimplanting the organ or tissue (this statute would require regulatory action to cover brain tissue).

Wyoming bans experimentation using live ex utero fetuses; prohibits donation of live or viable fetus for experimentation. Prohibits sale of fetal tissue for experimentation from a live or viable fetus obtained through a planned abortion.

SOURCE: Office of Technology Assessment, 1990.

- whether the fetus is dead or alive;
- whether the research involves a fetus prior to, during, or subsequent to an induced abortion;
- whether the pregnant woman consented to the research;
- whether the fetus is in the womb or outside the womb; and
- whether the fetus has reached a point or has acquired characteristics that would warrant treating it as a person, or has acquired some characteristic, such as the capability of experiencing pain, that would give it an important claim to protection (this factor is often expressed in terms of the fetus' viability or nonviability).

Many States' fetal research laws do not apply to research that is potentially therapeutic to the fetus; this exception is not applicable in the case of neural grafting, since the procedure is not being done for the benefit of the fetus. Nine States underscore their

ban on experimentation on fetuses by prohibiting anyone from donating a fetus for experimentation.

Research on Fetal Cadavers

Under State law, research involving fetal cadavers and living tissues from fetal cadavers is regulated under the Uniform Anatomical Gift Act (47), which has been adopted by all 50 States and the District of Columbia. However, some States have excluded fetuses from their provisions of the law. Research with fetal cadavers is also regulated in some States by fetal research statutes. According to the provisions of the UAGA, either parent may donate all or any part of a fetus "after or immediately before [its] death,' provided that the other parent does not oppose the gift. Under the UAGA, a "decedent' is defined to include "a stillborn infant or fetus." The Act covers the donation of all or any portions of the human body for purposes that include both educational and therapeutic benefits. Thus, if abortion and organ donation are both legal, this should also cover tissue donation (55).

Of the 25 States that have more specific laws governing fetal research, 14 have provisions regulating research with fetal cadavers (table 7-2). These laws deviate from the provisions of the UAGA either in their consent requirements or prohibitions they place on the uses of fetal tissue. Eight of these laws require the pregnant woman's consent for research but make no provision for consent or objection by the father. The California statute that allows research with fetal tissue is silent on the issue of parental consent. The remaining five States diverge from the UAGA, prohibiting any research with fetal cadavers except for pathological examinations or autopsies. The divergences of these 14 laws from the provisions of the UAGA are perhaps attributable to lawmakers' interests in regulating abortion and related practices. Of the 14, eight apply only to research with abortuses. Of the five statutes that prohibit any research except for pathological examinations, four apply exclusively to abortuses, and one puts more restrictions on research with fetal cadavers resulting from an induced abortion (table 7-2).

Research on Live Fetuses

There may be instances in which an experimental protocol requires that some action be undertaken on a dying or about-to-be-aborted fetus in order to better prepare the fetus for use as a donor of tissue. There are significant questions about whether such actions should be permitted. For example, some commentators argue that no research should be permitted on fetuses that are about to be aborted which would not be permissible on fetuses that would be carried to term (46). In addition, there are State statutory constraints on research on live fetuses. Federal regulations provide that, even in cases of federally funded fetal research, the State laws are applicable [46 CFR 46.201(b)].

State laws governing research on live fetuses severely constrain research that is not therapeutic to the fetus itself (thus covering neural grafting research, which is not therapeutic to the fetus). Of the 24 State fetal research laws that regulate research on live ex utero fetuses (see table 7-2),21 would appear to prohibit research involving neural grafting, either because the procedure is not therapeutic to the fetus or because all experimentation on such fetuses is prohibited. Of these 21 statutes, 5 permit diagnostic and remedial measures to preserve the life or health of the pregnant woman, perhaps leading to the incongruous result that the pregnant woman may donate fetal tissue to herself but to no one else. While it has been argued that an ex utero fetus is not technically a fetus (36), two of the remaining statutes would appear to permit research involving a live ex utero fetus, provided the pregnant woman has consented. The final statute prohibits only the farming of in vitro-fertilized embryos for research purposes and any use of such embryos other than to create a pregnancy.

Of the 14 States regulating research on live in utero fetuses, 13 would appear to prohibit neural grafting research, either because it is not therapeutic to the fetus itself or because all experimentation on such fetuses is prohibited. One State, South Dakota, would apparently permit it, as long as the pregnant woman consented.

Distinction Based on Whether the Research Is Done in Connection With an Abortion

The most significant factor in regulating research on dead or live fetuses and in determining the extent of restriction imposed appears to be whether the research concerns a fetus that has been or is to be obtained through an induced abortion. Most of the State fetal research statutes were passed as part of abortion legislation. Twelve of the 25 laws apply to research only where it concerns a fetus prior to or subsequent to an induced abortion (see table 7-2). Of the 13 that apply to fetuses more generally, 5 impose

more stringent restrictions on fetal research in conjunction with an abortion.

Another approach that has been used to ensure that fetal research does not encourage abortion is to prohibit the performance of an abortion where some or all of the consideration for the abortion is the donation of fetal remains for experimental use.

In the past, important scientific gains were made through experimentation in the context of an induced abortion. For example, prenatal diagnostic techniques have been developed in pregnant patients about to undergo abortions (27). The most appropriate tissue for neural grafting will probably come from elective, rather than spontaneous, abortions. Tissue from spontaneously aborted fetuses may not be appropriate for neural grafting since a fetal pathology may have lead to the miscarriage and since the fetus may have died in utero and deteriorated before being miscarried. Some persons argue that research involving fetuses from induced abortions, whether the fetus be living or dead, is morally impermissible on the grounds that it constitutes cooperation with an immoral practice. The point was made in the following way:

> If one objects to most abortions being performed in our society as immoral, is it morally proper to derive experimental profit from the products of such an abortion system? Is the progress achieved through such experimentation not likely to blunt the sensitivities of Americans to the immorality (injustice) of the procedure that made such advance possible, and thereby entrench attitudes injurious and unjust to nascent life? This is, in my judgment, a serious moral objection to experimentation on the products of most induced abortions (whether the fetus be living or dead, prior to abortion or post abortional) **(32).**

Many State fetal research laws regulate research only where it involves a fetus that is the subject of an abortion, and some impose a stricter standard on research involving fetuses to be aborted than on research involving fetuses to be carried to term. Against this view it is possible to argue that, even if abortion represents a moral wrong in some people's minds, the use of dead abortuses for certain types of research is not only morally legitimate but obligatory. It has been argued that research with fetuses to be aborted is morally justified, provided the research is aimed at deriving information potentially beneficial to other fetuses. This would be unlikely in the case of fetal tissue transplants to Parkinson's patients (7). One neurosurgeon has argued that there is a moral obligation to do good where possible; since the fetal cadaver is beyond help or hope, to waste its tissues is a moral wrong (50). It has been stated that, by allowing research intended to benefit future fetuses, "what we have done is add a moral good to a morally tragic situation" (28). On the other hand, it has been argued that this practice is comparable to the use of data obtained by Nazi researchers (44).

Payment in Connection With Fetal Experimentation

One of the greatest concerns regarding neural grafting-and the concern that State legislatures are likely to address first-is the possibility that the need for fetal tissue may encourage women to conceive for the sole purpose of donating tissue to relatives or selling it for profit. This could lead to the exploitation of women and intended recipients (33). Currently, 16 State fetal research statutes prohibit the sale of fetal tissue, 7 of them for any purpose and 9 for research purposes (see table 7-2). Some of these statutes apply only to induced abortions and thus would not preclude the sale of a miscarried fetus for tissue transplantation. The penalties attached to some of these laws are very stiff. Selling a viable abortus for experimentation in Wyoming, for example, subjects a person to a fine of not less than $10,000 and imprisonment of 1 to 14 years [Wyo. Stat. 35-6-115]. Several States have nonuniform UAGA provisions that prohibit transfer of organs or tissues, including fetal organs and tissues, for value. Moreover, some State laws would forbid the sale of fetuses even when they are not being used for research purposes, thus covering payment for neural grafting in the clinical setting.

Biotechnology companies create cell lines from fetal tissue, a fact which raises the possibility that a woman may donate fetal tissue to a company which may then exploit it commercially (57). The issue of commercial exploitation of cell lines was examined in a recent California case (42) (see ch. 8 for discussion). The court held that an individual has a protectable monetary interest in products made from his or her genetic material. The fact that a corporation might profit from fetal tissue whereas the woman who donated it is prevented from receiving consideration for it seems to violate the principle of this case. However, on appeal the California Supreme Court held that the plaintiff did not have a property right to his tissues and cells but did have a

right to informed consent for any use by others of his tissues and cells (43).

It is possible that, because a cell line is new tissue produced from the genetic material of, but not originally apart of, the aborted fetus, laws proscribing the sale of fetal tissue may not apply to cell lines. In fact, a Minnesota law prohibits the sale of living conceptuses or nonrenewable organs but does allow "the buying and selling of a cell culture line or lines taken from a non-living human conceptus . . ." [Minn. Stat. Ann. 145.1627(3)]. In contrast, Nevada's broadly worded statute making it a crime for anyone to use or "make available. . . the remains of an aborted embryo or fetus for any commercial purpose" could conceivably outlaw the production of cell lines from fetal tissue [Nev. Rev. Stat. Ann. 451.015]. Moreover, it could outlaw cell line transplants.

Interstate Transfer of a Fetus

Some State statutes also contain restrictions on the interstate transfer of fetal tissues. An Indiana law, for example, forbids transporting a fetus from an induced abortion to another State "for experimental purposes" [Ind. Code Ann. 35-l-58.5-6].

In Arkansas, there is a ban on 'possession" of the organ, tissue, or material of an aborted fetus [Ark. Stat. Ann. 20-17-802(d)]. However, the Arkansas statute expressly exempts from its provisions physicians and the instructional and research programs of institutions of higher education [Ark. Stat. Ann. 20-17-80 (e)].

GOVERNMENT OVERSIGHT

Issues and questions raised by the introduction and development of neural grafting procedures could make other government regulatory mechanisms relevant. For example, special concerns surrounding neural tissue transplants may require government oversight to protect the interests of the parties involved. Also, fetal rights is a relatively new area of the law, and many of the existing laws designed to protect human subjects in biomedical research do not cover fetal issues. Some of the anticipated problems are discussed below.

Potential Constitutional Challenges to Restrictions on Research

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. Those applying to experimentation on fetuses or in the context of abortion may violate the right to privacy (48). In addition, some legal commentators posit that there is a constitutional right to undertake or participate in research. Even if undertaking and participating in research were constitutionally protected, however, certain restrictions to further health and safety would be constitutionally permissible.

Laws governing research must meet certain standards of clarity in order to be constitutional. A Louisiana law prohibiting nontherapeutic experimentation on fetuses was declared unconstitutional by a Federal appeals court, because the term "experimentation' was so vague that it did not give researchers adequate notice about what kind of conduct was banned. The court said that the term "experimentation' was impermissible vague because physicians do not and cannot distinguish clearly between medical experimentation and medical tests. It noted that "even medical treatment can be reasonably described as both a test and an experiment," for example, "whenever the results of the treatment are observed, recorded, and introduced into the database that one or more physicians use in seeking better therapeutic methods" (37).

Although there is no specifically enumerated right to research in the Constitution, some commentators assert that support for such a right could be derived from the 14th amendment right to personal liberty and the first amendment right to free speech (52). Arguably, the right to participate as a research subject is protected by the 14th amendment's right to privacy, since an individual's decision to use his or her body in an experiment designed to further medical knowledge or to be of personal benefit is a private matter (52). This right to research consists of the freedom to pursue knowledge and the freedom to choose the means to achieve that knowledge (52). On the other hand, it has been argued that means have their own morality (44). The Supreme Court has stated that the right to liberty guaranteed by the 14th amendment encompassed freedom to "acquire useful knowledge . . . and generally to enjoy those privileges long recognized at common law as essential to the orderly pursuit of happiness by free men" (41). This language, arguably, applies not only to the researcher's right to scientific inquiry, but also to an individual's right to participate as a research subject (52). It could be interpreted as

supporting an individual's right to help acquire knowledge by participating as an experimental subject (52).

Some arguments hinge on the first amendment's protection of free speech, which, it can be argued, includes a right to learn new information. However, one must distinguish the freedom to pursue knowledge from the right to choose the method for achieving that knowledge. Although it is argued that government may not prohibit research in an attempt to prevent the development of new knowledge, it may restrict or prohibit the means used by researchers if the means intrude on interests in which the state has a legitimate concern (52). Therefore, both the Federal and State governments may regulate the researcher's methods in order to protect the rights of research subjects and community safety (52). Research may be restricted, for example, to protect the subject's right to autonomy and welfare by requiring informed, free, and competent consent; however, the state cannot arbitrarily regulate research solely because it deems the knowledge sought to be distasteful or subject to harmful use (52).

Fetal Remains Laws

Every jurisdiction makes some provision for the registration of deaths (usually by death certificate) and the disposition of dead bodies. Most States have a vital statistics statute governing death registration and issuance of permits for transporting or disposing of dead bodies. In most States, dead bodies must be disposed of in an authorized manner within a specified period of time, usually 72 hours after death. Any disposition of a dead body usually requires a permit, which is generally issued only after a death certificate has been filed. Most of these statutes also specify when fetal deaths must be registered and how to dispose of fetal remains. In addition, some States make separate provision for reporting fetal deaths and disposing of fetal remains. 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 two most common sources of authority for conducting research are research statutes and the UAGA. In addition, many States establish an administrative agency to distribute unclaimed dead bodies for scientific and educational purposes. Since these statutes typically require a lengthy holding period or embalming of the body, they do not provide useful authority for the use of fetal tissue in neural grafts. Moreover, anyone who conducts fetal tissue research that is not authorized by one of these statutes may be charged with corpse abuse or unauthorized dissection. The most common corpse abuse statute follows the Model Penal Code 250.10 and prohibits any use of a corpse that would offend "family sensibilities."

Most jurisdictions exempt fetuses in early stages of development from death certification and registration requirements. These States define "fetal deaths" or "stillbirths" requiring registration in terms of a minimum gestational period, a minimal weight, or both. Eight States apparently require fetal death certificates regardless of the age or weight of the fetus. Of the statutes that require fetal death certificates, at least five exempt deaths resulting from induced abortions. Finally, 13 States do not require death certificates for fetuses of any particular age or weight but do require at least some fetal deaths to be reported. Three of the statutes requiring some report of fetal deaths make special provision for reporting deaths resulting from induced abortions.

Some States require disposition permits regardless of the age or weight of the fetus, while at least six States directly exempt fetuses in early stages of development from permit requirements. Eighteen other States apparently obtain the same result indirectly, by anticipating that disposition permits will be issued only on the filing of a death certificate, but exempting fetuses in early stages of development from death certification requirements. In a few States, whether a permit is required depends on the kind of disposition planned rather than on any characteristic of the fetus.

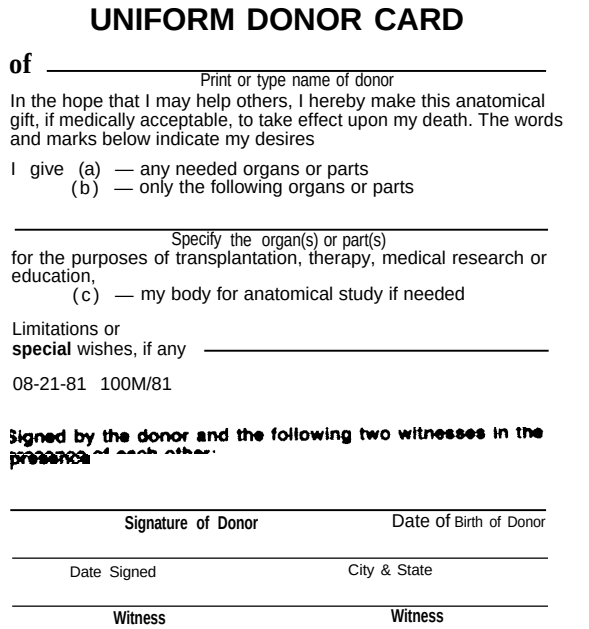
The most common kinds of dispositions of fetal remains are burial, cremation, and entombment. Kentucky apparently allows only burial of fetal remains [Ky. Rev. Stat. 213.160]. At least 16 statutes anticipate that a health-care institution will dispose of fetal remains and require the institution to report these dispositions. Finally, seven States that provide for fetal death certificates or death reports explicitly exclude fetuses in early stages of development from disposition requirements, make no specific provi-

sion for fetal remains, or authorize an administrative agency to decide what disposition is appropriate.

At least seven of the statutes governing the general disposition of dead bodies make some provision for parental consent to the disposition of fetal remains, while five statutes require parental consent for any disposition of a dead fetus, regardless of gestational age. One of the five statutes requires the pregnant woman's but not the partner's consent when the pregnant woman is unmarried, while the two remaining statutes require consent of a parent only in certain circumstances.

The reamer in which fetal remains are disposed of is also covered under the statutes of some States. The California penal statute clearly does not affect neural grafts; it merely prohibits disposition of fetal remains in sites open to public view [Cal. Penal Code 643]. The California Health and Safety Code requires that fetal remains be incinerated at the conclusion of research, but this provision does not apply to educational institutions [Cal. Health & Safety Code 25957(a)]. The Arkansas statute requires physicians performing abortions to ensure that fetal remains are disposed of in a similar manner to other human tissue [Ark. Stat. Ann. 20-17-802(a)], namely, "incineration, cremation, burial, or other sanitary means prescribed by the State health department" [Ark. Stat. Ann. 20-17-801(a)]. The laws of Florida, Georgia, Minnesota, and North Dakota allow any manner of disposition approved by the State health department. The Florida statute also requires the health department to promulgate rules consistent with the disposition of other human tissues [Fla. Stat. Ann. 390.012(2)]. Whether neural grafts are allowed in these States depends on what regulations are currently in force. Finally, the Massachusetts statute requires fetal remains to be disposed of at the parent's direction, whether by burial, entombment, cremation, or, if the hospital or attending physician is to dispose of the remains, by any method that does not create a public health hazard [Mass. Ann. Laws ch. 11,202]. In addition, the statute requires the hospital or attending physician to inform parents of their right to direct disposition and of any hospital policy governing disposition of fetal remains.

The fetal remains laws in some States have been subject to successful constitutional challenges. A recent Supreme Court case held that an ordinance requiring fetal remains to be disposed of in a humane and sanitary manner was impermissible vague (16). In addition, laws that specifically required a woman to decide, in advance of an abortion, whether the aborted fetus was to be buried, cremated, or disposed of at the hospital's discretion have been struck down as unconstitutionally interfering with the woman's right to privacy (29).



UNIFORM DONOR CARD

of _____
Print or type name of donor

In the hope that I may help others, I hereby make this anatomical gift, if medically acceptable, to take effect upon my death. The words and marks below indicate my desires

I give (a) — any needed organs or parts
(b) — only the following organs or parts

_____
Specify the organ(s) or part(s)
for the purposes of transplantation, therapy, medical research or education,
(c) — my body for anatomical study if needed

Limitations or **special** wishes, if any _____

08-21-81 100M/81

Signed by the donor and the following two witnesses in the presence of each other:

Signature of Donor Date of Birth of Donor

Date Signed City & State

Witness **Witness**

This is a legal document under the Uniform Anatomical **Gift Act or** similar laws

For further information consult your physician or

National Kidney Foundation of the National Capital Area, Inc.
2233 Wisconsin Ave., NW, Suite 320
Washington, DC 20007

Photo credit: Office ***of Technology Assessment***

***An* organ donation card.**

Uniform Anatomical Gift Act

The Uniform Anatomical Gift Act (47) is the only uniform body of law that might regulate acquisition or donation of fetal tissue implants. Forty-seven States and the District of Columbia presently conform to some form of the 1968 version of the UAGA. California, Connecticut, and Hawaii have adopted a new version of the UAGA, approved by the National Conference of Commissioners on Uniform State Laws in 1987. In fact, in the 25 States that lack fetal tissue research statutes, the UAGA is the primary legislation that would affect this technology (57).

