Chapter 6
Relevant Neurological Disorders

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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

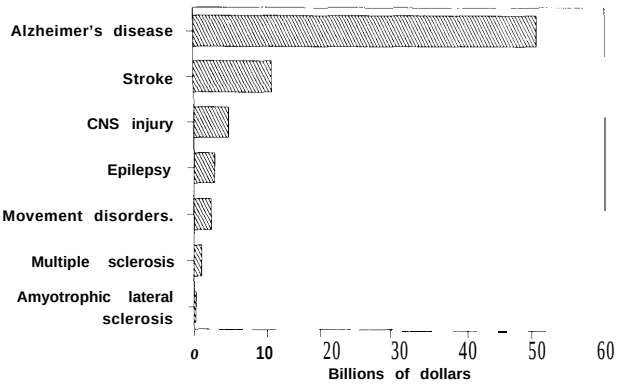
a Estimate of persons permanently disabled from head injury.

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.

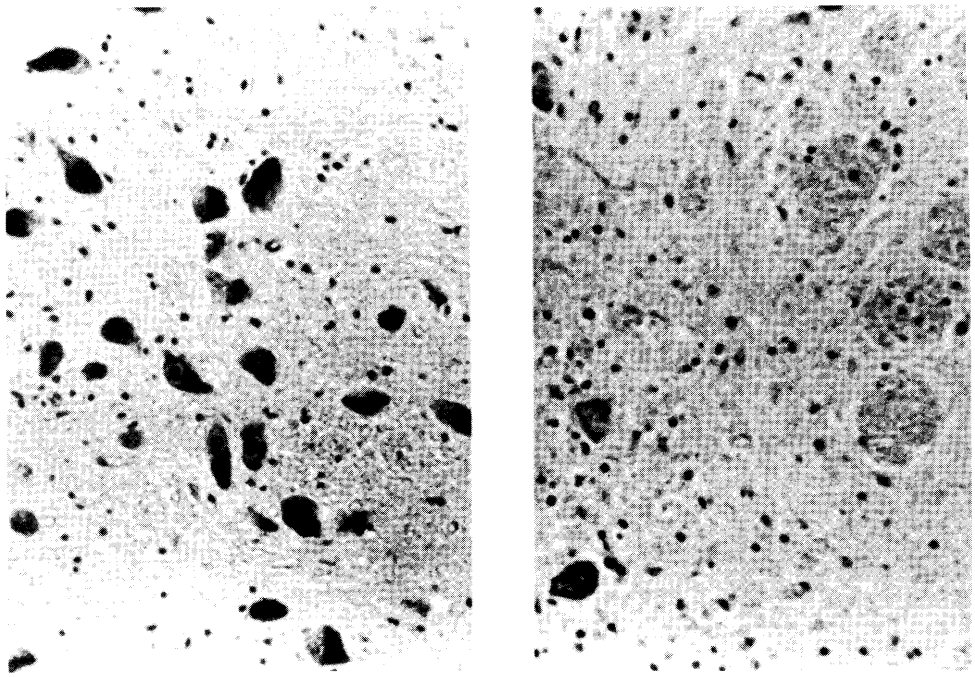


Photo credit: B. Pansky, Medical College of Ohio

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**

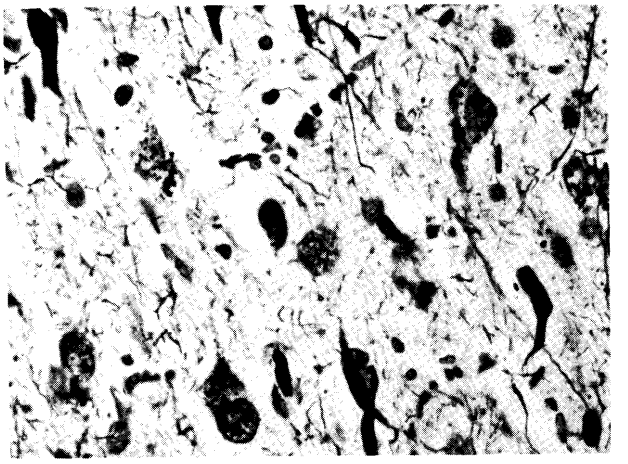


Photo credit: R. Restak, The Mind (New *York, NY: Bantam Books, 1988)*

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.**

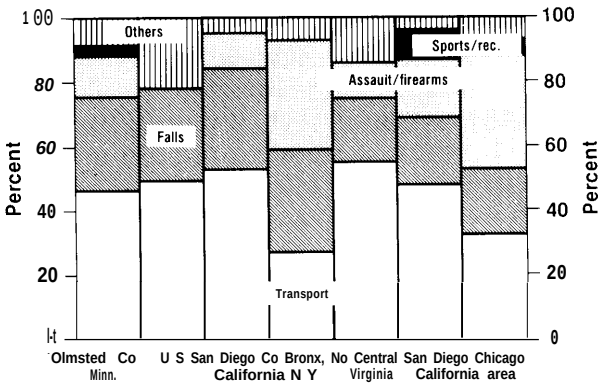
SOURCE: Department of Veterans Affairs, Spinal Cord Injury Service, Washington, DC, 1990.

