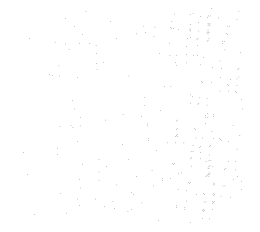


## Chapter 2

# Introduction



# CONTENTS

	<i>Page</i>
NATURE OF NEUROLOGICAL DISORDERS .....	20
Injury ... *. ... .. *	20
Disease .....	20
APPROACHES TO TREATMENT .....	21
HISTORICAL PERSPECTIVE .....	21
FEDERAL INTERESTS .....	22
THE OTA STUDY .....	24
CHAPTER 2 REFERENCES ... *. * .. *	24

## *Figure*

<i>Figure</i>	<i>Page</i>
2-1. Annual publications on Grafting Into the Nervous System .....	22

## *Tables*

<i>Table</i>	<i>Page</i>
2-1. Tissue and Organ Transplants in the United States, 1989 .....	19
2-2. Landmarks for Neural Grafting in Mammalian Central Nervous Systems .....	23
2-3. Federal Funding of Neural Grafting Research .....	24

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 2-1). 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

**Table 2-1—Tissue and Organ Transplants in the United States, 1989**

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

<sup>a</sup> 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.

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.

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 acetyl-

choline-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.

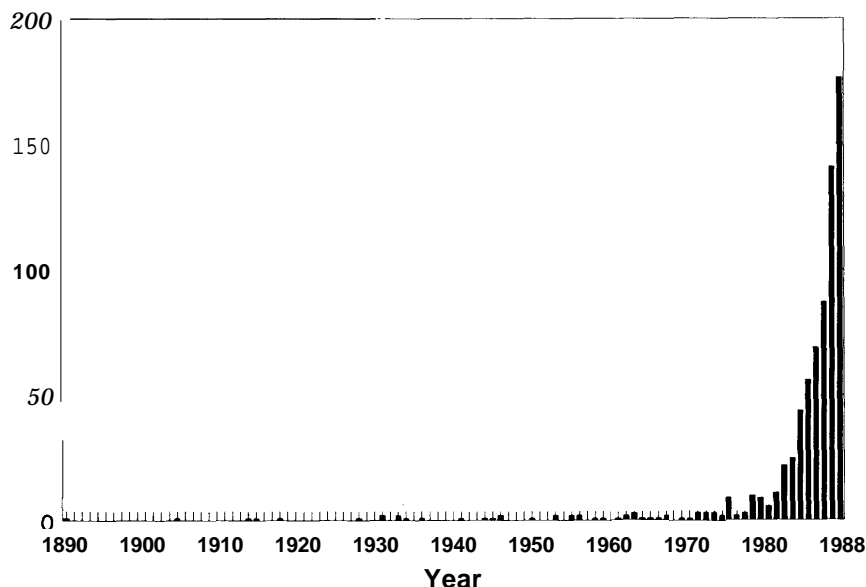
## HISTORICAL PERSPECTIVE

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 first 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 2-1). 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 2-1—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 in patients 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 <sup>a</sup>
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 . . . . .				
Department of Veterans Affairs . . . . .	0.3	0.3	0.5	0.4
National Science Foundation <sup>a</sup> . . . . .	0.4	0.5	0.5	0.5
	0.2	0.2	0.2	0.2

<sup>a</sup>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 identifies 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.

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