Specifically, the UAGA affects fetal tissue implants by including "a stillborn infant or fetus' in

the definition of "decedent" and by stating that "parts" includes "tissues" (47); however, not all States have included a fetal tissue provision in their version of the UAGA. According to the 1987 version of the Act, either parent may consent to the donation of fetal tissue; in reality, the consent of both parents is necessary because if either objects, a donor who knows of the objection may not accept the gift (47). The UAGA would appear to allow the parents of an aborted or stillborn fetus to designate a recipient, even though this practice would be in direct opposition to the recommendations of the *Report of the Human Fetal Tissue Transplantation Research Panel (67). The* panel expressed concern that such a practice might encourage abortions in order to donate fetal tissue for the treatment of relatives. Furthermore, because of the genetic nature of diseases such as diabetes and Huntington's disease, the effectiveness of the treatment might actually be jeopardized by implanting fetal cells which possess the same defect that the procedure is supposed to ameliorate (67). The UAGA and the NIH report differ on several points because the UAGA was written before the NIH report and before fetal transplants were thought to have so many possible applications (13).

In adopting the UAGA, many States added sections designed to facilitate and regulate the donation of tissue. The most common nonuniform provisions found in State laws either require hospitals to adopt an organ procurement protocol, which is designed to facilitate the procurement of donor tissue while recognizing the sensitivity of the relatives who must consent to the donation, or simply require hospital personnel to request the relative of a suitable decedent to make the decedent's organs available for donation (see table 7-2). In either case, physicians wishing to obtain fetal tissue would be required to request parental consent in a professional and sensitive manner. Those laws which require that consent be obtained would require doctors to inform all abortion patients of the possibility of donation for transplants, preferably after the abortion decision had been made. If the consent were sought prior to the decision to abort, it might conceivably influence the decision. For this reason, the Human Fetal Tissue Transplantation Research Panel recommends that the decision to obtain an abortion precede any request to donate tissue for implantation (67). These two procedures probably should be handled by two separate advisers, the supervising physician and the researcher (55).

In 1987 the National Conference of Commissioners on Uniform State Laws approved a new model UAGA, which has been adopted by at least seven States. The new version retains provisions allowing the next of kin to designate the fetal tissue recipient and incorporates changes designed to increase the number of organ donations, particularly through required request policies. Organ procurement professionals have traditionally gone to great lengths to assure the public that organ donation will not compromise the patient's medical care in any way. Accordingly, the family is approached about possible donation only after the patient has been declared dead by the physician. Following these guidelines, parents can be approached about possible donation only after the abortion and after the fetus has been declared dead. Language in the new version of the UAGA, however, suggests it may be permissible to seek consent before the abortion. The new version allows consent to be sought after or immediately before death (14).

The laws of at least eight States would protect recipients of fetal tissue by requiring that all donors be tested for HIV. An additional two States, while not requiring HIV testing of donors, have established standards that decrease the likelihood of AIDS-infected tissues being made available for donation.

Overall, the UAGA and its various manifestations provide some guidelines in the area of fetal tissue transplants. Because this Act was drafted before neural grafting technology became known, it is obviously not designed to address the specific and unique problems that these implants raise.

Compensation for Fetal Tissue in a Nonresearch Setting

There is much concern about the possibility that women will be paid for fetal tissue for transplantations. One commentator points to "the fear that permitting the commercialization of the fetal tissue transplantation system will result in the exploitation of the women who bear tissue for profit and of the critically-ill patients who want to acquire it" (59). The NIH panel recommended that sale of fetal tissue not be allowed, for two reasons:

- so as not to influence a woman's decision to abort; and
- so as not to induce an abortion facility to base its choice of abortion procedure on the profitability of the fetal tissue to be retrieved (22).

The prohibition on payment to organ donors generally prohibits payment to women for fetal tissue. In addition, a variety of State statutes also have the same prohibition (table 7-2).

The National Organ Transplant Act, passed under Congress' commerce clause authority, 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 DHHS list additional organs under the ban. Since the brain is not listed as one of the organs, payment for use of fetal brain tissue for transplantation will not be banned until the Secretary so designates.

In addition to the 16 State fetal research statutes that prohibit the sale of fetal tissues for purposes including research, seven State laws forbid the sale of fetuses or fetal material (see table 7-2). The Florida statute places a flat ban on selling, purchasing, or transferring a human embryo for valuable consideration and on offering or advertising to do so [Fla. Stat. Ann. 837.05(1)]. Nevada prohibits any commercial use of an aborted fetus or fetal material resulting from an abortion [Nev. Stat. Ann. 451.015]. Missouri prohibits knowingly offering or receiving any valuable consideration for the organs or tissues of an abortus, except payments for burial or other final disposition and for pathological examinations [Mo. Ann. Stat. 188.036(5)]. Utah prohibits sales and purchases of, or offers to buy or sell, unborn children [Utah Code Ann. 76-7-311]. The Georgia statute prohibits buying or selling a human fetus or fetal part [Ga. Code Ann. 48-401 *et seq.],* but the prohibition does not apply to donations under the UAGA, reimbursement of a living donor's actual expenses, or payment of costs associated with collecting, storing, and implanting a donated part [Ga. Code Am. 26-9957(b)]. Similarly, the Texas statute prohibits knowing and intentional transfers of fetal tissue for valuable consideration but excludes from "valuable consideration' fees paid to physicians, hospitals, and clinics for services rendered in the usual course of medical practice, reimbursement of legal or medical fees incurred to benefit the ultimate receiver of the tissue, and the donor's travel and housing expenses and lost wages [Tex. Penal Code 48.02]. Finally, in an unusual provision, Kentucky prohibits selling or purchasing a child for adoption or any other purpose [Ky. Rev. Stat. Ann. 199.590(2)]. Since the statute specifically excludes from its coverage in vitro fertilization in which the genetic donors are a married couple and the fertilized ovum is to be implanted in the wife, the Kentucky legislators seem to have intended 'child" to include the human organism from conception and "any purpose" to include medical and scientific procedures. Thus, this statute could be used to prohibit any agreement to pay the pregnant woman for fetal tissue made while the fetus is still alive.

At least 18 jurisdictions have laws forbidding payment to organ donors. Ten of the statutes are nonuniform UAGA provisions. The Delaware UAGA provision clearly does not prohibit payment to the pregnant woman for fetal tissue: it applies only to payments to a donor for disposition of his or her own body [Del. Code Ann. tit. 16, 2713(f)]. Whether the nine remaining UAGA provisions prohibit payment to the pregnant woman depends on two factors—whether any or all of the payment can be considered reasonable costs associated with the use of the tissue, and when the tissue will be removed.

The nonuniform provisions of nine States prohibit the purchase or sale of organs or tissue for valuable consideration but exclude from the definition of "valuable consideration' the costs of removing, transporting, inspecting, preserving, and reimplanting the organ or tissue. Three States exclude from "valuable consideration" "the expenses of travel, housing, and lost wages" incurred by the "donor." This suggests that the pregnant woman cannot be reimbursed for nonmedical losses and expenses without specific statutory authority. Moreover, under the UAGA, the term "donor" applies only to 'an individual who makes a gift of all or part of his body" (47). In the case of fetuses, the pregnant woman is not a donor, but someone authorized to consent to the gift of a decedent's remains. Thus, the pregnant woman may not be paid for agreeing to transfer the fetal remains, even under State laws (47).

Under the nonuniform provisions of four States, California, Hawaii, Idaho, and North Dakota, payment to the pregnant woman may be banned for another reason. These States prohibit sales and purchases of organs and tissues for valuable consideration when the organ or tissue is to be removed

after the decedent's death. Unless the fetal tissue is to be removed while the fetus is still alive (which may be forbidden under the State's fetal research or other statute), payment to the pregnant woman is forbidden under these anatomical gift act provisions. The California Anatomical *Gift* Act is supplemented by a penal provision that prohibits a person from knowingly acquiring, receiving, selling, or promoting the transfer or otherwise transferring any organ for transplantation for valuable consideration. It also prohibits the use of an organ known to have been transferred for valuable consideration. The law is directed against brokering organs rather than the direct sale by a donor to a recipient.

Of the eight statutes remaining that prohibit the sale of organs but are not part of the State UAGA, one clearly does not prohibit payments to the pregnant woman. The Tennessee statute prohibits only transfers of organs for valuable consideration that "affect commerce" [Tern. Code Ann. 68-30-401] and is presumably aimed at brokers. The law of the District of Columbia clearly prohibits such payments, and it excludes nothing of value from the definition of valuable consideration [D.C. Code Ann. 6-260(b)]. The remaining statutes are similar to the nonuniform anatomical gift act provisions previously discussed. Six allow reimbursement of reasonable expenses associated with the removal, preservation, and use of the donated organ, and four make an additional allowance for the donor's losses and expenses.

The Federal and State laws prohibiting payment to organ donors would ban more than just a cash payment to women. They would also cover payment of a woman's abortion expenses in order that she may donate fetal tissue (54). The reach of some State laws may also extend to payment to agencies that retrieve and process the fetal tissue. These agencies would not be able to "sell' tissue to physicians or patients; however, they would be able to recover their costs and overhead for obtaining the tissue. For example, the New York and West Virginia statutes exclude from the definition of 'valuable consideration" reimbursement of expenses incurred by nonprofit agencies and corporations in offering services related to the location, maintenance, and distribution of the donated organ [N.Y. Public Health Law 4307; W.Va. Code 16-19-7(a)].

Most of the statutes prohibiting transfers of organs for value define organ quite broadly and would cover most types of tissues and organs to be transplanted from fetuses. Other statutes are more limited in the body parts they cover and would require regulatory agency action to cover brain tissue. The Florida statute bans the sale of the kidney, liver, heart, lung, pancreas, bone, skin, or any other organ or tissue specified by rules adopted by the Department of Health and Rehabilitative Services [Fla. Stat. Ann. 873.01(3)(a)]. The New York statute begins with a larger list of items and then provides for regulatory expansion. It defines "human organ' as 'the human kidney, liver, heart, lung, bone marrow, and any other human organ or tissue as maybe designated by the commissioner but shall exclude blood" [N.Y Public Health Law 4307]. To the New York list, Wisconsin adds the pancreas, cornea, eye, bone, skin, and any other organ specified by the department except blood, blood products, and semen [Wisc. Stat. Ann. 146.345]. Michigan has by far the most comprehensive list: "human kidney, liver, heart, lung, pancreas, bone marrow, cornea, eye, bone, skin, cartilage, dura mater, ligaments, tendons, fascia, pituitary gland, and middle ear structures, and any other human organ specified by rule promulgated by the department' [Mich. Comp. Laws Ann. 333. 10204(3)(a)].

Finally, 10 States prohibit "trafficking" in dead bodies—that is, transferring dead bodies for valuable consideration (see table 7-2). These statutes are arguably drafted broadly enough to prohibit either payment to or receipt of payment by the pregnant woman for the use of fetal remains. Only one statute explicitly covers all bodies and bodily parts [La. Rev. Stat. Ann. 17:2280]. The remaining either cover bodies but do not refer to parts or limit their coverage to unclaimed bodies (those that have not been claimed for burial). The majority of States ban both purchases and sales of dead bodies, but three States prohibit only sales, and one State more broadly proscribes "delivering or receiving for speculation or pecuniary profit." In addition, five statutes prohibit transporting dead bodies out of State.

SUMMARY AND CONCLUSIONS

The use of neural grafts raises many legal issues, despite the fact that this procedure is showing some promise in the treatment of several disorders. There are grounds for Federal action in this area. To the extent that Federal funds are used to support research involving neural grafting or to pay for the clinical use of such procedures, Federal regulations may establish mandatory policies governing the conduct of such research. Even if Federal funds are not used, the Federal Government has powers under the commerce clause to regulate this activity. This power has served as the basis for the establishment of the FDA, the prohibition on payment to organ donors for transplantation involving interstate commerce, and the regulation of medical laboratories engaged in interstate commerce.

It is difficult to predict how the FDA will choose to regulate the various tissues and products of biotechnology that may be used in neural grafting. Questions of safety 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 may limit the ability of the FDA to regulate these materials, since it is unclear whether neural tissue grafts, cell lines, and products of biotechnology to be used as neural grafting materials are analogous to the other articles listed as biologics in the statute. Other legal issues include questions of FDA jurisdiction in relation to when a neural graft is produced and performed intrastate and in relation to the practice of medicine.

Some existing Federal policies governing experimentation and organ transplantation could affect tissue transplants. However, the Federal regulations on fetal research and the Federal law on transplantation were developed before the extensive, recent debate on fetal tissue transplantation. It might be appropriate to amend existing policies to address more directly the concerns raised by neural grafting. In particular, Federal regulations and law might be modified to provide that a woman not be paid valuable consideration for fetal tissue for transplantation and not be allowed to designate a donor. Federal regulations might also be amended to ensure that health-care professionals undertaking counseling and persons involved in abortion procedures are not also involved in the harvest and transplantation of fetal tissue.

CHAPTER 7 REFERENCES

1. Anderson, W., and Fletcher, J., "Gene Therapy in Humans: When Is It Ethical to *Begin? ''New England Journal of Medicine* 303:1293-1297, *1980.*
2. *Annas, G.,* Glantz, L., and Katz, B., *Informed Consent to Human Experimentation: The Subject's Dilemma* (Cambridge, MA: Ballinger, 1977).
3. Areen, J., "Statement on Legal Regulation of Fetal Tissue Transplant," ***Report of the Human Fetal Tissue Transplantation Research Panel (Bethesda, MD:*** National Institutes of Health, 1988).
4. Bakay, R., neuroscientist, Emory University, Atlanta, GA, personal communication, December 1989.
5. Barber, B., "The Ethics of Experimentation with Human Subjects," ***Scientific American 234*** (February): 25-31, 1976.
6. Barnett, H., Sackett, D., Taylor, D., et al., "Are the Results of the Extracranial-Intracranial Bypass Trial Generalizable?'' New ***England Journal of Medicine*** 316:820-824, *1987.*
7. Blank, R., Program for Biosocial Research, Social Science Research Institute, Northern Illinois University, DeKalb, IL, personal communication, Dec. 18, 1989.
8. Bonchek, L., "Are Randomized Trials Appropriate for Evaluating New Operations?" New *England Journal of Medicine* 301:44-45, *1979.*
9. Bonchek, L., letter, New ***England Journal of Medicine*** 301:1181-1183, *1979.*
10. Buc, N., Weil, Gotshal & Manges, Washington DC, personal communication, Dec. 18,1989.
11. Buchanan, A., and Brock, D.W., "Deciding for Others," ***Milbank Quarterly*** 64:17-94, *1986.*
12. Bunker, J., Hinkley, D., and McDermott, W., "Surgical Innovation and Its Evaluation," ***Science 200:937-941,*** 1978.
13. Carr, S., legislative analyst, Office of Governmental Relations, Association of American Medical Colleges, Washington, DC, personal communication, April 1990.
14. Center for Biomedical Ethics, ***The Use*** *of Human Fetal Tissue: Scientific, Ethical, and Policy Concerns (Minneapolis, MN:* University of Minnesota, 1990).
15. Christoffel, T., ***Health and the Law: A Handbook for Health Professionals (New*** York, NY: Free Press, 1982).
16. ***City of Akron v. Akron Center for Reproductive Health, Inc., 462*** U.S. 416 (1983).
17. Curran, W., "Forward," ***Consent to Treatment: A Practical Guide,*** F. Rozovsky (cd.) (Boston, MA: Little, Brown, 1984).

18. Fazzini, E., "Neural Transplants in Parkinson's Disease," paper presented at the International Symposium, Centrol Ramon y Cajal, Madrid, May 19-20, 1989.
19. Fletcher, J., "Moral Problems and Ethical Issues in Prospective Human Gene Therapy," *University of Virginia Law Review* 69:515-546, *1983.*
20. Fletcher, J., Dommel, J., and Cowell, D., "Consent to Research With Impaired Human Subjects," *IRB: A Review of Human Subjects Research 7* (November-December) :l-6, 1985.
21. Fowler, N., letter, New *England Journal of Medicine,* 301:1181, *1979.*
22. Fox, J., "Overview," *Report of the Human Fetal Tissue Transplantation Research Panel (Bethesda, MD:* National Institutes of Health, 1988).
23. Gill, T., and Lund, R., "Grafting into the Brain," testimony before the Human Fetal Tissue Transplantation Research Panel, National Institutes of Health, Bethesda, MD, Sept. 14, 1988.
24. Greenwald, R., Ryan, M., and Mulvihill, J., *Human Subjects Research: A Handbook for Institutional Review Boards (New* York, NY: Plenum Press, 1982).
25. Gunter, K., Division of Biological Investigational New Drugs, Center for Biologics Evaluation and Research, Food and Drug Administration, personal communication, Feb. 26, 1990.
26. *Halushka v. University of Saskatchewan, 53* D.L.R. 2d 436 (Sask. 1968).
27. Jackson, L., "Prenatal Genetic Diagnosis by Chorionic Villus Sampling (CVS)," *Seminars in Perinatology* 9:209-218, *1985.*
28. Lappe, M., "Balancing Obligations to the Living Human Fetus with the Needs for Experimentation," U.S. Department of Health, Education, and Welfare, National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, *Research on the* Fetus, DHEWPub. No. (OS) 76-127 (Washington, DC: U.S. Government Printing Office, 1975).
29. *Leigh v. Olsen, 497* F. Supp. 1340 (C.D.N.D. 1980).
30. Levine, R., *Ethics and Regulation of Clinical Research* (Baltimore, MD: Urban & Schwarzenberg, 1981).
31. Loh, L, letter, New *England Journal of Medicine* 301:1182, *1979.*
32. McCormick, R., "Experimentation on the Fetus: Policy Proposals," U.S. Department of Health, Education, and Welfare, National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, *Research on the Fetus* DHEW Pub. No. (OS) 76-127 (Washington, DC: U.S. Government Printing Office, 1975).
33. McCoy v. *Georgia Baptist Hospital, 167* Ga. App. 495,306 S.E.2d 746 (1983).
34. Mackler, B., ''Regulatory Issues Concerning Organs and Tissues," paper presented at the Annual Educational Conference of the Food and Drug Law Institute, Washington, DC, Dec. 13, 1989.
35. Mahowald, M.B., Areen, J., Hoffer, B.J., et al., "Transplantation of Neural Tissue from Fetuses," *Science* 235:4794, *1987.*
36. Mahowald, M.B., Silver, J., and Ratcheson, R.A., "The Ethical Options in Transplaning Fetal Tissue,' *Hastings Center Report* 17(February):9-15, 1987.
37. *Margaret S. v. Edwards, 794* F.2d 994 (5th Cir. 1986).
38. Merchant, B., and Hybritech, X., "Emerging Issues on Product Safety Evaluation," paper presented at the Annual Educational Conference of the Food and Drug Law Institute, Washington, DC, Dec. 13,1989.
39. Merrill, R.A., and Hutt, P.B., *Food and Drug Law: Cases and Materials* (Mineola, NY: Foundation Press, 1980).
40. Merz, B. "Neurobiologists Join Neurosurgeons in Urging Restraint in Parkinson's Surgery," *Journal of the American Medical Association* 216:2929, *1989.*
41. *Meyer v. Nebraska, 262* U.S. 390 (1923).
42. *Moore v. Regents of the University of California, 202 Cal.* App.3d 1230, 249 Cal. Rptr. 494 (1988), *reh. granted, 252 Cal.* Rptr. 816,763 P.2d 479, 1988.
43. *Moore v. Regents of the University of California,* Supreme Court of the State of California, Case Number S006987, July 9, 1990.
44. Moraczewski, A. S., Regional Director, Pope John XXIII Medical, Moral, Research, and Education Center, Houston, TX, personal communication, Dec. 18, 1989.
45. Mulford, R., "Experimentation on Human Beings," *Stanford Law Review* 20:99-117, *1967.*
46. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, U.S. Department of Health, Education, and Welfare, *Research on the Fetus: Report and Recommendations,* DHEW Pub. No. (OS) 76-127 (Washington, DC: U.S. Government Printing Office, 1975).
47. National Conference of Commissioners on Uniform State Laws, *Uniform Anatomical Gift Act,* annual conference, Chicago, IL, 1987.
48. Note, "State Prohibition of Fetal Experimentation and the Fundamental Right to Privacy," *Columbia Law Review* 88:1073-1097, *1988.*
49. Ramsey, P., *The Patient as Person: Explorations in Medical Ethics (New* Haven, CT: Yale University Press, 1970), pp. 11-19.
50. Redmond, D. E., neurosurgeon, Neurobehavioral Laboratory, Yale University School of Medicine, New Haven, CT, personal communication, May 1990.
51. Rettig, R. A., "The Politics of Organ Transplantation: A Parable of Our Time," *Organ Transplantation*