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

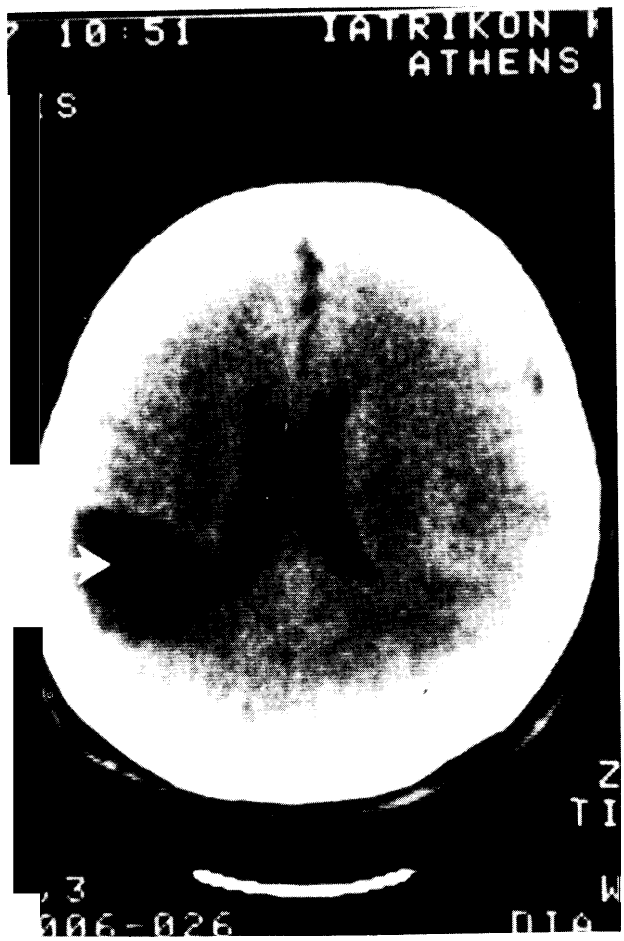


Photo credit: R. Restak,* The Mind (New *York,* NY: *Bantam Books, 1988)

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,

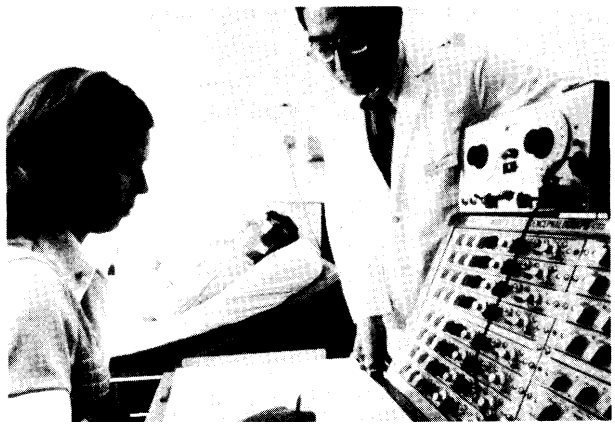


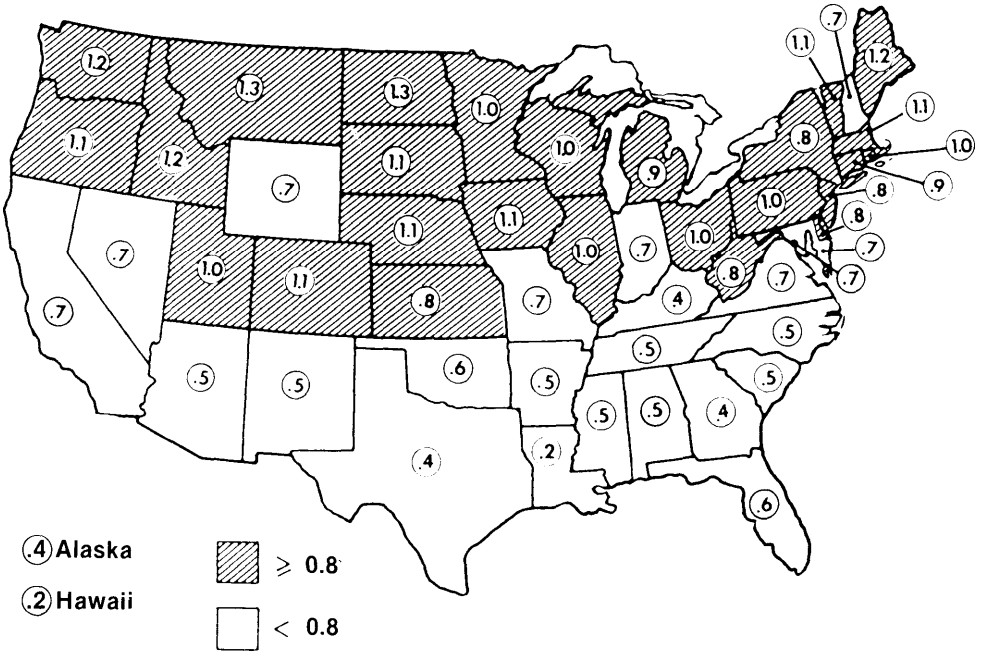
Photo credit: National Institutes of Health

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.

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