TREATMENT OF NEUROSURGICAL DISEASE IN THE NEW MILLENNIUM

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With the arrival of the new millennium, the field of neurosurgery faces tremendous opportunities and challenges. Technology-driven approaches to neurosurgery allow a dramatic change in priorities, from a past largely characterized by ablative approaches to diseases, to a future characterized increasingly by restorative approaches to neurosurgical diseases. Molecular approaches to neurosurgical problems allow greater precision and intracellular manipulation of neuronal function and offer hope for therapy in previously hopeless diseases. Perhaps the greatest challenge to neurosurgery in the new millennium, however, is the devastating effect on quality of care by profit-oriented health insurers, who not only deny patients access to care but fail to recognize the need for investment in improving the quality of care and developing new therapies for patients with neurosurgical disease.

PARADIGM SHIFT

In the past, neurosurgery has been a surgical specialty largely focused on ablative procedures: extirpation of a brain tumor, clipping an aneurysm, removing a herniated disc, and so forth. Over the past decade, a paradigm shift in priorities has occurred, and the field of neurosurgery is increasingly focusing on restorative approaches to disease conditions. Similarly, based on new computer-assisted technology, techniques now allow greater precision for delineation of abnormal tissue in the brain and spinal cord, permitting preservation of normal tissue during resection.

Cerebrovascular Neurosurgery

Within the subspecialty of cerebrovascular surgery, at Thomas Jefferson University in Philadelphia and at other tertiary care centers in this country, almost one half of the patients with cerebral aneurysms do not have invasive intracranial surgery. Instead, their aneurysms are treated endovascularly with the placement of coils, sealing the aneurysm, and recreating the normal flow dynamics of the blood vessels that contained the aneurysm.[3] As a result, a clot forms within the aneurysm, and an endothelial cell layer often forms, allowing blood flow to continue unimpeded. For arteriovenous malformations, characterized by a tangle of abnormal blood vessels that shunt blood from the arterial to the venous circulation, surgery was the choice in the past. Increasingly, particularly in inaccessible brain locations, arteriovenous malformations are treated with the placement of polymeric glues that stop the abnormal shunting, and surgical removal may be obviated. Endovascular approaches are now more commonly performed in patients who have critical stenosis because of atherosclerotic plaques in their carotid circulation, by placing

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a stent across the stenotic arterial segment. Finally, newer technologies are imminent, and will further refine the endovascular opportunities, including the application of stents that will permit blood flow from branch vessels through a porous material, and use of balloons that will allow distal blood flow while blocking access to a large aneurysm.

Functional Neurosurgery

The field of functional neurosurgery has been revolutionized by technology over the past several years, and the pace of discovery is accelerating. New devices that provide electromagnetic stimulation to brain or spinal cord regions offer hope for functional recovery in a number of disease conditions. Drug delivery systems also have been developed that replace missing or deficient neurotransmitters or peptides. For patients with Parkinson's disease, characterized by tremor, bradykinesia, other movement disorders, and, frequently, some cognitive deficits, the application of implantable stimulators to the corpus striatum, the target tissue for the nigrostriatal tract damaged by the disease, have offered many patients significant improvement in the quality of their life. For patients with intractable epilepsy, use of electrical stimulators on the vagus nerve and other brain regions have yielded encouraging results, although the physiology of the effect is poorly understood. Patients with intractable pain often benefit from implantation of spinal cord stimulators that alter the gain of the nociceptive system, reducing the pain signals travelling up into the brain. Patients with spinal cord injuries or other neurogenic bladder problems can have stimulators implanted that can control bladder and sphincter function. Finally, the application of pump technology allows patients with intractable cancer pain to have intrathecal delivery of morphine, or patients with severe spasticity to have intrathecal delivery of baclofen, with significant improvement in function in most patients.

Neuro-oncologic Neurosurgery

Although much progress has been made in the understanding of the molecular mechanisms of tumorogenesis, the reality is that for patients with malignant primary brain tumors, there have been no dramatic advances in prolonging quality life in the past few decades. A number of trends suggest that over the next few decades, however, this dismal reality may change. Certainly, based on new computer-driven image guidance systems, the precision of surgical removal of tumors can be significantly enhanced, preserving normal neural tissue. Using either the gamma knife or linear-accelerator-based radiosurgery, precise radiosurgical approaches to complex tumors and other brain lesions may be achieved. New polymeric and liposomal delivery systems permit localized delivery of chemotherapeutic agents directly to the tumor bed, obviating the need for systemic application, with its side effects. Once a better understanding of the molecular signals that are responsible for malignant brain tumors is achieved, it is likely that a multifaceted strategy that employs image-guided resection, select radiosurgery, and appropriate pharmacologic or molecular approaches will offer patients hope for a longer-term, higher-quality survival. Recent advances in immunotherapy, allowing targeted therapy against unique antigenic determinants on tumor cells, may add further specificity, and broaden the armamentarium of therapy for malignant brain tumors.