Policy: Issues and Prospects, J.F. Blumstein and F.A. Sloan (eds.) (Durham, NC: Duke University Press, 1989), pp. 191-227.
52. Robertson, J., "Compensating Injured Research Subjects: II, The Law," *Hastings Center Report* 6(December):29-31, 1976.
53. Robertson, J., "The Law of Institutional Review Boards," ***University of California at Los Angeles Law Review*** 26:484-549, *1979.*
54. Robertson, J., "Fetal Tissue Transplants," ***Washington University Law Quarterly*** 66:443-498, *1988.*
55. Rosner, J., Executive Director, United Parkinson Foundation, Chicago, IL, personal communication, May 1990.
56. Schwartz, R., "Institutional Review of Medical Research," ***Journal of Legal Medicine*** 4:143-166, *1983.*
57. Sheehan, A., "Fetal Tissue Implants: An Explosive Technology Needs National Action," ***Dickinson Law Review*** 92:895-916, *1988.*
58. ***State of Louisiana v. Mathews, 427*** F. Supp. 174 (D.C. La. 1977).
59. Terry, N., "Politics and Privacy: Refining the Ethical and Legal Issues in Fetal Tissue Transplantation," ***Washington University Law Quarterly*** 66:523-551, *1988.*
60. ***United States v. An Article of Drug. . . Bacto-Unidisk, 394*** U.S. 784 (1968), ***reh. denied, 395*** U.S. 954 (1%9).
61. ***United States v. Calise,*** 217 F. Supp. 705 (D. C.N.Y. 1962).
62. ***United States v. Evers, 453*** F. Supp. 1141 (D.C. Ala. 1978).
63. U.S. Congress, Office of Technology Assessment, ***Human Gene Therapy,*** OTA-BP-BA-32 *(Washing*ton, DC: U.S. Government Printing Office, December 1984).
64. U.S. Congress, Office of Technology Assessment, ***Losing a Million Minds: Confronting the Tragedy of Alzheimer's Disease and Other Dementias,*** OTA-BA-323 (Washington, DC: U.S. Government Printing Office, April 1987).
65. U.S. Congress, Office of Technology Assessment, ***Life-Sustaining Technologies and the Elderly,*** OTA-BA-306 (Washington, DC: U.S. Government Printing Office, July 1987).
66. U.S. Department of Health and Human Services, Public Health Service, Food and Drug Administration, testimony before the House Committee on Science and Technology, Subcommittee on Investigations and Oversight, Nov. 9, 1983.
67. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, ***Report of the*** *Human Fetal Tissue Transplantation Research Panel (Bethesda, MD: 1988).*
68. van der Linden, W., "Pitfalls in Randomized Surgical Trials," ***Surgery*** 87:258-262, 1980.
69. White, R.M., Associate Professor of Medicine and Oncology, Howard University Cancer Center, Washington, DC, personal communication, June 12, 1990.
70. Williamson, B., "Gene Therapy," ***Nature 298:416-418, 1982.***
71. Wion, A., Associate Chief Counsel for Drugs and Biologics, Food and Drug Administration, "Legal Issues Concerning Federal Regulation of Tissues," paper presented at the American Association of Tissue Banks-FDA colloquium, Washington, DC, Oct. 1, 1989.
72. Wion, A., Associate Chief Counsel for Drugs and Biologics, Food and Drug Administration, "Regulatory Issues Concerning Organs and Tissues," paper presented at the Annual Educational Conference of the Food and Drug Law Institute, Washington, DC, Dec. 13, 1989.
73. Woodcock, J., Director, Division of Biological Investigational New Drugs, Center for Biologics Evaluation and Research, Food and Drug Administration, letter to R. Chin, Office of Technology Assessment, received Oct. 26, 1989.
74. Woodcock, J., Director, Division of Biological Investigational New Drugs, Center for Biologics Evaluation and Research, Food and Drug Administration, letter to Wendy Pachter, Office of Technology Assessment, received Dec. 14, 1989.
75. Woodcock, J., Director, Division of Biological Investigational New Drugs, Center for Biologics Evaluation and Research, Food and Drug Administration, personal communication, June 1990.
76. Woody, K., "Legal and Ethical Concepts Involved in Informed Consent to Human Research," ***California Western Law Review*** 18:50-79, *1981.*

Chapter 8

Ethical Issues

CONTENTS

Boxes

Figure

Chapter 8
Ethical Issues

Neural grafting is a complex subject for ethical discussion because of the scope of the issues it raises. Ethical arguments surrounding neural grafting are part of the continuing debates about the morality of abortion and genetic manipulation, and they rekindle discussions about the treatment of research subjects and the meaning of informed consent. This chapter discusses ethical aspects of the various neural grafting technologies currently being researched.

Some ethical issues raised by neural grafting are not unique to this technology. One such issue is the allocation of scarce Federal resources, since funds committed to neural grafting might be spent on alternative biomedical research or other areas altogether. Questions about funding can be addressed with empirical evidence of the number of individuals affected by diseases, the availability of alternative treatments, and the economic costs that both the diseases and the treatments create for society. Another general ethical concern is the tension between the Federal Government's commitment to promoting the public health and funding biomedical research, and its responsibility to respond to public concern about certain research and its possible applications.

The various grafting materials used also raise ethical issues. Human fetal tissue, in particular, has generated extensive discussion in several forums. A moratorium on federally funded fetal tissue transplantation research was declared in March 1988 by the Secretary of Health and Human Services and was continued indefinitely in November 1989 (see app. A). As a result of this moratorium, a National Institutes of Health (NIH) advisory panel was convened and in 1988 issued a report on the ethics of fetal tissue transplantation (54). The panel's policy recommendations were accepted by a large majority of its members and were accepted unanimously by the NIH Director's Advisory Committee. However, the points on which panel members disagreed were never resolved, and no action was taken on the recommendations by the NIH Director or the Assistant Secretary for Health.

As the technology develops, the use of continuous cell lines as a source of grafting material may also create general concern. Advances in molecular biology suggest it may be possible to develop effective brain and spinal cord grafts by genetically manipulating cells before transplantation. Genetic manipulation of cells has generated considerable controversy since it was first introduced (49), but the somatic cell alterations that would be used for neural grafting are less troublesome than germ cell gene therapy. On the other hand, as cell lines have been developed, questions have been raised about ownership of tissues. Uncertainty about how to determine the rightful ownership of cell lines could complicate the use of this material considerably.

The treatment of patients who receive neural grafts is another area of ethical concern. Issues of protecting patients from undue risk and obtaining adequate informed consent are not unique to neural grafting, but they warrant special attention for this technology. At this stage of research, some persons question whether the risks to research subjects are comparable to the expected benefits. It is also questionable whether requirements for informed consent can be met, given the vulnerability of some persons with neurological disorders.

This chapter describes the ethical concerns that have been raised about neural grafting. It identifies issues and presents the various arguments surrounding them in order to represent the spectrum of attitudes expressed in public debate.

ISSUES RELATED TO RESEARCH FUNDING

Public funding of biomedical technology involves broad analyses of the economic benefits and costs, as well as the social benefits and ethical consequences, a new technology might have. 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 persons believe that justice requires the expenditure of funds in areas where they can benefit the greatest proportion of the population rather than a few disadvantaged individuals. If neural grafting techniques are very expensive to study or to provide as medical

Box 8-A—Just Distribution of Resources and the Funding of Heart Transplants

"On February 1, 1980, the 12 lay trustees of the Massachusetts General Hospital announced their decision not to permit heart transplants at that institution 'at the present time. They noted that it was difficult to turn away even one patient in need of a heart transplant, but they underlined the importance of making such decisions 'in terms of the greatest good for the greatest number. ' In June of that same year, Patricia Harris, then secretary of the Department of Health and Human Services, withdrew an earlier tentative authorization for Medicare to pay for heart transplants because of the need to evaluate the technology's 'social consequences,' including its costs. In 1987, legislators in Oregon made an equally dramatic change in the Oregon Medicaid program (the State-Federal program that provides funds to cover medical needs for financially needy citizens in the State). They decided not to pay for most transplants in order to use their limited budget for other purposes, In particular, they noted that the money that would have covered approximately 30 heart, liver, bone marrow, and pancreas transplants would instead be used to provide regular prenatal care for 1,500 pregnant women. The altered allocation was justified by its proponents because it would save more lives. '

The controversy about the funding of heart transplants is an example of the generic ethical issues that may surround an expensive medical therapy. Neural grafting could provoke similar considerations.

SOURCE: T.L. Beauchamp and J.F. Childress, "The Principle of Justice," *Principles of Biomedical Ethics (New York, NY: Oxford* University Press, 1989), pp. 286-287.

therapy, budget restrictions could require that neural grafting activity be limited (see box 8-A).

Questions arise about whether the research and application of technologies such as neural grafting ought to receive Federal support. Some critics consider it unjust to spend a great deal of money to benefit a few persons or to develop a surgical technique for a relatively uncommon condition when the same funds might be used to develop medical treatments that would benefit many more persons. In order to determine whether expenditure of public funds for neural grafting research constitutes just allocation of resources, some background information is required. The following questions are not ethical issues, but answers to them could help the Federal government decide whether to fund neural grafting.

What kinds of diseases might be treated with this technology?

It has been argued that the government ought to fund research that seeks to cure neurological disorders that affect large numbers of U.S. citizens (2). Neural grafting is a possible therapy for Parkinson's disease, Huntington's disease, Alzheimer's disease, spinal cord injury, and other neurological disorders, although whether neural grafting will be successful in any of these remains to be seen (see ch. 5).

What impact do these diseases currently have on society and what threat do they hold for the future?

Neurological disorders exact a high financial toll from society, although measures of their costs and statistics on the number of persons affected vary considerably (see ch. 6). Neural grafting has been suggested as a possible therapy for some age-related diseases, e.g., Parkinson's disease, Alzheimer's disease, and stroke. Should neural grafts prove effective for such diseases and should the prevalence of these diseases increase with an aging society, the demand for neural grafts might increase as well.

What alternative surgical or medical treatments are available?

If neural grafting is more effective and less expensive than alternative treatments for neurological disorders, an ethical argument could be made for Federal support of neural grafting. For most neurological disorders, however, including Parkinson's disease, Huntington's disease, spinal cord injury, and Alzheimer's disease, no cures are available and control of symptoms is inadequate. Symptoms of Parkinson's disease are often treated with L-dopa, but this drug is palliative (it treats only the symptoms of the disease and not the cause), and its benefits diminish as the disease progresses. Some alternative treatments are available or in the process of being developed. For example, a new drug called deprenyl shows promise for slowing the progression of Parkinson's disease (see ch. 6), although it does not stop the progression or affect advanced stages of the disease (45). While neural grafting is a promising

treatment for Parkinson's disease at this time, it, too, may be only palliative (see ch. 5). Fair allocation of health care resources may require that the financial costs of neurological disorders now and in the future be estimated and compared to the costs of neural grafting and alternative treatments. However, fair allocation may also require that resources spent on neurological disorders reflect the impact of these diseases on society.

To what extent does the Federal Government's commitment to funding biomedical research extend to neural grafting research?

Because neural grafting techniques are still being studied, the question at this point is whether the government has an obligation to support neural grafting research. Given the government's commitment to support basic scientific research and to further the health of the Nation, it might be expected that basic research which could aid in developing new neural grafting technologies would be funded. This is, in fact, the case: Only research on the implantation of human fetal tissue from induced[1] abortions does not receive Federal funds (53,57). The moratorium on Federal funding for human fetal tissue grafting research was declared because specific ethical issues surrounding this research came into conflict with the government's general commitment to fund basic research. The ethical issues related to fetal tissue grafting will be discussed later in this chapter.

Would funding neural grafting require the government to redirect limited funds from other areas of research?

It has been suggested that, in order to fund neural grafting research, resources might be provided at the expense of other projects that could lead to more effective or less controversial treatments for neurological disorders (38) or increased "understanding of the fundamental biological principles underlying the normal function and dysfunction of the human nervous system" (11). In general, Congress allocates funds for biomedical research to Federal research agencies, but the distribution of those funds to the institutes within the agencies and then to individual investigators falls outside Congress's purview (12). Federal research grants are made on the basis of merit, as determined through peer review of research protocols. Neural grafting research receives Federal funding when grant proposals scientifically warrant that support. Withholding research funds from neural grafting frees resources for other projects, but there is no guarantee that those funds will be put toward other neurological research.

ISSUES RELATED TO TISSUE SOURCE

Questions about the propriety of federally funded neural grafting research are not limited to resource allocation-they also address the propriety of using various graft materials. As discussed in chapter 4, a number of neural grafting materials are used, some of which are more ethically problematic than others. Autografts and allografts using adult tissue are relatively free of ethical controversy: For example, the primary ethical reasons for not doing adrenal medullary autografts to treat Parkinson's disease are likely to be related to protection of the research subject rather than to the source of the grafting material.

Fetal Tissue

Adult human neural tissue is not a suitable material for grafting, so scientists have turned to human fetal neural tissue. Fetal tissue is promising from a scientific point of view, but it is also the most ethically controversial grafting material because it is usually obtained from abortions.

While use of aborted fetal tissue in research is not new, the current ethical arguments surrounding its use and the Federal attitude toward funding such research reflect a different level of concern than has previously been demonstrated. The use of human fetal cells played an important role in the development of vaccines for polio and other childhood diseases (20,48), and research on the transplantation of fetal thymus glands into infants with DiGeorge's syndrome was performed in the United States 20 years ago (7,30). The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (hereafter referred to as the National Commission) scrutinized ethical issues related to the use of fetal tissue in research and

[1]The Department of Health and Human Services referred to "induced abortion" in the fetal tissue transplantation moratorium (57). Where the moratorium or Federal activity surrounding it is discussed in this chapter, "induced abortion" will be used. Where a distinction is made between different types of induced abortion, more specific terminology will be used.

developed the guidelines used to create the 1975 Federal regulations for use of fetal tissue in research (52). The National Commission's report and the regulations that developed from it [45 CFR 46] focused on research performed on living fetuses and paid little attention to fetal cadavers. Both specified only that research on cadaveric fetal tissue should "be conducted in accordance with commonly held convictions about respect for the dead, and in accordance with State and local laws" (10). No moral distinction was made about the means of fetal death. As a result, research using aborted fetal tissue for experimental purposes has been, and continues to be, relatively uncontroversial. The moratorium on Federal funding of research involving transplantation of human fetal tissue obtained from induced abortions into humans is a recent exception (see app. A).

Fetal Research v. Fetal Tissue Transplantation Research

What makes transplantation research different from other research that uses cadaveric fetal tissue? Some persons perceive a significant ethical difference. In fetal research,[2] cadaveric fetal tissue is used to *develop* a treatment; in fetal tissue transplantation research, fetal tissue *is the* treatment (43). These persons question whether fetal tissue should be used to benefit an individual recipient.

On the other hand, some persons perceive no ethical difference between the transplantation of cadaveric adult organs and tissues and those of cadaveric fetuses. Unless the decedent has explicitly refused to donate body parts, adult cadaveric tissues may be donated by the next of kin as a gift and may be removed for transplantation by a coroner or medical examiner. Once these conditions are met, tissues may be used to benefit a single recipient. In this view, cadavers do not have protectable interests, and tissue from dead fetuses is no different than tissue from dead adults.

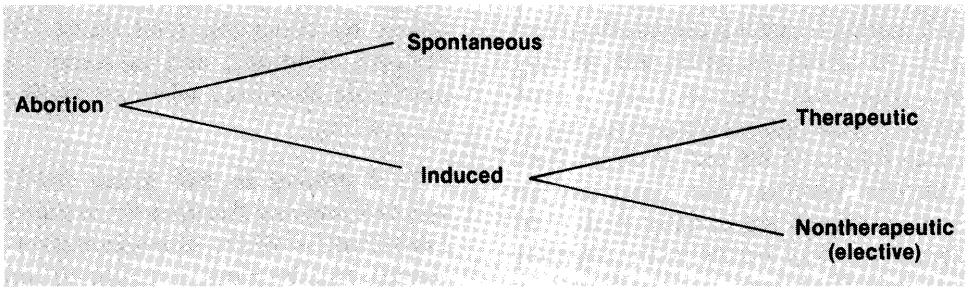
Procurement of Fetal Tissue

Most ethical objections to the use of fetal tissue for neural grafting relate to tissue procured from nontherapeutic induced abortions (to be referred to hereafter as elective abortions) (see figure 8-l). Many persons who object to the use of fetal tissue from elective abortions have suggested that fetal tissue from spontaneous abortions (miscarriages) could be used for transplantation without ethical objection because fetal death is not intended. The first human fetal nervous system grafts used tissue from spontaneous abortions (29), but since spontaneous abortions are seldom anticipated and usually take place outside a hospital, it is difficult to collect the tissue for grafting. Tissue from therapeutic induced abortions for cervical cancer or ectopic pregnancy has also been suggested as an ethically unobjectionable alternative, since protection of the pregnant woman's life, not the termination of pregnancy, is the primary purpose of the abortion. There is some question, however, as to whether a physiological anomaly that caused the pregnancy to be terminated (as evidenced by spontaneous abortion, ectopic pregnancy, or cancer) would make the tissue inappropriate for grafting (10,39). Ectopic pregnancy is more likely to result from a physiological anomaly of the woman than a defect in the fetus (17), but without thorough genetic and physiological testing, the use of tissue from spontaneous and therapeutic induced abortions for neural grafting might be considered unethical because of the risk to the recipient if the graft material is infected with a virus or bacteria or has a genetic anomaly that could affect the recipient (3,10,39). While grafting fetal tissue from spontaneous abortions and therapeutic induced abortions could avoid association of neural grafting with elective abortion, it may not be a practical source of graft material.

Some persons object to the use of electively aborted fetal tissue for grafting because procurement of the neural tissue might cause pain or even death to the fetus. Research has indicated that neural tissue from electively aborted fetuses between 8 and 12 weeks of development is the most clinically appropriate for neural grafting (48). This early stage of development makes it unlikely that a fetus would be viable after an abortion procedure (5). First-trimester abortions are usually performed by vacuum aspiration, a procedure that seldom results in a live, or even intact, fetus (10). Concern has been expressed, however, that elective abortions performed at a later gestational age might allow a fetus to survive the procedure and that the separation of neural tissue for the graft would not only cause great pain but could

[2]The National Commission report and the Federal regulations for fetal research identify several types: activities directed toward fetuses in utero as subjects, activities directed toward viable fetuses ex utero, activities directed toward nonviable fetuses ex utero, and activities involving the dead fetus, fetal material, or the placenta [45 CFR 46].

Figure 8-l—Types of Abortion and Morally Relevant Differences Among Them



Without any qualification, the term "abortion" reveals nothing except that a pregnancy has ended. This termination is not usually considered morally bad in itself. Spontaneous abortions may be considered unfortunate but are not usually considered morally blameworthy. The abortions that usually generate ethical controversy are those that are induced.

There are two types of induced abortions: therapeutic and nontherapeutic. Although some persons object to any induced abortion on the grounds that the premature termination of fetal life constitutes murder, others find that moral distinctions may be made, depending on the reason for the abortion. Conditions such as cancer of the cervix or uterus and ectopic pregnancy will usually lead to the death of both the pregnant woman and the fetus if the pregnancy is not aborted. If the life of the woman is endangered by cervical cancer, the Roman Catholic Church teaches that "the treatment is not really an abortion, even though the fetus dies. The intent of the action is the removal of the life threatening rendition, and the death of the fetus is a foreseen but unintentional consequence." Other persons argue that when a fetus's and a woman's rights to life conflict, the woman's life maybe saved at the expense of the fetus's. There are many other points of view on this question. Although there is some disagreement as to whether a pregnancy maybe terminated if bringing the pregnancy to term will result in the death of the woman but the birth of a baby, therapeutic induced abortion is not as controversial as nontherapeutic induced (elective) abortion. Many reasons have been put forth for both the morality and the immorality of nontherapeutic induced abortion.