Spine Surgery

Although most spine surgery still focuses on ablative techniques, including removal of discs and compressive bony lesions, restorative approaches to spine disorders are burgeoning.[4] Mostly because of novel instrumentation systems, reconstruction of the spine is now possible, allowing quicker mobilization of postoperative patients, and providing the necessary three-dimensional support for appropriate bone fusion to occur. As the molecular basis of bone formation is further unravelled, it is likely that spinal instrumentation, combined with molecular approaches, will lead to the best outcomes.

THE MOLECULAR REVOLUTION

Perhaps the greatest change in neurosurgery is the advent of molecular approaches to a field that has hitherto been macromolecular in its outlook. Molecular neurosurgery takes advantage of a neurosurgeon's access to the brain and spine, but minimizes the interference with normal function by focusing on altering the molecular milieu of the target region. Much of molecular neurosurgery is based on the relatively recent capability to introduce genetic

material into cells of the nervous system, or gene therapy. Although there have been relatively few clinical trials of gene therapy for neurologic disorders, the likelihood is that over the next decade, genetic intervention in neurologic diseases will play an important role in improving the quality of life of many patients. *Gene therapy* has become a catch-all term that refers to the introduction of genetic information into cells in the body and using this genetic information to direct the synthesis of proteins that have a beneficial effect in a disease process. A variety of techniques have been developed that fall under the umbrella of "gene therapy," but they may be broadly divided into two categories: in vivo gene therapy and ex vivo gene therapy. In vivo gene therapy involves direct transfer of genetic information into cells in the body, such that the body itself produces the desired protein, be it insulin for diabetes, a clotting factor in hemophilia, a neurotransmitter in neurologic diseases, or others. A number of gene transfer systems have been developed that permit this direct gene transfer, including the application of viruses that have been debilitated so that they are not responsible for disease, but rather act as a means of delivering the gene into a cell. Another approach has been used that is based on developing artificial membranes that can permit introduction into cells. In contrast, ex vivo gene therapy involves transferring genes into tissue or cells that are subsequently implanted or grafted into the body, whereby the desired protein can exert its effect. Examples include the transplantation of transfected tissue now producing dopamine into the brain of animal models of Parkinson's disease.

The advent of gene therapy represents a major breakthrough in medical technology. In the past, most drugs have functioned by interacting with receptors on cells, and these receptors, in turn, conveyed information into the cell, altering its function. Gene therapy, in contrast, is based on direct intervention within the cell, by altering the set of instructions that direct its function, essentially bypassing the need for drug-receptor interactions as a middleman. The result is greater specificity and more efficient opportunities to directly alter the course of a number of human diseases.

Gene Therapy for Parkinson's Disease

Parkinson's disease is a common neurodegenerative disease, affecting more than 600,000 people in the United States alone. It is often insidious and causes significant suffering for its victims and their families. Included among its manifestations are a debilitating tremor, a halting gait, poor coordination, alterations in mentation, and progressive neurologic decline. Drug therapies are available, largely based on replacing the missing neurotransmitter, dopamine, in the brain of patients. Patients typically ingest the biosynthetic precursor to dopamine, l-dopa, or dopamine receptor analogues, which can replace the function of missing dopamine in an area of the brain, the corpus striatum. This region of the brain is largely responsible for the coordination of motor activity in the body; hence, its dysfunction leads to tremor, gait disturbance, and other manifestations. Dopamine also plays a role in cognitive function, and often Parkinsonian patients also demonstrate some degree of impairment.

Although drug therapy has improved the lives of Parkinson's disease patients significantly, the efficacy of these drugs often wears off after several years, and, increasingly within our society, Parkinsonian patients are progressing symptomatically as their response to drugs diminishes.

A number of research programs have pioneered the application of gene therapy techniques for Parkinson's disease.[1] The mainstay of this approach has been to transfer genes responsible for dopamine production into cells within the damaged area of the brain, the corpus striatum. In preclinical studies in cultured cells, and then in animal models of Parkinson's disease (including the rat and primate models), the authors and others have been able to use a variety of viral and nonviral vectors to introduce the key genes responsible for dopamine biosynthesis (including tyrosine hydroxylase and aromatic amino acid decarboxylase), and increase dopamine production in situ. In the animal models, the Parkinson's symptoms reverse, and animals have marked improvement in their neurologic function for up to years following one surgical introduction of the therapeutic vector, compared with controls. A number of research groups have supplemented this dopamine restorative approach with neuroprotective and neuroregenerative gene therapy, which aims to prevent the initial damage in the brain from occurring, and enticing the damaged neurons to regenerate and restore function. Ultimately, a combined approach based on dopamine restoration and neuroprotection and regeneration is likely to offer the best hope for functional recovery in patients with this disease. Much progress has

been made over the past decade in the development of gene therapy for Parkinson's disease, and it is likely that over the next few years, clinical trials will be initiated.