SOURCES: Adapted from M.B. Mahowald, "Neural Fetal Tissue Transplantation: Should We Do What We Can Do?" *Neurologic Clinics* 7:745-757, 1989; A. Moraczewski, regional director, Pope John XXIII Medical, Moral, Research, and Education Center, Houston, TX, personal communication, April 1990.

actually cause the death of the fetus (27). The use of a living fetus for transplantation is a form of vivisection, which is generally recognized to be unethical and which, moreover, is prohibited by Federal law: As long as the fetus is alive, its tissues may not be removed for any research or therapeutic procedure [45 CFR 46]. The distinction between a live fetus and a dead fetus with living tissue is extremely important in this regard.

Arguments For and Against Human Fetal Tissue Transplantation Research

Arguments for and against using electively aborted fetal tissue for neural grafting address the issues raised by research already under way and the future use of fetal tissue grafting on a large scale. These arguments raise four main questions:

- . Is the means of fetal death ethically relevant to any subsequent use of the tissue?
- . Is it ethical to use electively aborted fetal tissue as therapeutic treatment for another individual?
- . What are the ethical implications of a public policy that supports fetal tissue transplantation research?
- Whose consent, if any, is necessary for the use of aborted fetal tissue for neural grafting?

Is the means of fetal death ethically relevant to any subsequent use of the tissue ?-While disputes over the morality of abortion have complicated and politicized discussions about the use of electively aborted fetal tissue for neural grafting, the ethical *relevance* of an elective abortion to the transplantation of fetal tissue is the true subject of public debate. Both opponents and supporters of elective abortion rights have articulated a number of reasons for supporting fetal tissue transplantation research, and both have also identified reasons for not doing so.

The main argument supporting fetal tissue transplantation states that there is no relevant difference between the transplantation of cadaveric fetal tissue (i.e., tissue from a dead fetus) and any other cadaveric tissue. (This position has been taken by both supporters and opponents of elective abortion.) The argument, which claims that it is not unethical to use tissue from elective abortion, is based on the

premise that by the time the fetus becomes a possible source of transplantation tissue it is already dead and that the reamer of death is irrelevant to any subsequent use. The NIH Human Fetal Tissue Transplantation Research Panel compared the use of tissue from a dead fetus and the use of tissue from accident and murder victims. The persons from whom organs are obtained are already dead, and using the organs in no way harms them, deprives them of respect, objectifies them, or uses them as a means to another's end. Neither does it indicate approval of the death or the manner in which it was brought about. On the contrary, using organs and tissues from these victims is thought to allow some good to come from their death and thus is morally permissible.

Another argument suggests that there is a moral obligation to help others when it is possible to do so and thus it is unethical *not* **to** use tissue from elective abortions. Some persons believe that since the aborted fetus is already dead and its tissue legally may be used for research and medical treatments, and since fetal tissue grafts may benefit others, preventing use of that tissue is ethically reprehensible. They believe that since the dead have no interests to protect, using fetal tissue does not harm the fetus physically or morally. They believe that using cadaveric fetal tissue for grafts that relieve suffering is morally good and thus perceive an ethical imperative to use that tissue to help others.

Other persons disagree with the claim that the means of fetal death is morally irrelevant to the use of the tissue for grafting and perceive a moral obligation ***not*** to use fetal tissue for transplantation. Many of these persons also strongly oppose abortion. One argument is that using electively aborted fetal tissue for neural grafting indicates indifference to the means of fetal death. Another argument says that using aborted fetal tissue for neural grafts constitutes *post facto* complicity in murder (8). Those who hold this position argue that because abortion is murder, the procurement of fetal tissue from abortion clinics requires collaboration with murderers. For example, since surgeons who perform neural grafting must have access to fetal tissue, they must work hand-in-hand with abortionists to obtain the tissue while the cells are still alive. Unlike surgeons who retrieve organs from murder or accident victims, those who retrieve and transplant aborted fetal tissue participate retroactively in the killing by obtaining the consent of the pregnant woman for use of the tissue (in cases where this is done), by collecting fetal tissue from those who perform abortions, and in some cases by killing nonviable abortuses when separating neural tissue for grafting.

Is it ethical to use tissue from an electively aborted fetus as therapeutic treatment for another individual?—While transplantation of cadaveric tissues has become a common practice and is regulated under the Uniform Anatomical Gift Act (UAGA) in all 50 States (see ch. 7), some persons object to the use of fetal tissue for transplantation into individual recipients on the principle that one should not treat the fetus as the means to another's end. They believe the "consideration of any class of human subjects as no more than a commodity to be used for the benefit of others is wrong" (27). They do not believe that the alleviation of suffering justifies the use of aborted tissue. In their belief, no matter how good an outcome might derive from fetal tissue transplantation, it does not justify the moral devaluation of the fetus necessary for that outcome to occur.

Other persons question why the transplantation of cadaveric fetal tissue should be treated differently from the transplantation of any other cadaveric tissue. The use of cadaveric adult organs is rarely regarded as indicative of disrespect, commodification, or devaluation (56). Why, then, should transplantation of cadaveric fetal tissue be considered a moral devaluation? Some persons believe transplantation of cadaveric tissue into individuals is more acceptable than using it for general research, since "it may do more good to heal than simply learn how to heal" (31).

What are the possible consequences of a public policy that supports fetal tissue transplantation research?—Some persons are concerned that Federal funding of fetal tissue transplantation research would lead to an increase in the number of abortions performed in the United States. The Department of Health and Human Services (DHHS) expressed this concern in continuing the human fetal tissue transplantation research moratorium in November 1989. These persons believe women may decide to abort if they believe fetal tissue could help another person and that women who are ambivalent about their pregnancies will consider fetal tissue grafting a justification for having an abortion (35). If fetal tissue grafting research shows promise for Parkin-

son's disease or other disorders, they argue, the supply of fetal tissue will not satisfy the demand. Elective abortion might implicitly or explicitly be encouraged in order to make more fetal tissue available. Some persons believe it would be ethically unacceptable if the ability to donate fetal tissue for grafting influenced even one woman's decision to have an abortion (35).

Other persons disagree that elective abortion would have to be encouraged to make fetal tissue available for grafting. Some claim that the number of elective abortions already being performed in the United States would provide adequate tissue even if neural grafting became standard practice (13). As is the case with kidneys, hearts, and other body tissues that are transplanted, the number of neural grafting procedures performed could be limited to the amount of fetal tissue already available (30). Also, the development of continuous cell lines might make it unnecessary in some cases to procure newly aborted tissue. Fetal tissue might be used to start a cell line without increasing the number of abortions that take place and might not therefore be ethically objectionable to some persons (34). 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, either because of a need for grafting material or because women perceive an altruistic justification for elective abortion.

Women's groups in particular have objected to the claim that the opportunity to donate fetal tissue for transplantation after an elective abortion would affect a woman's decision to terminate a pregnancy, even if she did believe that this use of fetal tissue would do good. Other persons argue that requiring anonymity between tissue donors and graft recipients would make specified donation impossible in the event that a woman wanted to provide neural grafting material for a specific recipient.

Whose consent, if any, is necessary for the use of aborted fetal tissue for neural grafting?--Consent is generally required for participants in research protocols and for donors of tissue. It is not certain, however, what role consent would play in donating fetal tissue for neural grafting research, and there is debate about who should give it.

The donation of adult cadaveric tissue for transplantation, and fetal tissue in some States, is regulated under the UAGA (see ch. 7). As fetal tissue grafting research progresses, the models for obtaining consent may have to be modified to include fetal tissue donation, or a new model may have to be created. Those who believe fetal tissue transplantation is analogous to the transplantation of other cadaveric tissue find it appropriate for the next of kin, in this case the woman who has the abortion, to give consent to use fetal tissue for transplantation. However, some persons challenge the woman's authority to give this consent, since, according to their view, she is also the cause of the fetus's death. Consent for fetal tissue use in neural grafting falls between existing regulations and practices.

Some persons hold that a woman's prerogative to donate fetal tissue stems not from her legal status as next of kin, but from a basic right to control her own body and its products. They believe that seeking consent to examine or use fetal remains is consistent with the treatment accorded any other tissue or organ removed during surgery, thus to deny a woman the opportunity to specify what should happen to aborted fetal tissue would be to deny her autonomy (10). Consent should be obtained out of respect for the interests of the woman, who may want the tissue to be handled a certain way after the abortion procedure. For example, some women may hope to benefit another person by donating aborted fetal tissue for transplantation, while other women may want to dispose of the tissue. Whatever the decision and whatever the reason for it, these persons argue that the decision should be the woman's.

Some persons believe that fetal tissue is not the woman's to donate. They believe that no fetus is property merely because it is sustained by another person's body; more important, they believe that after the abortion has taken place and the fetus is no longer part of the body, a woman's claim to bodily property carries even less weight (8,11). These persons argue that the only reason to obtain the consent of the pregnant woman would be for her to act as proxy for a fetus to be used in research [under the Protection of Human Subjects Act [45 CFR 46]. Proxy decisionmaking assumes the surrogate decisionmaker's commitment to act in the interests of the incompetent. Since the woman clearly does not intend to protect the fetus, they believe it is inappropriate for her to act as the fetus' proxy; she should have no say over what happens to the tissue (8).

The donation of cadaveric tissue need not be seen strictly in terms of property or proxy, however. The donation of adult cadaveric tissues by family members is done in the context of a gift-giving model that neither recognizes property rights on the part of the family nor grants guardianship or proxy. The fact that the woman's consent is obtained does not necessarily mean she acts as proxy for the fetus, since her role would be to consent to tissue donation, not research participation. Some persons believe fetal tissue donation is consistent with the accepted gift-giving model for organ donation and constitutes an altruistic act women are morally free to take. Others, however, believe that electively aborted fetal tissue is an inappropriate gift (10).

It has also been suggested that no consent is needed to use fetal tissue for grafting research. Since electively aborted fetal tissue is normally discarded without any specification on the woman's part, it might be justifiable to consider the abortus abandoned and to use it without consent. This method might avoid the obstacles created by views of competing rights (the woman v. the fetus); however, refusing to acknowledge protectable interests on the part of either the woman or the fetus could be interpreted as exploitation. Although tissues and organs from adult cadavers can be used for transplantation without the consent of family members, some women might prefer that the tissue not be used for transplantation. Using the fetal tissue without the consent of the woman could create more problems than it solves.

If it is decided that it is ethically appropriate or necessary to obtain the woman's consent, the question of when to solicit consent is raised. There is some agreement that consent should be obtained only after the woman has conclusively decided to abort, in order to separate the decision to abort from the decision to donate fetal tissue (1,32,48,54). It may also be possible to obtain consent tier the elective abortion has been performed and the tissue has been identified as suitable for transplantation, especially if the tissue is frozen before transplantation, although this option is not entirely free of ethical problems (see box 4-A).

The protocol used in one privately funded fetal tissue transplantation trial solicited consent from the woman after the abortion had been completed (16). The consent form specified that fetal tissue was being solicited for research purposes, which could include fetal tissue transplantation research. This approach provides the woman an opportunity to prevent the use of the tissue for grafting, while not influencing her decision to maintain or terminate the pregnancy. Other investigators may choose not to request consent immediately after abortion because it could be emotionally stressful for the woman (14), although some persons believe that there is no difference between requesting consent for tissue from a woman who has just aborted a pregnancy and requesting organ donation from the family of a deceased adult.

The consent forms used for other fetal tissue research may not be comprehensive enough to address all aspects of grafting. It is not clear whether the abortion consent forms which allow fetal tissue to be donated for research should include clauses specifying that the tissue might be used for transplantation. A separate consent form for fetal tissue transplantation might be appropriate.

Relationships Among the Questions-Attitudes toward consent for the donation of fetal tissue for transplantation are likely to be consistent with beliefs about the relevance of the means of fetal death to fetal tissue transplantation, the appropriateness of using cadaveric fetal tissue for therapeutic purposes, and the ethical implications of public policy that supports this research. The present discussion delineates issues for the sake of illustrating different aspects of the debate, but the arguments of individuals and groups who discuss the ethics of fetal tissue transplantation research are often more fluid.

For example, some persons who oppose fetal tissue transplantation research because they believe such grafting is complicitous with murder readily link three of the four questions discussed above. They feel that the means of fetal death is relevant to grafting fetal tissue because elective abortion is the unjust killing of innocent human beings. A woman who has an abortion therefore should not serve as its proxy. Public support should not be given to fetal tissue transplantation research because it would constitute public approbation for unjust killing (26).

Similarly, some persons who do not object to fetal tissue grafting research argue that the means of fetal death is irrelevant. They believe that once a fetus is dead, it has no interests to protect and maybe treated in the same reamer as adult cadaveric tissue. Consent for its use should therefore be solicited from

the next of kin, which in this case is likely to be the woman who has the abortion. These persons feel that public support of fetal tissue transplantation research would be consistent with other fetal tissue research and cadaveric organ donation and would have no specific ethical implications.

Issues Surrounding Fetal Tissue Transplants as Standard Therapy

The preceding arguments have been presented in public debates about the ethical implications of fetal tissue transplantation research. Some of the potential problems can be illustrated dramatically by describing the consequences should fetal tissue grafting become standard therapy. ("Standard therapy" describes procedures that are no longer regulated as research.)

Some persons have expressed concern that Federal support of fetal tissue transplantation through funding or regulation of the procedure would legitimize and institutionalize elective abortion.[3] Others persons contend that since elective abortion is legal, and since the Federal Government profits from it by taxing abortion clinics (3), it is already both legitimate and institutionalized. They argue that claims that Federal support of neural grafting research would further institutionalize the practice carry no weight. Fetal tissue from elective abortions would be used after the abortion has already taken place and would have no effect on law or policy concerning abortion itself. Still other persons believe that even though elective abortion is legal, it should not be encouraged. If fetal tissue transplantation is accepted as a medical treatment, they believe it maybe impossible to make abortion illegal again. Even some persons who support the freedom to have an abortion do not necessarily consider it a practice they would like to see endorsed by a public policy; i.e., while abortion should be legal, it does not follow that fetal tissue should be used for neural grafting.

Another concern is that the use of electively aborted fetal tissue as standard therapy may lead to commercial exploitation of fetuses. This concern has also been expressed in more extreme terms: Some argue that using aborted fetal tissue for neural grafting may make it a commercially desirable commodity and lead to the establishment of a fetal tissue industry. As in the development of reproductive technologies and the increase of surrogate motherhood, the growing demand for neural grafts might cause the fetus to be increasingly perceived only as a potential source of grafting material. It has been argued that the fetus should neither be endowed with a financial value, as it would be in a commercial exchange, nor be conceived for the sole purpose of using its tissue for transplantation (1,13,48,54). In 1988, the National Organ Transplant Act was amended to prohibit the sale of certain fetal organs and tissues, although neural tissue is not specified [Public Law 100-607].

Precautions against this consequence have been suggested. If it were likely that women could be coerced into conceiving and aborting in order to provide fetal tissue to benefit others, profit restrictions might create a disincentive. Payments to women who abort, including compensation for the cost of the abortion procedure, might be prohibited, as might payments to doctors, clinics, or any other parties involved in the abortion procedure. Tissue banks used to distribute fetal tissue maybe prohibited from profiting from their role. To prevent women from conceiving in order to provide tissue for grafts, specification of tissue recipients, including the woman herself, might also be prohibited (1,32,48,54).

Concern has been expressed that women, as the ''producers' of fetal tissue, could also be commercially exploited in order to obtain tissue in adequate quantities and of useful gestational age. There has been some suggestion that women who are ambivalent about terminating their pregnancies may be vulnerable to coercion by a physician who wants the fetal tissue for research or for another patient. This threat might be removed by requiring absolute separation of the doctors who perform abortions and those who do transplantation. One way to accomplish this might be to establish tissue banks for fetal tissue distribution, as is being done in Great Britain (44).

On the other hand, there have been strong objections to the assumption that women have limited abilities to make their own reproductive choices and that they can be easily coerced. Similar concerns have been raised about women who act as

[3]Legitimation is described by the Center for Biomedical Ethics (10) as the justification of an act or practice "in such a manner that others become more inclined to regard it as acceptable and to engage in it." Institutionalization may be seen to carry legitimation one step further, in that institutions (in this case the U.S. Government), by incorporating a practice, accept and engage in it, and in some cases profit financially from it.

surrogate mothers. The charge that the practice of surrogacy exploits women has been called paternalistic because:

> It questions women's ability to know their own interests and to enter into a contractual arrangement knowingly and competently. There may well be a coercive aspect to commercial surrogacy, since money. . . can serve as a coercive inducement to do something a person might not otherwise do voluntarily. . . . What they are really saying is that those who elect to enter surrogacy arrangements are incompetent to choose and stand in need of protection (28).

Many persons also have rejected the argument that women need to be protected from solicitation of fetal tissue.

The question of whether a woman's medical care might be altered (either with or without her consent) in order to obtain tissue of an appropriate gestational age and in the best possible condition for grafting has also been raised (33). There is general agreement that the means and timing of an abortion should be based on the pregnant woman's medical needs and not on the future use of the fetal tissue (32,48,54). On the other hand, not all variations in medical treatment will cause harm to the woman. Requiring that the woman's medical care always be placed first, that the timing and method of abortion not be altered, that separate doctors perform abortion and neural grafting procedures, and that only first-trimester abortuses be used might ensure that obstetrical care is not compromised for the sake of neural grafting.

Some fear that using electively aborted fetal tissue for grafting would gradually erode respect for human life. This argument can be seen in terms of a slippery slope, and what is perched at the top of the slope is our view of humanity. The concern is that, as society becomes accustomed to a new technology and its social consequences, social effects which now seem extreme or immoral might become acceptable. The increments by which society moves toward policies that are now appalling to some persons may pass unnoticed, and the result might be a society that by current standards is ethically unacceptable. A gradual acceptance of new developments, however, does not necessarily mean that ethical standards erode. Another interpretation of the same evidence might be that society learns from experience and that as current fears are proven unfounded or preventable, they are cast away.

When the practice of retrieving organs from accident and homicide victims first began in the 1960s, many persons held similar fears about whether transplanting those organs was morally acceptable without the prior consent of either the deceased or the deceased's next of kin (21). This concern was alleviated to a large extent as it became clear that cadaveric tissue could be transplanted without violating most ethical standards for treatment of the dead [although some religious traditions continue to oppose the practice (40)]. Each State established standards for the use of cadaveric tissue that respected not only the cadaver, but the families who were asked to make the decision to donate. Although familial consent for cadaveric organs is not a legal necessity in all cases, it is customarily obtained before organs are removed. This practice has alleviated many fears about moral violations against both the deceased and the living. Fetal tissue use might be regulated in a similar manner.

There is some concern that, since there is no distinct time when a procedure stops being research and becomes standard therapy, fetal tissue grafting might be put into widespread use despite ethical objections to it and without ethical norms to guide it (see ch. 7). If such research becomes standard therapy, there may be no way to control or restrict its use, even if ethical reasons are found for doing so. If an experimental therapy, especially one funded with tax dollars, proves successful, it might be extremely difficult to deny that treatment to a demanding public, whatever social and ethical consequences it might have and whatever alternative treatments might be forthcoming. It can also be argued that it is unfair to withhold a treatment from the taxpayers who funded the research that developed it.

It is not necessarily the case, however, that fetal tissue grafting techniques will become standard therapy (41). While it is reasonable to expect that they will, continuing research could reveal information about the etiologies of diseases and the mechanisms of neural repair that suggest better or less controversial alternatives to fetal tissue. Fetal tissue transplantation research may lay the groundwork for other therapies without ever being used widely itself. In that case, present concerns could prove unfounded.

At this stage of scientific research it is difficult to predict accurately what the consequences of widespread fetal tissue grafting are likely to be. By the

time adequate research has been done and a procedure is proven effective, there maybe a more certain factual basis for any ethical discussions. At the same time, Federal standards for the procurement of tissue and regulation of technology transfer might prevent many of the anticipated consequences.

Cell Lines

Continuous cell lines (CCLs) promise self-perpetuating cells that can be propagated indefinitely. When the small number of cells used to initiate a cell line are derived from a consenting participant, there are few ethical implications related to the tissue itself, although there may be questions of ownership of the cell lines (50). CCLs derived from fetal tissue may be one of the more scientifically promising neural grafting materials, but ethical issues arise from the fact that cadaveric fetal tissue may be used to start them, and ownership of the tissue will be difficult to determine.

The use of CCLs could either perpetuate or resolve the debate about the use of electively aborted fetal tissue for transplantation, depending on which of the arguments described in the previous section are accepted. Those who believe that elective abortion is immoral and that any subsequent use of the tissue is also immoral are likely to object to fetal tissue CCLs for the same reason they object to fetal tissue transplantation (8).

Objections may be weaker, however, on the part of persons who object to fetal tissue transplantation on the grounds that it might promote abortion (11,34), decrease the value of human life, or use the fetus as the means to another's end. Theoretically, only a few cells from a fetus would be needed for all future fetal tissue grafting. Thus, far less tissue would be needed to start a CCL than would be needed to provide a neural graft. If fetal tissue from spontaneous or therapeutic abortions is thoroughly tested for any genetic anomalies or disease, such tissue might be used for cell lines, ensuring that fetal tissue grafts will not increase the number of elective abortions that take place. Using CCLs might also make it improbable that a woman would conceive in order to provide aid to a specific recipient. Continuous fetal cell lines may make it possible to use fetal tissue for transplantation without leading to anticipated undesirable consequences.

Ownership of Tissue Used in Cell Lines

The question of whether the person whose cells are used to start a cell line has proprietary claim over the line is another new and as yet unresolved issue. A California appellate court ruled in 1988 in *Moore v. Regents of the University of California (37)* that a plaintiff whose tumorous spleen was used to start a commercially profitable CCL without his permission has property claims over his body tissues and any commercial products derived from them. The California Supreme Court reversed this decision in July 1990-the majority, consenting, and dissenting opinions were all based on ethical concerns, although they reached different conclusions (see box 8-B). Until this issue is decided by legislative action or the U.S. Supreme Court, however, there are no clear legal rules for identifying property rights over body parts.

The question of ownership of fetal CCLs adds to the confusion. Claims that women have property rights over fetal tissue have been challenged in debates about abortion and consent for tissue donation, and these claims may be more contentious if bodily property becomes marketable.[4] Because the development of CCLs can be very profitable, questions of ownership of body tissues and cell lines derived from them have become increasingly important.

As previously discussed, it has not been established whether the basis for requiring consent for the use of aborted fetal tissue from the woman who elects the abortion is an acknowledgement of her ownership or her guardianship of fetal tissue, or even whether her consent is seen as appropriate at all. If fetal tissue donation is an act of altruism, the same justification used for other types of fetal tissue research may hold. It is arguable, however, that altruism is not the motivation for a gesture that could be extremely profitable to the person who gives consent. If the consent requirement is based on an assumption of ownership, consent provides a means for the donation of personal property. But should a pregnant woman be considered a partial owner of the cell line, based on proprietary rights? Is it ethical to regard the woman as the owner of fetal tissue that can be used in a commercial undertaking? Is she

4"In the ..... case, the appellate court held that "... even though full property rights are not recognized in a dead body, a limited property interest has been found. . . .[However, w]e are not calledupon, nor are we attempting, to resolve the complex issues relating to the human fetus".

Box 8-B—Moore *v.* Regents of the University of California

The case John Moore brought against the investigators who used his body tissues to start a commercial continuous cell line raises fundamental questions concerning a patient's right to the control of his or her own body and whether the commercial exploitation of a patient's cells by medical care providers, without the patient consent, gives rise to an action for damages.

In 1976, Moore sought medical treatment at the Medical Center of the University of California, Los Angeles, for a condition known as hairy-cell leukemia As a necessary part of the treatment for this disease, Moore's spleen was removed.

Without the patient's knowledge or consent to donate his cells for research, the medical staff examined the excised tissue and determined that Moore's spleen cells had unique qualities. Through genetic engineering, they developed from the spleen cells a cell line that is capable of producing pharmaceutical products of enormous therapeutic and commercial value. The university patented the cell line, along with methods of producing many products from it, The university also entered into a series of commercial agreements for rights to the cell line and its products with two corporations. The commercial value of the products was predicted to be approximately $3 billion by 1990.

Moore sued the university and the corporations on several grounds, one of which was that "had he known what was taking place, he would not have consented to the splenectomy for these research and commercial activities; would have insisted on participating in control of the use of his blood and bodily substances; would not have permitted these materials to be used by defendants solely for their independent research, commercial activity, and economic benefit; would have considered treatment at another medical facility where his wishes would have been carried out; and would have sought participation in the economic benefit.

The first court dismissed the case. The appellate court found that:

> The Protection of Human Subjects in Medical Experimentation Act, adopted m 1978, expresses a strong public policy that medical experimentation on human subjects "shall be undertaken with due respect **to the preciousness** of human life and the ***right of individuals to determine what is done to their own bodies" [Cal.*** Health & Safety Code 24171] [emphasis added]. . . . The essence of a property interest-the ultimate right of control--therefore exists with regard to one's own human body.

The **California** Supreme Court found in July 1990 that:

> Neither the Court of Appeals' opinion, the parties' briefs, nor our research ***discloses*** a case holding that a **person retains** a sufficient interest in excised cells to support a cause of action for conversion. . . . There are three reasons why it is inappropriate to impose liability for conversion based upon the allegations of Moore's complaint. First, a fair balancing of the relevant policy considerations counsels against extending the tort. Second, problems in this area are better suited to legislative resolution. Third, the tort of conversion is not necessary to protect patients' rights.

Rather than deciding on property rights over body tissues, the Supreme Court held:

> . . . that a physician who is seeking a patient's consent for a medical procedure must, in order to satisfy his fiduciary duty and to obtain the patient's informed consent, disclose personal interests unrelated to the patient's health, whether research or economic, that may affect his medical judgment.

This decision applies only to California Without congressional action or a ruling by the U.S. Supreme Court, State courts and legislatures are free to decide for themselves whether an individual who donates body tissue should be thought to own it or be able to profit from its use in the development of cell lines and other biologics.

SOURCES: Moore v. *Regents of tbe University of California,* 202 Cal. App.3d 1230,249 Cal. Rptr. 494 (1988), reh. granted, 252 Cal. Rptr. 816, 763 P.2d 479 (1988); Moore v. *Regents of the University of California, Supreme Court* of the State of California, case No. ***S006987, July 9,*** 1990.

entitled to profit from the fetal cell line, or would that constitute exploitation of the fetus?

It might be possible to prevent women who donate fetal tissue from profiting from cell line development, but what about allowing investigators to profit from the cell line? This, too, could be perceived as exploitation of the fetus. Also, denying the woman any profit from products of her own body but allowing others to-profit may be exploitative of and discriminatory against those women.

Waiving the consent requirement might be one way of avoiding these pitfalls. This would indicate that a woman does not have proprietary rights to the fetus and that a proxy donation is inappropriate in

this case. It might ensure that fetal tissue is not donated purely for personal profit and eliminate competition for women to donate their fetuses in order to profit. On the other hand, if consent is not obtained from women, this omission could be seen as denial of autonomy or exploitation. The recent *Moore* decision could make patients more reluctant to donate tissues and organs for research.

The question of ownership of fetal tissue used for CCLs will have to be addressed by State or Federal legislatures at some point. The fact that cell line development may be financially profitable complicates fetal tissue donation for scientific purposes. If a woman who undergoes an abortion donates fetal tissue for cell line development and profits from the cell line, it could be perceived as exploitation of the fetus. If she does not receive any payment from a commercially profitable cell line, but other persons do profit from it, it could be perceived as exploitation of both her and the fetus. If consent is not obtained from the woman, it may constitute a denial of her autonomy. Finally, if one believes that the individual from whom cells are obtained to start a CCL is the only one who should consent to this use, then consent should only be obtained from the fetus. Should fetal tissue cell lines be prohibited? Should the scientists who develop cell lines be denied the opportunity to profit financially from them? Are there justifications for using fetal tissue to start CCLs that make it unnecessary to decide whether fetal tissue ought to be considered property? These questions are only beginning to be addressed.

Genetic Manipulation of Cells Used for Grafting

Genetically modified cells have been used for neural grafting in animal experiments. The possibility of using them in humans raises the question of whether it is ethical to manipulate genes that would be passed on to future generations. As this debate has developed, it has become clear that somatic cell gene therapy (which modifies the DNA of certain differentiated cells in the body that cannot be passed to offspring) is relatively uncontroversial; it is germ cell gene therapy (which modifies undifferentiated cells that may later become gametes and thus may be passed to offspring) that creates concern (49). Genetic manipulation of CCLs for neural grafting would constitute somatic cell gene therapy and thus remove any possibility of inheritance.

Many of the fears expressed about genetic manipulation have to do with possible eugenic misuses—namely, the use of gene therapy to promote or exaggerate desired qualities in individuals rather than to correct anomalies that lead to illness. At this time it is difficult to see how gene therapy could be performed on cells for enhancement purposes: Not enough is known about the brain to design grafts that would improve particular physical or intellectual abilities. Instead, gene therapy might be used to design grafts that could alleviate specific neurological disorders in a host—by producing neurotrophic factors or neurotransmitters, for example. Grafts could be engineered to compensate for specific deficiencies in the recipient.

ISSUES RELATED TO GRAFT RECIPIENTS

Neural grafting also presents ethical issues related to the graft recipients. These ethical questions exist for any new procedure, but they may be especially pertinent to clinical (human) trials of neural grafting.

Federal law dictates that federally funded protocols must be sent to an Institutional Review Board (IRB) for approval of the legal and ethical features of protocol design [45 CFR 46], particularly features relating to treatment of research subjects. Of the seven criteria for IRB approval of research, two may pose problems for neural grafting research. These are the requirements that risks to subjects be reasonably comparable to the expected benefits and that the investigator obtain the subject's informed consent to participate in research.

Risks to Research Subjects

Risks **to** subjects are always difficult to determine at the beginning of clinical trials; it has been suggested that the lack of knowledge about how grafts work may make the risks associated with neural grafting particularly difficult to determine (27). The question that arises when anew therapy is presented for experimentation on human subjects is whether there is evidence that it promises significant benefit to the patient and does not present undue risk. This risk-benefit analysis is performed by several parties involved with the research protocol: the investigator, the IRB, and the prospective research subjects and their families.

Considerable debate surrounds the experimental use of fetal and adrenal tissue grafts to treat persons with Parkinson's disease (see ch. 5). In fact, some persons believe investigators had not gathered

enough data from animal studies to warrant progressing to clinical trials (22,36) and, therefore, may have been unable to meet their responsibilities to vulnerable human research subjects. Some persons claim that it is impossible for investigators or subjects involved in neural grafting research to balance risks and benefits unless they can estimate realistically what those benefits and risks will be. That claim, however, may be made of all clinical research (25). Some persons have argued that the patient undergoing neural grafting for the treatment of Parkinson's disease may be risking more than is justified if the graft is unsuccessful, if it is affected by the same neurodegenerative processes that made the graft necessary in the first place (19,27) [although it has been pointed out that the original degeneration in Parkinson's disease takes place over the course of several decades (5)], or if there is a delayed immunological response to the graft that proves more harmful than the disease.

Information should be obtained from the least possible amount of research conducted during the shortest possible period of time (9). The number of trials performed is another important consideration in protecting research subjects from unnecessary risks. Some observers suggest that controlled studies and pooled results from different locations may be the most efficient means of deriving data. This suggests single-protocol research pursued at multiple centers, formation of a comprehensive database, constant monitoring and interpreting of data, as well as constant updating of information given to subjects for informed consent (18). On the other hand, if neural grafting research on a particular disease is deemed an important public health priority, it might proceed more quickly and in accordance with diverse research protocols. In order for the transition to be made from clinical trials to therapeutic use in this case, many more patients will have to be enlisted as subjects; the human costs, as well as the medical and research costs, may be very high (18).

Informed Consent

One important ethical question is whether neural grafting protocols conform to standards of protection for research subjects. Since informed consent requires "[a] description of any reasonably foreseeable risks or discomforts to the subject [and] a description of any benefits to the subject or to others which may reasonably be expected from the research' [45 CFR 46.116], each patient must conduct a risk-benefit analysis of his or her own. This entails two kinds of information, the scientific and the personal (15). The first is made up of the objective data about the disease, alternative treatments, and social support systems and agencies; the second encompasses the subjective data related to the patient's experience.

The objective data for this analysis must be provided by the researcher. It should include the prognosis if the disease runs its course, the availability of alternative treatments, the fact that the procedure is experimental, the extent of uncertainty involved in the surgery, the intended and possible long-term outcomes of surgery, the availability of social support systems and agencies to aid recovery, and a thorough description of what the surgery will involve, including the pain and suffering likely to accompany the procedure and the immediate recovery from it, as well as risks of complications. The hard data will vary depending on the disease, the age of the patient, and the type of graft used.

The subjective data needed for a risk-benefit analysis can only come from the patient, for they involve the patient's perception of his or her quality of life. Quality of life is a concept that describes the experience of the individual, what kind of life is possible given the person's condition, and whether that condition will allow the individual to have a life that he or she views as worth living (23). There may be differences, however, between how a person perceives the quality of his or her own life, how an observer *assumes* he or she perceives the quality of his or her life, and how an observer *evaluates the* quality of that person's life (51). The severe physical and emotional suffering associated with neurological disease and injury are frequently thought to create poor quality of life, but it is important that patients have the freedom and medical information necessary to make their own quality of life evaluations.

The same conditions that depreciate the quality of life of individuals with neurological diseases and spinal cord injuries may make these persons especially susceptible to coercion. While the possibility of undue influence exists in any research situation, patients with neurological disorders may be especially vulnerable to judgments about their quality of life made by researchers or family members. One reason is that patients who have an apparently permanent injury or an incurable disease may be

tempted to try anything that might be of help. In many cases, there are few or no alternative treatments or support services for neurological disorders, and what treatments there are may have limited efficacy. For some patients, this lack of alternatives constitutes sufficient reason to participate in neural grafting research. A necessary condition for all research subjects, however, is that they be free to make uncoerced, informed choices.

Some patients with neurological injuries or disease may be incapable of performing the ethical cost-benefit analyses necessary for truly informed consent (6). In these cases, a patient may have to rely instead on the judgment of a family member or legal guardian. The proxy decisionmaker should attempt to evaluate the quality of the patient's life on the same basis the patient would have used. Open communication about what investigators and patients (or their proxies) perceive as the relevant factors in the decision to participate in research is necessary if a patient is to do a risk-benefit analysis without coercion. Given adequate scientific data by the researcher, the patient or proxy can predict more realistically what benefits the patient is likely to gain by undergoing neural grafting surgery.

Three factors make it difficult for investigators to give accurate information about the probable risks and benefits of neural grafting procedures. First, it is uncertain at this early stage of research what the risks and benefits of neural grafting are likely to be. Second, it maybe tempting for investigators to paint a more positive picture than is warranted because of their own high expectations. Finally, researchers may filter empirical evidence through their interpretations of the patient's current or future quality of life, rather than allowing patients to draw their own conclusions (18). These factors apply to all clinical research, but sensitivity to limitations may be especially important for neural grafting research. The solicitation of informed consent from neurological patients or their families must be done with their vulnerability in mind, making clear to the patient or family the degree of uncertainty for the experimental procedure. Although it is impossible in any research setting for a patient to be totally informed of risks and benefits, in the case of neural grafting it may be extremely important for patients to be aware of the scientific limitations at this time.

There may be reasons besides possible changes in quality of life for an individual to turn down the opportunity to receive a neural graft. For some subjects, neural grafting presents a chance for medical science to overcome disease; but for others, neural grafting may present a threat to personal identity and sense of self, aspects of the human mind that are, to some persons, the very essence of humanity (18). The ability to do neural grafting raises questions about whether the mind can be explained in terms of the brain. It is difficult to know what physical functions of the brain define a person's existence as a unique individual or are essential to the retention of his or her personal identity across time. Consequently, some would argue, there is no way to predict the extent to which neural grafting in the brain will or will not interfere with the functions of the mind that determine individuality, personhood, or a sense of self. These are metaphysical questions rather than ethical ones, but they are important considerations for persons in a position to receive neural grafts.

SUMMARY AND CONCLUSIONS

Neural grafting includes a variety of materials and surgical procedures used to investigate and treat a number of neurological disorders. As the grafting materials and techniques viny, so do the ethical issues surrounding them. Whether the Federal Government becomes involved in funding or regulating fetal tissue grafting or not, research in fetal tissue transplantation continues.

Some of the ethical issues surrounding neural grafting are common to any new area of biomedical research or treatment. They include whether to use public funds to support neural grafting research or neural grafting as a standard medical treatment. They also include economic questions about how to establish health-care priorities and how to allocate resources for research.

There are currently few alternative treatments for neurological disorders. Some persons feel that, because neural grafting is an exciting and possibly profitable area of research, it may get more support than alternatives and reduce the impetus to find less expensive, less risky, and less controversial treatments for neurological disorders (38). Decreased support for neural grafting research, however, does not necessarily make funds available for research into other treatments for neurological disease and injury (12). In order to resolve some of the questions about fair distribution of resources, it might be

helpful to evaluate neural grafting in relation to treatments for other diseases and other treatments for neurological disorders, 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 neurological disorders, and the number of people likely to be affected in the future.

Ethical issues arising from the surgical procedures and the materials used in the neural grafting process also demand attention. Some of these issues are analogous to issues that have been dealt with already and are reflected in Federal regulations; e.g., informed consent and the protection of research subjects were addressed in the 1970s. Existing regulations, however, may not adequately protect neural graft recipients from the risks unique to brain implantation surgery. The possibility of doing a sufficient risk-benefit analysis has been challenged on the grounds that not enough animal research has been done to know what the benefits of neural grafting are likely to be. Obtaining informed consent from persons with neurological disease may be difficult, both because the risks and benefits cannot be realistically estimated at this time and because of the possible cognitive limitations of persons with some neurological disorders.

On the other hand, there are several reasons why the Federal Government should not involve itself in surgical development. Research risks to the subject are almost always unknown in early clinical trials (24). Furthermore, much surgical innovation, including neural grafting, is therapeutic as well as experimental (25) and, therefore, may be more likely to hold the promise of benefit for the subject [although some commentators have called "therapeutic research" an oxymoron (46)]. Neural grafting investigators should conduct research in a noncoercive manner consistent with the treatment of other research subjects. While it is important for persons developing new surgical techniques to be aware of moral considerations, ethical and practical arguments may be made for allowing, even encouraging, such innovation.

Thus far, the greatest ethical controversy surrounds the use of fetal tissue from elective abortions for neural grafting. Positions taken on the morality of fetal tissue grafting, however, do not depend strictly on a person's beliefs about the morality of elective abortion. Both supporters and opponents of abortion have articulated reasons for denying funding for fetal tissue grafting research, and both have identified reasons for providing it. Tissue from spontaneous abortions, ectopic pregnancies (42), and fetal tissue cell lines have been suggested as ethically acceptable alternatives.

Many different positions are taken regarding the ethics of using fetal tissue obtained from elective abortions for neural grafting. Some of these considerations include the implications of a public policy that either supports or restricts the use of aborted fetal tissue for grafting and the possible consequences of such a policy. It has been suggested that using electively aborted fetal tissue for neural grafting will both harm individual fetuses and deny fetuses respect. It has also been suggested that groups besides fetuses-e. g., women and society at large-may be adversely affected by a policy that endorses fetal tissue transplantation. A number of the arguments against fetal tissue transplantation are based on predictions about its future social effects. While it is important to anticipate potential problems, it is impossible to know at this time whether the consequences predicted will come to pass.

Some persons believe that once a fetus is dead, it no longer has interests to protect and that it is inappropriate for the Federal Government to withhold funding for research that may benefit many sufferers of neurological disorders. A number of groups in the United States and abroad have proposed safeguards for protecting social values and vulnerable groups, while allowing biomedical science to move forward (32,48,54,55) (see app. A, box A-2). It has been suggested that these protections would be most effective with Federal involvement in the research process (4,47). Despite the similarities of the safeguards recognized by the various study groups and the fact that both existing DHHS regulations and Federal laws already implement many of the suggested guidelines (58), some persons remain skeptical about the feasibility of implementing these measures.

The solicitation of consent for the use of tissue from cadaveric fetuses presents another ethical question. Controversy exists about whether the woman who elects the abortion is the appropriate person to give consent and when consent should be solicited. Both the regulations for the protection of research subjects and those for the donation of

cadaveric body parts can help in determiningg the appropriate donor of electively aborted fetal tissue, but these regulations do not explicitly cover the donation of fetal tissue for transplantation research.

The use of fetal tissue to start continuous cell lines further complicates the issue of consent, because questions are raised about whether the donor of tissue used to start a CCL may profit financially from it. Although it maybe deemed appropriate for a woman who aborts to give her consent to use of fetal tissue, it may not be considered appropriate for her to profit financially. 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 the proper treatment of fetal tissue remain unanswered.

CHAPTER 8 REFERENCES

1. American Medical Association, Council on Scientific Affairs and Council on Ethical and Judicial Affairs, "Medical Applications of Fetal Tissue Transplantation," ***Journal of the American Medical Association*** 263:565-570, 1990.
2. American Paralysis Association, testimony before the U.S. House of Representatives Committee on Energy and Commerce, Subcommittee on Health and the Environment, hearings on Human Fetal Tissue Transplantation, Apr. 2, 1990.
3. Annas, G.J., and Elias, S., "The Politics of Transplantation of Human Fetal Tissue," New ***England Journal of Medicine*** 320:1079-1082, ***1989.***
4. Annas, G.J., and Elias, S., letter, New ***England Journal of Medicine*** 321:1609, 1989.
5. Bakay, R.A.E., associate professor of surgery, section of neurosurgery, Emory University School of Medicine, Atlanta, GA, personal communication, December 1989.
6. Blank, R., professor of sociology and associate director, program for Biosocial Research, Northern Illinois University, DeKalb, IL, personal communication, December 1989.
7. Buckley, R.H., "Fetal Thymus Transplantation for the Correction of Congenital Absence of the Thymus (DiGeorge's Syndrome)," testimony before the HumanFetal Tissue Transplantation Research Panel, National Institutes of Health, Bethesda, MD, Sept. 14, 1988.
8. Burtchaell, J.T., "University Policy on Experimental Use of Aborted Fetal Tissue," ***IRB: A Review of Human Subjects Research*** 10:7-11, ***1988.***
9. Caplan, A.L., testimony before the Human Fetal Tissue Transplantation Research Panel, National Institutes of Health, Bethesda, MD, Sept. 15, 1988.
10. Center for Biomedical Ethics, ***The Use of Human Fetal Tissue: Scientific, Ethical, and Policy Concerns (Minneapolis, MN:*** University of Minnesota, 1990).
11. Crutchner, K.A., testimony before the House of Representatives Committee on Energy and Commerce, Subcommittee on Health and the Environment, hearings on Human Fetal Tissue Transplantation Research, Apr. 2, 1990.
12. Davis, M., senior policy analyst, Office of Health Planning and Evaluation, Division of Policy Analysis, U.S. Department of Health and Human Services, personal communication, April 1990.
13. Fine, A., "The Ethics of Fetal Tissue Transplants," ***Hastings Center Report*** 18:5-8, 1988.
14. Fine, A., associate professor, Department of Physiology and Biophysics, Dalhousie University School of Medicine, Halifax, Nova Scotia, Canada, personal communication, April 1990.
15. Forrow, L., Wartman, S.A., and Brock, D.W., "Science, Ethics, and the Making of Clinical Decisions: Implications for Risk Factor Intervention," ***Journal of the American Medical Association 259:3161-3167, 1988.***
16. Freed, C., professor of medicine and pharmacology, University of Colorado, Denver, CO, personal communication, December 1989.
17. Fung, C.H.K., and Lo, J.W., "Alternatives To Using Fetal Tissue From Induced Abortions" [letter], ***Journal of the American Medical Association*** 264: ***34, 1990.***
18. ***Gervais,*** K.G., "Neural Transplants and Nerve Regeneration Technologies: Ethical Issues," prepared for the Office of Technology Assessment, U.S. Congress, Washington, DC, 1989.
19. Gill, T.J., and Lund, R.D., "Grafting Into the Brain," testimony before the Human Fetal Tissue Transplantation Research Panel, National Institutes of Health, Bethesda, MD, Sept. 14, 1988.
20. Hansen, J.T., and Sladek, J.R., Jr., "Fetal Research," ***Science*** 246:775-779, ***1989.***
21. Hastings Center Project on Organ Transplantation, ***Ethical, Legal and Policy Issues Pertaining to Solid Organ Procurement*** (Hastings-on Hudson, NY: The Hastings Center, 1985).
22. Landau, W.M., "Artificial Intelligence: The Brain Transplant Cure for Parkinsonism," ***Neurology 40:*** 733-740, 1990.
23. Lappe, M., "Ethics at the Center of Life: Protecting Vulnerable Subjects," ***Hastings Center Report*** 8:1 ***1-13, 1978.***
24. Lebacqz, K., and Jensen, A.R., statement, U.S. Department of Health, Education, and Welfare, National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, ***Research on the Fetus: Report and Recommenda-***

tions, DHEW Pub. No. (0S)76-127 (Washington, DC: U.S. Government Printing Office, 1975).

25. McCarthy, C.R., "RegulatoryAspects of the Distinction Between Research and Medical Practice," *IRB: A Review of Human Subjects Research* 6:7-8, 1984.
26. McCarthy, D., Roman Catholic priest, Church of Saint Antoninus, Cincinnati, OH, personal communication, April 1990.
27. McCullagh, P., *The Foetus as Transplant Donor: Scientific, Social and Ethical Perspectives* (Chichester, Australia: John Wiley & Sons, 1987).
28. Macklin, R., "Is There Anything Wrong With Surrogate Motherhood? An Ethical Analysis," Law, *Medicine, and Health Care* 16(Spring/Summer):57-64, 1988.
29. Madrazo, I., Leon, V., Torres, C., et al., "Transplantation of Fetal Substantial Nigra and Adrenal Medulla to the Caudate Nucleus in Two Patients With Parkinson's Disease" [letter], New *EnglandJournal of Medicine* 318:51, *1988.*
30. Mahoney, M.J., "The Nature and Extent of Research Involving Living Human Fetuses,' U.S. Department of Health, Education, and Welfare, National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, *Research on the Fetus: Appendix,* DHEW Pub. No. (OS) 76-128 (Washington, DC: U.S. Government Printing Office, 1975).
31. Mahowald, M.B., professor, Center for Clinical Medical Ethics, University of Chicago, Chicago, IL, personal communication, May 1990.
32. Mahowald, M.B., Areen, J., Hoffer, B.J., et al., "Transplantation of Neural Tissue From Fetuses" [letter], *Science* 235:1307-1308, *1987.*
33. Mahowald, M.B., Silver, J., and Ratcheson, R.A., "The Ethical Options in Transplanting Fetal Tissue," *Hastings Center Report* 17:9-15, *1987.*
34. Mason, J.O., "Should the Fetal Tissue Transplantation Research Ban Be Lifted?" *Journal of NIH Research* 2:17-18, *1990.*
35. Mason, J. O., testimony before the U.S. House of Respresentatives Committee on Energy and Commerce, Subcommittee on Health and the Environment, hearings on Human Fetal Tissue Transplantation Research, Apr. 2, 1990.
36. Merz, B., "Neurologists Join Neurosurgeons in Urging Restraint in Parkinson's Surgery,' *Journal of the American Medical Association* 261:2929, *1989.*
37. *Moore v. Regents of the University of California, 202 Cal.* App.3d 1230, 249 Cal. Rptr. 494 (1988), reh. granted, 252 Cal. Rptr. 816,763 P.2d 479 (1988).
38. Moraczewski, A. S., regional director, Pope John XXIII Medical, Moral, Research, and Education Center, Houston, TX, personal communication, April 1990.
39. Murphy, J.B., "TheEthics of Research Using Human Fetal Tissue" [letter], New *England Journal of Medicine* 321:1608, *1989.*
40. Murray, T.H., "Who Owns the Body? On the Ethics of Using Human Tissue for Commerical Purposes," *IRB: A Review of Human Subjects Research* 8: *1-5, 1986.*
41. Murray, T.H., "Ethical Issues in Research on Human Fetal Tissue Transplantation," testimony before the Human Fetal Tissue Transplantation Research Panel, National Institutes of Health, Bethesda, MD, Sept. 15, 1988.
42. Nolan, K., *''Genug ist Genug:* A Fetus Is Not a Kidney," *Hastings Center Report* 18:13-19, *1988.*
43. Nolan, K., "Public Policy Considerations in the Use of Human Fetal Tissue,' testimony before the Human Fetal Tissue Transplantation Research Panel, National Institutes of Health, Bethesda, MD, Sept. 14, 1988.
44. Polkinghorne, J., Hoffenberg, R., Kennedy, I., et al., *Review of the Guidance on the Research Use of Fetuses and Fetal Material* (London: Her Majesty's Stationery Office, July 1989).
45. Redmond, D. E., neurosurgeon, Neurobehavioral Laboratory, Yale University School of Medicine, New Haven, CT, personal communication, April 1990.
46. Rolleston, F., and Miller, J,R., "Therapy or Research: A Need for Precision," *IRB: A Review of Human Subjects Research* 3:1-3, 1981.
47. Ryan, K., testimony before the U.S. House of Representatives Committee on Energy and Commerce, Subcommittee on Health and the Environment, hearings on Human Fetal Tissue Transplantation Research, Apr. 2, 1990.
48. Stanford University Medical Center Committee on Ethics, "Special Report: The Ethical Use of Human Fetal Tissue in Medicine," New *England Journal of Medicine* 320:1093-1096, *1989.*
49. U.S. Congress, Office of Technology Assessment, *Human Gene Therapy—A Background Paper,* OTA-BP-BA-32 (Washington, DC: U.S. Government Printing Office, December 1984).
50. U.S. Congress, Office of Technology Assessment, New *Developments in Biotechnology: Ownership of Tissues and Cells—Special Report, OTA-BA-337* (Washington, DC: U.S. Government Printing Office, March 1987).
51. U.S. Congress Office of Technology Assessment, *Life-Sustaining Technologies and the Elderly,* OTA-BA-306 (Washington, DC: U.S. Government Printing Office, July 1987).
52. U.S. Department of Health, Education, and Welfare, National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, *Research on the Fetus: Report and Recommenda-*

tions DHEW Pub. No. (0S)76-127 (Washington, DC: U.S. Government Printing Office, 1975).

53. U.S. Department of Health and Human Services, statement by **Louis** W. Sullivan, Secretary, Nov. 2, 1989.
54. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, ***Report of the Human Fetal Tissue Transplantation Research Panel (Bethesda, MD: 1988).***
55. Walters, L., testimony before the U.S. House of Representatives Committee on Energy and Commerce, Subcommittee on Health and the Environment, hearings on Human Fetal Tissue **Transplantation** Research, Apr. 2, 1990.
56. **Wikler,** D., professor of philosophy, University of Wisconsin, Madison, WI, personal communication, April 1990.
57. **Windom,** R.E., Assistant Secretary for Health, U.S. Department of Health and Human Services, memorandum to **J.B. Wyngaarden,** Director, National Institutes of Health, Mar. 22, 1988.
58, **Wyngaarden, J.B.,** Director, National Institutes of Health, memorandum to Robert E. **Windom,** Assistant Secretary for Health, U.S. Department of Health and Human Services, Jan. 19, 1989.

Appendixes

Appendix A

DHHS Moratorium on Human Fetal Tissue Transplantation Research

While human fetal tissue transplantation research is a promising and exciting area of scientific study at this time, it has also created considerable controversy. The public debate is in one sense a straightforward, although complicated, discussion about the ethics of public funding of research that uses electively aborted human fetal tissue. for transplantation; however, the Federal Government's response to the controversy has itself raised questions.

In March 1988, a moratorium was imposed on the use of human fetal tissue from induced abortions for transplantation until the ethical issues surrounding this use could be adequately studied. Nineteen months after it was initiated, the moratorium was extended indefinitely by the new Secretary of Health and Human Services. Added to the ethical issues initially presented for discussion, the Federal Government's actions in this matter have been questioned on legal and ethical bases (3). It may be instructive to trace the events leading up to the moratorium, the activities of the National Institutes of Health (NIH) Human Fetal Tissue Transplantation Research Panel, and the events following the panel's report(l 1) and its acceptance by the NIH Director's Advisory Committee.

Events Preceding the Moratorium

Fetal tissue has long been used in research (2,4)-including research involving the transplantation of fetal thymus tissue into humans—and the ethical questions it raises have been addressed by an executive branch commission and in Federal regulations [45 CFR 46]. When fetal tissue began to be used for neural grafting in the mid-1980s, however, some questioned whether these regulations adequately address all the issues raised by this research. In fiscal year 1987, NIH funded about $11.2 million of nontherapeutic human fetal-tissue research (10). In 1987, a research protocol for implantation of fetal neural tissue from induced abortions into persons suffering from Parkinson's disease was proposed by a researcher at the National Institute of Neurological Disorders and Stroke (NINDS). The Institutional Review Board at the NIH clinical center reviewed the scientific, legal, and ethical issues raised by the protocol and accepted it for funding, yet the nature of the research was considered sufficiently controversial by the director of NINDS to be submitted for the approval of the Director of NIH. The Director voluntarily sought approval from the Department of Health and Human Services (DHHS) to review and approve the protocol. In response, the Assistant Secretary for Health issued a temporary moratorium on all fetal tissue transplantation research using tissue from induced abortions until NIH could convene an advisory committee to examine the use of human fetal tissue from induced abortions for transplantation and make recommendations for its use. The advisory committee was asked to address 10 questions (see box A-l).

Although the intramural NIH proposal stimulated significant ethical debate, NIH funds had already been granted that year for an extramural protocol to study the effects of fetal pancreatic islet cells on juvenile diabetes. It is unclear why the intramural proposal received closer scrutiny than the extramural protocol.

One factor that may have impeded the decisionmaking processes within NIH is the lack of an authoritative body within the Federal Government to address ethical issues raised by biomedical research and treatment and to make policy decisions regarding them. The Ethics Advisory Board (EAB) that had existed within DHHS to address questions of this sort was disbanded in 1980. While the scientific, ethical, and legal features of the Parkinson's disease protocol were approved by the NIH Institutional Review Board, the protocol was regarded as problematic first by the director of the Institute performing the research and then by the Director of NIH. The Director of NIH was forced to turn to the Assistant Secretary for Health for advice on appropriate action.

Although the conditions of the moratorium were not retroactive, the investigators who had received NIH funds for fetal pancreatic islet cell transplantation voluntarily suspended their research because of the controversy. Since that time, only research funded by private institutions has continued. Although most privately funded fetal tissue transplantation has been stopped voluntarily, some initiatives in this area have continued. In late 1988, at the University of Colorado Health Sciences Center, physicians implanted fetal cells obtained from an induced abortion into the brain of a 52-year-old Denver man who had been suffering from Parkinson's disease for 20 years (l). Also in late 1988, physicians at Yale Medical School implanted human fetal cells into the brain of a woman suffering from Parkinson's disease, after first freezing the cells and testing their viability (6). The fetal cells used in this surgery were donated by a woman who had had an induced abortion in her first trimester (6).

The Report of the NIH Human Fetal Tissue Transplantation Research Panel

In **response to the questions presented by the Assistant Secretary for Health, the Human Fetal Tissue Transplan-**

Box A-l--Questions Addressed to the NIH Human Fetal Tissue Transplantation Research Panel

- Is an induced abortion of moral relevance to the decision to use human fetal tissue for research? Would the answer to this question provide any insight on whether and how this research should proceed?
- Does the use of the fetal tissue in research encourage women to have an abortion that they might otherwise not undertake? If so, are there ways to minimize such encouragement?
- As a legal matter, does the very process of obtaining informed consent from the pregnant woman constitute a prohibited ''inducement' to terminate the pregnancy for the purposes of the research-thus precluding research of this sort under HHS regulations?
- Is maternal consent a sufficient condition for the use of the tissue, or should additional consent be obtained? If so, what should be the substance and who should be the source(s) of the consent, and what procedures should be implemented to obtain it?
- Should there be and could there be a prohibition on the donation of fetal tissue between family members, or friends and acquaintances? Would a prohibition on donation between family members jeopardize the likelihood of clinical success?
- If transplantation using fetal tissue ❄□❑○ induced abortions becomes more common, what impact is likely to occur on activities and procedures employed by abortion clinics? In particular, is the optimal or safest way to perform an abortion likely to be in conflict with preservation of the fetal tissue? Is there any way to ensure that induced abortions are not intentionally delayed in order to have a second trimester fetus for research and transplantation?
- What actual steps are involved in procuring the tissue from the source to the researcher? Are there any payments involved? What types of payments in this situation, if any, would fall inside or outside the scope of the Hyde Amendment?
- According to HHS regulations, research on dead fetuses must be conducted in compliance with State and local laws. A few States' enacted version [sic] of the Uniform Anatomical Gift Act contains restrictions on the research application of dead fetal tissue after an induced abortion. In those States, do these restrictions apply to therapeutic transplantation of dead fetal tissue after an induced abortion? If so, what are the consequences for NIH-funded researchers in those States?
- For those diseases for which transplantation using fetal tissue has been proposed, have enough animal studies been performed to justify proceeding to human transplants? Because induced abortions during the first trimester are less risky to the woman, have there been enough animal studies for each of those diseases to justify the reliance on the equivalent of the second trimester human fetus?
- What is the likelihood that transplantation using fetal cell cultures will be successful? Will this obviate the need for fresh fetal tissue? In what time frame might this occur?

SOURCE: U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, *Report of the Human Fetal Tissue Transplantation Research Panel (Bethesda, MD: 1988).*

tation Research Panel convened, heard testimony from a variety of experts and interest groups, and submitted a report to the NIH Director late in 1988. A unanimous agreement was not reached among the 21 panel members, but the panel's report concluded (17 to 4) that the funding of research involving the transplantation of human fetal tissue obtained from induced abortions is acceptable public policy as long as carefully crafted safeguards are in place (see box A-2).

Although adamant dissent was voiced by four panel members, the report and its recommendations were accepted unanimously by the NIH Director's Advisory Committee. The advisory committee recommended that the moratorium on fetal tissue transplantation research be lifted. The Director of NIH concurred with this position in a memorandum to the Assistant Secretary for Health in January 1989 (12).

Events Following Acceptance of the Panel Report

The Assistant Secretary, upon the instruction of the DHHS Secretary, deferred action on the panel's recommendation that the Federal Government lift the moratorium (5). The new administration took no action until the new Assistant Secretary for Health recommended to the new DHHS Secretary in October 1989 that the ban be continued. The Secretary continued the moratorium indefinitely in November 1989 (9). No action was taken to implement any of the recommendations of the advisory panel's report.

The legal and ethical bases of the continuation of the moratorium have since been challenged. The moratorium was originally declared as a temporary measure until the ethical issues raised by fetal tissue transplantation could be addressed and recommendations could be made. The fact that it has been continued indefinitely without any

Box A-2—Recommendations of the NIH Human Fetal Tissue Transplantation Research Panel

- The decision to terminate a pregnancy and the procedures of abortion should be kept independent from the retrieval and use of fetal tissue.
- The timing and method of abortion should not be influenced by the potential uses of fetal tissue for transplantation ***or*** medical research.
- Fetal tissue from induced abortions should not be used in medical research without the prior consent of the pregnant woman.
- The decision and consent to abort must precede discussion of the possible use of the fetal tissue and any request for such consent as might be required for that use.
- The pregnant woman should be prohibited from designating the recipient of the fetal tissue transplant.
- Payments and other forms of remuneration and compensation associated with the procurement of fetal tissue should be prohibited, except payment for reasonable expenses occasioned by the actual retrieval, storage, preparation, and transportation of the tissues.
- Potential recipients of such tissues, as well as research and health care participants, should be properly informed as to the source of the tissues in question.
- Procedures must be adopted that accord human fetal tissue the same respect accorded other cadaver human tissues entitled to respect.

SOURCE: U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, *Report of the Human Fetal Tissue Transplantation Research Panel (Bethesda, MD: 1988).*

official announcement or opportunity for public debate has caused some to challenge its legal basis (7). The ethical basis of the continuation has also been challenged, since the reasons for its continuance had been rejected by the advisory panel upon whose recommendations the moratorium was supposed to be contingent (8).

On April 2, 1990, the U.S. House of Representatives Committee on Energy and Commerce's Subcommittee on Health and the Environment held hearings on human fetal tissue transplantation research. The subcommittee heard testimony from members of the NIH Human Fetal Tissue Transplantation Research Panel, representatives of organizations representing persons with various diseases that fetal tissue grafting may treat, members of the scientific community, and the Assistant Secretary for Health. Strong views for and against the continued moratorium on fetal tissue transplantation research were expressed.

While on one level the ethical debate was clearly and publicly articulated, the events leading up to the moratorium and those that followed the NIH advisory committee's acceptance of the panel's recommendations raise questions of their own. These events add another layer of ethical considerations to the fetal tissue transplantation controversy: Is the procedure for ethical decisionmaking in government subject to the same scrutiny as the issues it is used to address? Again, the absence of a Federal agency for deliberation of bioethical issues maybe noted. These events may also be interpreted as a question about the relationship between personal moral or ethical convictions and the appropriate shape of public policy in a pluralistic society.

Appendix A References

1. Associated Press, "Denver Scientists To Keep Using Tissue," Apr. 19, 1988.
2. Hansen, J.T., and Sladek, J.R., Jr., "Fetal Research," ***Science 246:775-779, 1989.***
3. Hilts, P.J., "U.S. Aides See Shaky Legal Basis for Ban on Fetal Tissue Research," New ***York Times,*** Jan. 30, 1990.
4. Lehrman, D., ***Summary: Fetal Research and Fetal Tissue Research*** **(Washington, DC: Association** of American Medical Colleges, 1988).
5. Mesce, D., "Former NIH Director Wants Fetal Tissue Research Ban Ended," Associated Press, Oct. 16, 1989.
6. New ***York Times,*** "Doctors Implant Frozen Fetal Cells," Dec. 13, 1988.
7. Palca, J., ''Fetal Research Ban on Shaky Ground?' ***Science 247:629, 1990.***
8. U.S. Congress, House of Representatives, Committee on Government Operations, Subcommittee on Human Resources and Intergovernmental Relations, letter from Ted Weiss, chairman, to Louis W. Sullivan, Secretary of Health and Human Services, Jan. 26, 1990.
9. U.S. Department of Health and Human Services, statement by Louis W. Sullivan, secretary, Nov. 2, 1989.
10. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, ***Report on Human Fetal Tissue Research Supported by the National Institutes of Health in Fiscal Year 1987.***
11. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, ***Report of the Human Fetal Tissue Transplantation Research Panel*** (Bethesda, MD: 1988).
12. Wyngaarden, J.B., Director, National Institutes of Health, memorandum to Robert E. Windom, Assistant Secretary for Health, U.S. Department of Health and Human Services, Jan. 19, 1989.

Appendix B

Participants in the Workshop on New Developments in Spinal Cord Injury: Acute Interventions and Neural Grafts

June 12, 1989

Sponsored by the Office of Technology Assessment
and
American Paralysis Association
Paralyzed Veterans of America

Jerry Silver, Ph. D., ***Workshop Chairman***
Case Western Reserve University
Cleveland, OH

Douglas Anderson, Ph.D.
VA Hospital
Cincinnati, OH

Thomas E. Anderson, Ph.D.
General Motors Research Laboratories
Warren, MI

Jerry Bernstein, Ph.D.
VA Medical Center
Washington, DC

Barbara S. Bregman, Ph.D.
Georgetown University
Washington, DC

Carson J. Cornbrooks, Ph.D.
University of Vermont College of Medicine
Burlington, VT

Allan I. Faden, M.D.
VA Medical Center
San Francisco, CA

Earl R. Feringa, M.D.
VA Medical Center
Augusta, GA

Barth Green, M.D.
University of Miami School of Medicine
Miami, FL

Edward Hall, Ph.D.
UpJohn Co.
Kalamazoo, MI

Marston Manthorpe, Ph.D.
University of California, San Diego
La Jell% CA

Paul J. Reier, Ph.D.
University of Florida College of Medicine
Gainesville, FL

Fredrick J. Seil, M.D.
VA Medical Center
Portland, OR

Brad T. Stokes, Ph.D.
Ohio State University
Columbus, OH

Wise Young, M.D.
New York University Medical Center
New York, NY

Jean R. Wrathall, Ph.D.
Georgetown University
Washington, DC

Contractor:

Julie Ann Miller
Washington, D.C.

Appendix C
Decade of the Brain

Public Law 101-58, 101st Congress, Joint Resolution

Whereas it is estimated that 50 million Americans are affected each year by disorders and disabilities that involve the brain, including the major mental illnesses; inherited and degenerative diseases; stroke; epilepsy; addictive disorders; injury resulting from prenatal events, environmental neurotoxins, and trauma; and speech, language, hearing, and other cognitive disorders;

Whereas it is estimated that treatment, rehabilitation and related costs of disorders and disabilities that affect the brain represents a total economic burden of $305 billion annually;

Whereas the people of the Nation should be aware of the exciting research advances on the brain and of the availability of effective treatment of disorders and disabilities that affect the brain;

Whereas a technological revolution occurring in the brain sciences, resulting in such procedures as positron emission tomography and magnetic resonance imaging, permits clinical researches to observe the living brain noninvasively and in exquisite detail, to define brain systems that are implicated in specific disorders and disabilities, to study complex neuropeptides and behavior as well as to begin to learn about the complex structures underlying memory;

Whereas scientific information on the brain is amassing at an enormous rate, and the field of computer and information sciences has reached a level of sophistication sufficient to handle neuroscience data in a manner that would be maximally useful to both basic researches and clinicians dealing with brain function and dysfunction;

Whereas advances in mathematics, physics, computational science, and brain imaging technologies have made possible the initiation of significant work in imaging brain function and pathology, modeling neural networks and simulating their dynamic interactions;

Whereas comprehending the reality of the nervous system is still on the frontier of technological innovation requiring a comprehensive effort to decipher how individual neurons, by their collective action, give rise to human intelligence;

Whereas fundamental discoveries at the molecular and cellular levels of the organization of the brain are clarifying the role of the brain in translating neurophysiologic events into behavior, thought, and emotion;

Whereas molecular biology and molecular genetics have yielded strategies effective in preventing several forms of severe mental retardation and are contributing to promising breakthroughs in the study of inheritable neurological disorders, such as Huntington's disease, and mental disorders, such as affective illnesses;

Whereas the capacity to map the biochemical circuitry of neurotransmitters and neuromodulators will permit the rational design of potent medications possessing minimal adverse effects that will act on the discrete neurochemical deficits associated with such disorders as Parkinson's disease, schizophrenia and Alzheimer's disease;

Whereas the incidence of necrologic, psychiatric, psychological, and cognitive disorders and disabilities experienced by older persons will increase in the future as the number of older persons increases;

Whereas studies of the brain and central nervous system will contribute not only to the relief of necrologic, psychiatric, psychological, and cognitive, disorders, but also to the management of fertility and infertility, cardiovascular disease, infectious and parasitic diseases, developmental disabilities and immunologic disorders, as well as to an understanding of behavioral factors that underlie the leading preventable causes of death in this Nation;

Whereas the central nervous and immune systems are both signaling systems which serve the entire organism, are direct connections between the nervous and immune system, and whereas studies of the modulatory effects of each system on the other will enhance our understanding of diseases as diverse as the major psychiatric disorders, acquired immune deficiency syndrome, and autoimmune disorders;

Whereas recent discoveries have led to fundamental insights as to why people abuse drugs, how abused drugs affect brain function leading to addiction, and how some of these drugs cause permanent brain damage;

Whereas studies of the brain will contribute to the development of new treatments that will curtail the craving for drugs, break the addictive effects of drugs, prevent the brain-mediated "high" caused by certain abused drugs, and lessen the damage done to the developing minds of babies, who are the innocent victims of drug abuse;

Whereas treatment for persons with head injury, developmental disabilities, speech, hearing, and other cognitive functions is increasing in availability and effectiveness;

Whereas the study of the brain involves the multidisciplinary efforts of scientist, from such diverse areas as physiology, biochemistry, psychology, psychiatry, mo-

lecular biology, anatomy, medicine, genetics, and many others working together toward the common goals of better understanding the structure of the brain and how it affects our development, health, and behavior;

Whereas the Nobel Prize for Medicine of Physiology has been awarded to 15 neuroscientist within the past 25 years, an achievement that underscores the excitement and productivity of the study of the brain and central nervous system and its potential for contributing to the health of humanity;

Whereas the people of the Nation should be concerned with research into disorders and disabilities that affect the brain, and should recognize prevention and treatment of such disorders and disabilities as a health priority;

Whereas the declaration of the Decade of the Brain will focus needed government attention on research, treatment, and rehabilitation in this area: Now, therefore, be it ***Resolved by the Senate and House of Representatives of the United States of America in Congress Assembled,*** That **the** decade beginning January 1, 1990, hereby is designated the "Decade of the Brain," and the President of the United States is authorized and requested to issue a proclamation calling upon all public officials and the people of the United States to observe such decade with appropriate programs and activities.

Approved July 25, 1989.

LEGISLATIVE HISTORY--H.J. Res. 174 (S. J. Res. 173):
CONGRESSIONAL RECORD, Vol. 135 (1989):
June 29, considered and passed House.
July 13, considered and passed Senate.

Appendix D
Acknowledgments

OTA would like to thank the members of the advisory panel who commented on drafts of this report, the contractors who provided material for this assessment, and the many individuals and organizations that supplied information for the study. In addition, OTA acknowledges the following individuals for their review of drafts of this report.

Douglas Anderson
VA Hospital
Cincinnati, OH

Thomas E. Anderson
General Motors Research Laboratories
Warren, MI

Lori Andrews
American Bar Foundation
Chicago, IL

Michael Appuzzo
American Association of Neurological Surgeons
Los Angeles, CA

Adrienne Asch
New Jersey Bioethics Commission
Princeton, NJ

Nancy Beang
Society for Neuroscience
Washington, DC

Barbara S. Bregman
Georgetown University
Washington, DC

Margaret Brown
American Paralysis Association
Springfield, NJ

David W. Cahill
University of South Florida
Tampa, FL

Margaret Calvano
National Multiple Sclerosis Society
New York NY

Sarah Carr
Association of American Medical Colleges
Washington, DC

Charles E. Carson
Spinal Cord Society
Fergus Falls, MN

Ronald A. Carson
University of Texas Medical Branch
Galveston, TX

Cheryl M. Chanaud
Paralyzed Veterans of America
Washington, DC

K. Danner Clouser
The Milton S. Hershey Medical Center
Hershey, PA

Carl W. Cotman
University of California, Irvine
Irvine, CA

Philip Cohen
Huntington Disease Society of America
New York, NY

Arthur Coquelin
Texas Tech University Health Sciences Center
Lubbock TX

Keith Crutcher
University of Cincinnati College of Medicine
Cincinnati, OH

Miriam Davis
National Institute for Environmental Health Sciences
Bethesda, MD

Gary B. Ellis
Institute of Medicine
Washington, DC

Anne Etgen
Albert Einstein College of Medicine
Bronx, NY

R. Mark Evans
American Medical Association
Chicago, IL

Alan Fine
Dalhousie University School of Medicine
Halifax, N.S.

Thomas Freeman
University of South Florida
College of Medicine
Tampa, FL

Elizabeth D. Gee
University of Colorado at Boulder
Boulder, CO

Christopher Goetz
United Parkinson Foundation
Chicago, IL

Lawrence Golbe
Robert Wood Johnson Medical School
New Brunswick NJ

Rachel Benson Gold
The Alan Guttmacher Institute
Washington, DC

Murray Goldstein
National Institute of Neurological Disorders and Stroke
Bethesda, MD

Roger Gorski
University of California-Ire Angeles,
School of Medicine
Los Angeles, CA

Debra S. Grega, Ph.D.
Boehringer Mannheim Biochemical
Indianapolis, IN

W. Allen Hauser
G. H. Sergievsky Center
New York NY

John T. Howard
University of California, Irvine
Irvine, CA

William Ketterer
National Institutes of Health
Bethesda, MD

Frances Kissling
Catholics for a Free Choice
Washington, DC

Lynn Kline
The Amyotrophic Lateral Sclerosis Association
Woodland Hills, CA

Jeffrey H. Kordower
University of Illinois at Chicago
Chicago, IL

Mary Grace Kovar
National Center for Health Statistics
Hyattsville, MD

L.T. Kurland
Mayo clinic
Rochester, MN

Edward R. Laws, Jr.
American Association of Neurological Surgeons
Washington, DC

Carl Leventhal
National Institute of Neurological Disorders and Stroke
Bethesda, MD

Abraham Lieberman
Barrow Neurological Institute
Phoenix, AZ

David E. Lilienfeld
The Mount Sinai School of Medicine
New York NY

Ronald M. Lindsay
Regeneron Pharmaceuticals, Inc.
Tarrytown, NY

Rev. Donald McCarthy
St. Antoninus Church
Cincinnati, OH

Gianpaolo Maestrone
American Parkinson's Disease Association
New York NY

Anne C. Maher
Chester Springs, PA

Stephen E. Nadeau
VA Medical Center
Gainesville, FL

David Orentlicher
American Medical Association
Chicago, IL

Creighton H. Phelps
Alzheimer's Association
Chicago, IL

Roger Porter,
National Institute of Neurological Disorders and Stroke
Bethesda, MD

Ali H. **Rajput**
University of Saskatchewan
Saskatoon, Canada

Michael R. Rask
American Academy of Neurological and
Orthopedic Surgeons
Las Vegas, NV

Robert B. Raskin
UpJohn Co.
Kalamazoo, MI

Robert A. Ratcheson
Case Western Reserve University School of Medicine
Cleveland, OH

Donald E. Redmond
Yale University School of Medicine
New Haven, CT

Paul J. Reier
University of Florida College of Medicine
Gainesville, FL

Donald J. Reis
Cornell University Medical College
New York NY

Clifford Rose
World Federation of Neurology
London, England

Jeffrey M. Rosenstein
The George Washington University
School of Medicine
Washington, DC

Judy Rosner
United Parkinson Foundation
Chicago, IL

Leslie **Steven** Rothenberg
University of California-Los Angeles,
School of Medicine
Los Angeles, CA

Thomas A. Shannon
Worcester Polytechnic Institute
Worcester, MA

Daniel Sosin
Centers for Disease Control
Atlanta, GA

Caroline Tanner
Rush Medical Center
Chicago, IL

John M. Tew
University of Cincinnati College of Medicine
Cincinnati, OH

Bruce D. Weinstein
West Virginia University School of Medicine
Morgantown, WV

Robert M. white
Howard University
Washington, DC

Daniel Wilder
University of Wisconsin
Madison, WI

Janet Woodcock
Food and Drug Administration
Bethesda, MD

Appendix E

List of Contractor Documents

For this report, OTA commissioned eight papers on various topics related to neural grafting.

"Epidemiology and Etiology of Parkinson's Disease," A.H. Rajput, 1988.
"The Immunological Aspects of Neural Grafting," W.F. Hickey, 1989.
"Neural Grafting in the Treatment of Parkinson's Disease: Past, Present, and Future," T. Freeman, 1989.
"Transplantation of Adrenal Tissue into the Nervous System," A. Fine, 1989.
"Reconstructing the Brain: New Strategies for Brain Disease," R. McKay, 1989.
"Legal and Regulatory Issues for Neural Grafts," L. Andrews, 1989.
"New Developments in Neuroscience: Neural Transplants and Nerve Regeneration Technologies, Ethical Issues," K. Gervais, 1989.
"New Developments in Neuroscience: Historical and Ethical Issues in Neural Transplants," R. Pinkus, 1989.

Appendix F
Acronyms and Glossary of Terms

Acronyms

AANs —American Association of Neurological Surgeons
ACTH —adrenocorticotropic hormone
ADAMHA —Alcohol, Drug Abuse, and Mental Health Administration
AHCPR —Agency for Health Care Policy and Research
AIDS —acquired immunodeficiency syndrome
ALS-P-D —amyotrophic lateral sclerosis-Parkinson's disease-dementia
BEAC —Biomedical Ethics Advisory Committee
BMAA —Beta-N-methyl amino-L-alanine
CCL -continuous cell line
CNS -central nervous system
CSF -cerebrospinal fluid
DHHS —Department of Health and Human Services
FDA —Food and Drug Administration
FFDCA —Federal Food, Drug, and Cosmetic Act
GABA —gamma-aminobutyric acid
GnRH —gonadotrophin-releasing hormone
GRAFT --General Registry of Adrenal-Fetal Transplantation
HAMM —human amnion membrane matrix
HCFA —Health Care Financing Administration
HIV —human immunodeficiency virus
IND —investigational new drug application
IRB —Institutional Review Board
LC —locus ceruleus
MAO-B —monoamine oxidase B
MND —motor neuron disease
MPP+ —methylpyridine
MPTP —l-methyl-4-phenyl-l,2,3,6-tetrahydropyridine
NDA —new drug application
NGF —nerve growth factor
NIH —National Institutes of Health
NINDS —National Institute of Neurological Disorders and Stroke
NOTA —National Organ Transplant Act
6-OHDA -6-hydroxydopamine
PHSA —Public Health Service Act
PMA —premarket approval
PNS —peripheral nervous system
PSP —progressive supranuclear palsy
TH —tyrosine hydroxylase
THA —tetrahydroaminoacridine
UAGA —Uniform Anatomical Gift Act
UPF —United Parkinson Foundation
VP —vasopressin

Glossary of Terms

Abortion: The termination of pregnancy, whether spontaneous (occurring naturally, a miscarriage) or induced. Induced abortions may be therapeutic (to treat a medical condition of the pregnant woman) or nontherapeutic (elective).

Abortus: An aborted fetus. See ***fetus.***

Acetylcholine: A neurotransmitter involved in learning and memory. Acetylcholine is diminished in Alzheimer's disease. See ***neurotransmitter.***

Adrenal medulla: The innermost region of the adrenal gland; cells from this region can produce dopamine in the brain and are potential candidates for neural grafting, particularly to relieve the symptoms of Parkinson's disease. See ***chromaffin cell.***

AIDS, acquired immunodeficiency syndrome: A condition in which the body's immune system is depressed due to infection by a retrovirus. See ***HIV, retrovirus.***

Allograft: Tissue or cells transplanted between individuals of the same species.

Alzheimer's disease: A neurodegenerative disease caused by abnormality and death of nerve cells in several areas of the brain; the nerve cell loss is associated with a deficit of several chemicals in the brain, notably acetylcholine, resulting in dementia. The cause of the nerve cell abnormality and loss is unknown.

Amyotrophic lateral sclerosis, ALS, Lou Gehrig's disease: A neurodegenerative disease caused by death of nerve cells in the central nervous system that control muscle movement. Paralysis, but not dementia, results. The cause of the nerve cell death is unknown.

Animal model: An animal that shares or in which can be replicated features of human disorders and that is used in experimental studies of those disorders. Animal models may be homologous (sharing a common origin) or analogous (being similar in effect) to the human disease or injury being studied.

Astrocyte: A type of glial cell in the central nervous system; after injury to the central nervous system, astrocytes form a scar at the site of nerve damage and block regeneration of axons. See ***glial cell.***

Autograft: A transplant in which the recipient's own tissue or cells are use& autografts pose no problem of rejection by the recipient and provide a ready source of grafting material. Adrenal medullary grafts are an example of autografts. See *adrenal medulla, rejection.*

Autonomic nervous system: Cells in the central and peripheral nervous systems that control such involuntary functions of the body as temperature, metabolism, and response to stress.

Axon: The long extension of the neuron along which electrical impulses travel. See *neuron*.

Basal ganglia: A group of nuclei in the upper part of the brain that help mediate movement. See *substantial nigra, striatum*.

Biologic: A biological product for the prevention, treatment, diagnosis, or cure of human diseases or injuries; examples are vaccines, blood, and antitoxins.

Blood-brain barrier: A layer of tightly juxtaposed endothelial cells in blood vessel walls that protects much of the central nervous system by selectively filtering out some substances while allowing others to pass from the blood into the brain. See ***endothelial cell.***

Brain: One of the two components of the central nervous system, the brain consists of the cerebral cortex, the cerebellum, the upper brain, and the brain stem. The brain is the center of thought, action, and emotion. It receives sensory impulses and transmits motor impulses.

Brain stem: The lowest part of the brain, connecting the cerebral cortex and upper brain to the spinal cord. Nuclei in the brain stem regulate essential bodily functions such as heart rate, blood pressure, and respiratory activity. See *nucleus.*

Cadaveric fetal tissue: Tissue obtained from a dead fetus.

Catecholamine: A class of neurotransmitter including dopamine, norepinephrine, and epinephrine (a hormone secreted by the adrenal medulla).

Cell body: The relatively compact portion of the neuron, which contains the nucleus. Compare ***axon, dendrite.***

Cell* culture:** Cells grown in the laboratory; although the cells proliferate, they do not organize into tissue. See ***primary cell culture, cell line, and ***continuous cell line.***

Cell* line:** A group of cells derived from a primary culture at the time of first subculture; an established cell line has the potential for indefinite subculture in vitro. See ***continuous cell line.

Cell* suspension:** Individual cells separated out from solid tissue and placed in a supporting fluid; also, as a form of neural grafting, injection of such cells into a host central nervous system. Compare ***solid tissue graft.

Central nervous system, CNS: One of the **two major divisions of the nervous system, made up of the brain and spinal cord. Compare *peripheral nervous system.***

Cerebral cortex: The rounded upper portion of the brain, consisting of layers of neural cells and the pathways that connect them. The cerebral cortex is divided into four lobes on each side and is the part of the brain in which thinking and decisionmaking take place. See ***brain.***

Cerebrospinal fluid: Fluid manufactured in the brain and contained within the brain and spinal cord; it circulates in the central nervous system and is absorbed into and removed by veins.

Chromaffin cell: A nonneuronal cell in the adrenal medulla derived from precursor cells that also generate neurons in the autonomic nervous system. Chromaffin cells produce neurotransmitters that are chemically related to those synthesized in the autonomic and central nervous systems. See ***adrenal medulla, precursor cell.***

Clinical test, clinical research: Experimental analysis (as of drugs or surgery) using human beings.

Conceptus: The product of conception. See embryo, ***fetus.***

Continuous cell line: Sustained, self-propagating cells in culture; such cells may arise spontaneously in primary cell culture, be derived from tumors, or be created through genetic engineering. See cell ***culture, genetically engineered cell.***

Cryopreservation: The freezing and storage of cells or tissue at -1960 centigrade for use later.

Dementia: Loss of intellectual function.

Demyelinating **disorder: See *demyelination, multiple sclerosis.***

Demyelination: Destruction of the myelin sheath, whether through injury or disease. See ***myelin sheath.***

Dendrite: Branched extension of the neuron cell body which receives impulses from another neuron. See ***synapse.***

Deprenyl: A drug shown to slow the progression of Parkinson's disease in clinical trials by blocking the activity of MAO-B. See ***MAO-B.***

Device: Broadly, an instrument, apparatus, implant, in vitro reagent, or other similar or related article intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease, or intended to affect the structure or function of the body, that works through nonchemical, nonmetabolic means.

Differentiation: The stage of development during which brain cells stop dividing and acquire distinct characteristics and functions. Compare ***migration, proliferation.***

Dopamine: A neurotransmitter that in insufficient amounts produces the symptoms of Parkinson's disease. See *catecholamine, neurotransmitter.*

Dorsal root: The portion of the nerve root that brings sensory information from the body to the spinal cord. See ***nerve root.***

Drug: An article (other than foods or devices) intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease and designed to affect the structure or any function of the body.

Dura mater: The tough, outermost membrane surrounding the brain and spinal cord.

Elective abortion: See ***abortion.***

Embryo: The conceptus from fertilization until the end of the eighth week See *fetus.*

Endocrine system: The endocrine glands (such as the thyroid and pituitary glands) and the hormones they secrete.

Endothelial cell: A type of cell lining the blood vessel wall that can trigger an immune response (and hence graft rejection). See ***blood-brain barrier.***

Epilepsy: Disruption in the normal electrical activity of the brain, resulting in seizures; epilepsy is diagnosed if more than one seizure occurs and those seizures are due to central nervous system dysfunction.

Excitotoxin: A chemical substance (kainic acid, ibotenic acid, or quinolinic acid) that, when injected into the brain, kills nerve cells by overstimulating them.

Ex utero: Outside the uterus.

Fetus: In a legal context, the conceptus at all stages of development; in a Federal regulatory context, the conceptus after implantation; in a scientific context, the conceptus from the end of the eighth week to the moment of birth. Compare embryo.

Fibroblast: A connective tissue cell, found in the skin, that can be induced through genetic engineering to produce some chemicals (such as dopamine and nerve growth factor) found in the brain.

Ganglion, ganglia: Term for a group of neurons that are usually located outside the central nervous system. Compare *basal ganglia.*

Genetic engineering: Altering the genetic makeup of a cell.

Genetically engineered cell: A cell into which new genes have **been inserted**

Germ cell: A reproductive (egg or sperm) cell or its precursors. Compare ***somatic cell.***

Glial cell, glia: A basic cell type of the nervous system. Glial cells appear to perform support functions for neurons: namely, nutrition, insulation (through the production of myelin), and structural support. Compare ***neuron. See astrocyte, microglia, oligodendrocyte, Schwann cell.***

Hippocampus: A **nucleus in the brain crucial to learning and memory.**

HIV, human immunodeficiency virus: The retrovirus associated with AIDS and AIDS-related complex. See ***retrovirus.***

Huntington's disease: A genetic neurodegenerative disease caused by death of nerve cells in the striatum (producing abnormal movement) and elsewhere in the cerebral cortex (producing dementia). The cause of the nerve cell death is unknown.

Hypothalamus: A collection of nuclei in the brain that control such behaviors as eating and drinking and are involved in regulating the endocrine system. The hypothalamus also produces hormones itself. See ***endocrine system.***

Immune response: Reaction of the immune system to foreign matter. See ***immune system.***

Immune system: A collection of organs, tissues, cells, and molecules in mammals that seeks out, identifies, destroys, and remembers foreign organs, tissues, cells, and molecules; the immune system protects the animal from disease-causing organisms in the environment. See ***rejection.***

Immunological privilege: The concept that the central nervous system is not as closely monitored by the immune system as the rest of the body and is therefore less susceptible to graft rejection.

Immunoreactive: Capable of provoking a response from the immune system.

Immunosuppression: The use of drugs to prevent graft rejection by restraining the response of the immune system to foreign material.

Incidence: The number of new cases of a disorder occurring during a given period of time (usually 1 year) within a given geographical area. ***Compare prevalence.***

Incidence rate: Incidence per unit of population. See *incidence.*

Induced abortion: See *abortion.*

Informed consent: As applied to human research, the agreement of a person (or his or her legally authorized representative) to serve as a research subject, in full knowledge of all anticipated risks and benefits of the experiment. Informed consent requires that the researcher impart to the prospective subject any information that might influence the subject's decision to participate or not participate in the research, including an explanation of the methodology to be used, the availability of alternative therapies, and the prospective subject's freedom to withdraw from the experiment at any time, without prejudice.

Institutionalize: To incorporate an act or practice into a structured, often formal, system. Compare ***legitimate.***

Institutional Review Board, IRB: A group established by an institution conducting medical research to assess the legal, ethical, and scientific aspects of that research on human subjects. IRB approval is required by the Department of Health and Human Services before proposals can receive Federal funding. IRBs must review research protocols on a regular basis, but not less than once a year.

In utero: In the uterus.

Investigational device exemption: Application to FDA by a manufacturer for permission to ship a device prior to obtaining premarket approval, in order to conduct studies of safety and efficacy. ***See premarket approval application.***

Investigational new drug application, IND: Request by a manufacturer for exemption from FDA's premarket approval requirement; an IND is sought for shipment of a drug for investigational use by qualified experts, in order to study the safety and efficacy of the drug.

In vitro: Literally, in glass; in the laboratory; outside the body.

In vivo: In the body.

Isograft: Tissue transplanted from one identical twin to another; isografts pose no problem of rejection by the identical twin who receives the graft.

Kindled model: An animal model of epilepsy that is thought to be analogous to temporal lobe epilepsy in humans. See ***animal model.***

L-dopa, Levodopa: The precursor of the neurotransmitter dopamine. L-dopa is the standard therapy for persons with Parkinson's disease.

Legitimate: To give legal status to an actor practice; to show or affirm an act or practice to be justified. Compare ***institutionalize.***

Limbic system: Structures in the brain that are associated with some aspects of emotion and behavior. See ***hippocampus, hypothalamus.***

Locus ceruleus: A nucleus of the brain that inhibits the ability to induce seizures in the kindled model of epilepsy. See kindled *model.*

Lymphatic drainage: The movement of fluids, molecules, foreign particles, and cells from various tissues in the body through the lymph system to the immune system; a means by which grafted cells reach the host's immune system and trigger rejection.

MAO-B, monoamine oxidase B: An enzyme that breaks down certain neurotransmitters. It can also convert other chemicals to toxins that destroy substantial nigra cells, thereby producing parkinsonism. ***See parkinsonism.***

Microglia: A type of glial cell in the central nervous system thought to enter the immune system and initiate graft rejection.

Migration: The movement of immature cells in the brain to the site where they will mature and remain permanently. Compare *differentiation, proliferation.*

Minimal risk: Term used to denote that the chance of harm anticipated in proposed research is no greater than that encountered in daily life or during the performance of routine physical or psychological tests.

Mortality rate: The number of deaths during a given period of time (usually 1 year), within a given geographical area, per unit of population.

Motor neuron disease: A type of neurodegenerative disease in which neurons in the central nervous system that control muscle movement are destroyed. See *amyotrophic lateral sclerosis.*

MPTP, l-methyl-4-phenyl-l,2,3,6-tetrahydropyridine: A synthetic narcotic that can cause parkinsonism in humans.

Multiple sclerosis, MS: A demyelinating disease characterized by an array of symptoms (such as loss of coordination, slurred speech, and dizziness), depending on wherein the central nervous system the lesions occur. See *demyelination.*

Myelin: A fatty substance (of which the myelin sheath surrounding axons is made) that acts as an electrical insulator to speed the conduction of nerve impulses. Myelin is formed in the peripheral nervous system by Schwann cells and in the central nervous system by *oligodendrocytes. See myelin sheath, oligodendrocyte, Schwann cell.*

Myelin sheath: Concentric layers of myelin surrounding the axons of some neurons. The myelin sheath speeds the conduction of electrical impulses. See ***myelin, oligodendrocyte, Schwann cell.***

Nerve fiber: An axon **and its surrounding myelin sheath.**

Nerve growth factor, NGF: A protein that promotes axon growth in some areas of the peripheral nervous system and plays a role in the development of vertebrate sensory and autonomic systems. In the central nervous system, it appears to protect from damage some populations of cells that synthesize acetylcholine.

Nerve root: One of a collection of nerves that are attached to and demarcate the 30 segments of the spinal cord. Nerve fibers enter and leave the spinal cord at one of the 31 nerve roots. These fibers link the peripheral and central nervous systems, bringing sensory information from the body to the spinal **cord and motor information from the spinal cord to the body. See *dorsal root.***

Neural grafting: The transplantation (implantation) of cells or tissue into the brain or spinal cord. As **used in this report, it** refers to various treatment goals (such as promotion of growth or provision of needed chemicals), materials (such as adrenal medulla or fetal central nervous system tissue) and methods (such as cell suspensions or cell lines) of grafting. See cell ***line, cell suspension.***

Neuritic plaque: Abnormal cluster of degenerating neurons, other brain cells, and protein in the areas between neurons; found in the brains of persons with Alzheimer's disease.

Neurodegenerative disorder: A class of neurological disease marked by loss of a particular population or populations of nerve cells in the central nervous system. Symptoms vary and depend on the neurons lost. See, for example, ***Parkinson's disease, Huntington's disease, Alzheimer's disease,*** and ***amyotrophic lateral sclerosis.***

Neurofibrillary tangle: Accumulation of twisted protein filaments inside nerve cells; found in the brains of persons with Alzheimer's disease.

Neurological disorder: Disease of, or injury to, the central nervous system.

Neuron, nerve cell: The basic functional unit of the nervous system. The neuron is typically composed of a relatively compact cell body containing the nucleus; several short, radiating extensions, or processes (dendrites); and one long process (the axon) with twig-like branches along its length and at its end. Information in the form of electrical impulses travels from the dendrites, through the cell body, and along the axon to other cells. Sensory neurons send information to the brain and spinal cord; motor neurons send instructions to muscles, organs, and glands. See axon, ***dendrite.***

Neurotransmitter: Specialized chemical messenger (e.g. acetylcholine, dopamine, norepinephrine, serotonin) synthesized and secreted by neurons that sends a nerve impulse from one nerve cell to another. Neurotransmitters are released into the synaptic space between neurons, bind to the dendrites of other neurons, and initiate a message in those neurons. Some neurotransmitters stimulate the release of neurotransmitters from other neurons, while others inhibit the release of neurotransmitters from other neurons. Neurotransmitters are also released at synapses between neurons and other targets (e.g., muscles, glands). See ***synapse, synaptic space.***

Neurotrophic factor: Chemical produced by some neurons and glial cells that affects the growth and development, maintenance of function, and response to injury of neurons. See ***trophic factor, tropic factor,* and *nerve growth factor.***

***New* drug:** A drug not generally recognized by qualified experts as safe and effective for use under the conditions prescribed, recommended, or suggested on the label, 01 which has been recognized as safe and effective but which has not been used to a material extent or for a material time.

New drug application, NDA: Submission by a manufacturer to the FDA of information on a new drug, including full reports of studies of safety and efficacy, specimens of proposed labelling, and methods of manufacture, processing, and packing. Approval of the NDA is required before a new drug can be introduced into commerce. See ***investigational new drug application.***

Nontherapeutic abortion: See *abortion.*

Nontherapeutic research: Studies involving human subjects designed to further scientific knowledge about a disorder or process, with no anticipated direct benefit to the subjects themselves.

Norepinephrine: See *catecholamine, neurotransmitter.*

Nucleus, nuclei: A group of cells in the brain, but generally outside the cerebral cortex, that share the same anatomical region and to varying degrees the same function. The hippocampus, locus ceruleus, and substantial nigra are examples of nuclei.

Oligodendrocyte: A type of glial cell that forms myelin in the central nervous system; oligodendrocytes appear to inhibit the regrowth of damaged axons in the central nervous system. Compare ***Schwann cell; see glial cell, myelin, myelin sheath.***

On-off phenomenon: In Parkinson's disease, alternating periods in which the patient's motor symptoms are under control (on) or severe and uncontrolled (off); the phenomenon occurs regardless of drug dosage.

Paraneuron: Cells that share a common heritage with cells in the nervous system. ***See chromaffin cells.***

Paraplegia: Paralysis and loss of sensation from the waist down as a result of damage to the middle or lower portions of the spinal cord.

Parkinsonism: A group of neurological disorders with various causes (e.g., drugs, toxic chemicals, brain tumors, and recurrent head injury). Symptoms include abnormally decreased motor activity, tremor, and rigidity. The most common type of parkinsonism is Parkinson's disease. See ***Parkinson's disease.***

Parkinson's disease, idiopathic Parkinson's disease: A neurodegenerative disease caused by death of nerve cells in the substantial nigra and the resulting loss of dopamine in the brain; symptoms are tremor, slowing of movement, and rigidity. The cause of the nerve cell death is unknown. Compare *parkinsonism.*

Peripheral nervous system, PNS: One of the two major divisions of the nervous system, made up of the nerves and ganglia outside the brain and spinal cord. Nerves in the peripheral nervous system connect the central nervous system and sensory organs, other organs, blood vessels, glands, and muscles. Compare *central nervous system.*

Precursor cell: An undifferentiated embryonic cell that **may** develop into one or another type of mature cell. See ***differentiation.***

Premarket approval application, PMA: Application required by the FDA for certain devices; this application demonstrating safety and efficacy must be submitted to and approved by the FDA before the device can be introduced to the market.

Prevalence: Total number of cases of a disorder in existence at any given time in a given area. Compare ***incidence.***

Prevalence rate: Prevalence per unit of population.

Primary cell culture: Cells taken directly from an organism and grown in vitro; most replicate a fixed number of times or not at all. Compare ***continuous cell line.***

Proliferation: The reproduction or multiplication of similar forms of brain cells; the stage of development preceding migration and differentiation. Compare ***differentiation, migration.***

Protocol, research protocol: A complete description of a proposed scientific experiment.

Quadriplegic: Paralysis and loss of sensation from the shoulders down as a result of damage to the upper spinal cord.

Regeneration: Regrowth of tissue. In the nervous system, regeneration often refers to regrowth of a damaged axon. See ***axon.***

Rejection, graft rejection: The destruction by the immune system of foreign tissue; specifically, destruction of foreign tissue transplanted into a recipient's body from a donor's body.

Replication: The process of duplicating or reproducing itself, as cells. Compare ***proliferation.***

Retrograde cell death: The killing, due to axonal damage, of neurons located some distance away from

the site of an injury in the central nervous system.

Retrovirus: Any of a group of RNA-containing viruses that produce reverse transcriptase, which catalyzes the production of DNA using the virus's RNA as a template; the DNA is incorporated into the genome of the infected cells. The AIDS virus is a retrovirus, as are many infection- and tumor-producing viruses.

Risk-benefit analysis: A determination of whether the risks to health of using a drug or procedure exceed the therapeutic and quality-of-life benefits that accrue from its use.

Schwann cell: A glial cell in the peripheral nervous system that produces myelin for the myelin sheath surrounding axons. Schwann cells also support regrowth of the axons of peripheral nerves. Compare ***oligodendrocyte; see myelin, myelin sheath.***

Solid tissue graft: Apiece of tissue placed into the brain or spinal cord; such tissue contains more than one type of cell and therefore may be more likely than a cell suspension to provoke an immune response. See ***endothelial cell;*** **compare cell *suspension.***

Somatic cell: Any cell in the body except reproductive cells and their precursors. Compare germ ***cell.***

Spinal cord: A component of the central nervous system, the spinal cord is a core of neuronal cell bodies surrounded by axons that extends from the bottom of the brain down the spinal column. The spinal cord is divided into 30 segments. See ***brain, central nervous system.***

Spontaneous abortion: See *abortion.*

Standard therapy: Procedures no longer regulated as research.

Stereotactic surgery: A type of brain surgery; specifically, the implantation of tissue into the brain by means of a needle inserted through a small hole in the skull.

Striatum, corpus striatum: Part of the basal ganglia located in the upper part of the brain; the striatum receives dopamine from cells in the substantial nigra. See ***substantial nigra.***

Stroke: A **sudden interruption of normal blood flow to the brain, caused by blockage or rupture of a blood vessel,** that may result in **a wide range of neurological deficits (such as coma, paralysis, or inability to speak), depending on wherein the brain the lesion occurred.**

Substantial nigra: A nucleus in the brain; neurons in the substantial nigra produce dopamine and send their axons to the striatum. The cells of the substantial nigra degenerate in Parkinson's disease. See *striatum, Parkinson's disease.*

Synapse: The site at which an impulse is transmitted from the axon of one nerve cell to the dendrite of another nerve cell, typically by a neurotransmitter. See *neurotransmitter.*

Synaptic space: A narrow gap between two adjacent neurons into which neurotransmitters are secreted. See ***neurotransmitter, synapse.***

Synaptic sprouting: A **process of limited regrowth following damage to the central nervous system whereby fibers from nearby, undamaged axons form new branches and establish new synapses to replace some of the lost ones.**

Thalamus: A collection of nuclei in the brain that are involved in analyzing sensory and motor information.

Therapeutic research: Studies involving human subjects that are designed to cure or palliate a disorder existing in those subjects.

Trophic factor: A chemical that promotes the growth of axons and the survival of neurons.

Tropic factor: A chemical that provides a surface or substrate for axon growth and guides the axon toward its target.

Upper brain: The portion of the brain between the cerebral cortex and the brain stem. See *brain stem, cerebral cortex.*

Vector: Transmitter of disease.

Ventricle: Cavity in the brain that contains cerebrospinal fluid. See ***cerebrospinal fluid.***

Viable: Capable of living; specifically, a fetus capable of living outside the womb.

Xenograft: Tissue transplanted from one species to another.

Index

Related OTA Reports

- **Neurotoxicity: Identifying and Controlling Poisons of the Nervous System—Special Report.** Describes the scope of the public health threat posed by neurotoxic substances; Federal research, testing, monitoring, and regulatory programs to address it; and the economic considerations associated with testing and regulatory programs. 4/90; 350 p.

  GPO stock ##052-O03-Ol184-l; $15.00

- **Biological Rhythms and Shift Work.** Examines biological rhythms and the role they play in regulating a variety of physiological and cognitive functions and the effects disruption of biological rhythms can have on those functions. In progress.

- **The Biological Basis** of **Mental Illness. The** report will evaluate research that has advanced the understanding of genetic and other biological factors underlying mental disorders, and the resulting implications of such research for diagnosis, treatment, and Federal policy. In progress.