Gene Therapy for Stroke

Stroke is the third leading cause of death in the United States, and its incidence has climbed, with respect to the top two. Unfortunately, by the time a stroke patient reaches medical attention, frequently it is too late to prevent the stroke from occurring. There is, however, a window of opportunity to intervene in patients who have had a stroke, and prevent the stroke from extending the area of damage in the brain. A number of research groups have developed approaches to gene therapy in stroke, differentiating the types of stroke by their pathogenesis. One approach that has been developed is focused on a specific type of stroke that affects more than 30,000 Americans each year, associated with hemorrhage from an aneurysm. As a result of the hemorrhage, within a few days the blood vessels near the hemorrhage constrict, reducing the flow of blood into the brain to a critical level, often resulting in significant ischemic damage to the brain. This blood vessel constriction (or vasospasm) may be amenable to genetic intervention. Gene transfer vectors have been developed that encode proteins (such as the enzyme, nitric oxide synthase) that can be delivered directly into the blood vessel wall, using a catheter which result in the production of substances (such as nitric oxide) that induce the blood vessel to dilate, allowing restoration of normal blood flow. Application of this approach to animal models of brain hemorrhage with vasospasm will allow determination of its clinical applicability to human patients. This approach may also be combined with balloon angioplasty, already used to help dilate vasospastic arteries in the brain.

Another form of stroke is caused by a thromboembolic clot that travels into a blood vessel in the brain and lodges in the small distal branches, or clot that forms inside the blood vessel, blocking blood flow through a blood vessel. As a result, an acute stroke occurs because the affected brain region is denied adequate blood flow, including inadequate delivery of oxygen and nutrients required for normal metabolism. Although the initial damage might not be averted, within 48 hours the damaged, ischemic tissue releases additional excitotoxic substances that then extend the region of the stroke to the neighboring tissue, or penumbra, particularly susceptible to injury. As a result, the stroke expands and the neurologic deficit may increase, leading to further disability in a patient. Approaches toward genetic intervention in stroke have focused on delivering into the penumbral region, or at-risk brain tissue, genes that produce proteins that protect the brain, essentially reducing its likelihood of damage. For example, research groups have developed viral vectors that express human heat shock protein (72 kd) that protects neurons in culture against simulated strokelike conditions. These groups have initiated animal studies, with the hope that this approach can be applied to human patients.

Gene Therapy for Inherited Neurometabolic Diseases

Although less common than some of the disease entities listed previously, the broad realm of inherited metabolic diseases poses one of the most difficult challenges, and creates some of the most individual devastation, faced by patients. Often parents discover that their infant is not developing properly because of an inherited disease, and the child is then condemned to die, or the parents find out even before the child is born that it will suffer significantly from a disease inherited from them. Gene therapy offers, for the first time in many cases, a major advance in the treatment of such diseases. The authors have recently initiated the world's first human clinical gene therapy trial for an inherited neurologic disease, Canavan disease, and have treated 14 children with this rare, fatal disease. Children with Canavan disease are born with a mutation in a single enzyme, N-acetyl-aspartoacylase, which causes accumulation of a toxic compound in the brain, N-acetyl-aspartate. This compound then induces degeneration of white matter in the brain, and the children progressively deteriorate, typically succumbing to the disease process by age 7. Until now, there has been no hope of therapy for these children, but the authors have developed a gene therapy vector that expresses the normal enzyme, and have introduced this by way of intraventricular injection into the brain of these children in a Food and Drug Administration Phase I approved clinical trial, with very encouraging results. This has served as a prototype for other related diseases, some of which are more common.

Gene Therapy for Epilepsy

Although *epilepsy* refers to a number of disease conditions, one of the most common forms of epilepsy is temporal lobe epilepsy, responsible for complex-partial seizures. New medications and new surgical approaches have been developed that offer elimination of seizures in up to 75% of patients, but the costs for these therapies are high, and they have significant side effects. A number of research groups have developed approaches to genetic intervention in epilepsy, based on the concept that by altering the ratio of inhibitory to excitatory neurotransmitters in the mesial temporal lobe (the location responsible for the onset of seizures), the threshold for seizures might be increased, and seizure frequency reduced.[2] In animal models of focal seizure disorders, introduction of gene transfer vectors encoding inhibitory neurotransmitters (such as introducing the gene encoding the enzyme responsible for production of gamma-aminobutyric acid [GABA], the prevalent inhibitory transmitter in the brain), seizures may be arrested completely. Eventual application to human patients suffering from focal seizure disorders is envisaged over the next 2 to 3 years.

Gene Therapy for Brain and Pituitary Tumors

Although there currently are significant limitations in the application of gene therapy to malignant brain tumors, it is possible that over the next decade, based on a better understanding of the molecular mechanisms of tumorogenesis, meaningful progress will be made. At this time, the fundamental problem is that malignant primary brain tumors have fingerlike extensions of malignant cells into normal brain tissue, rendering it impossible to completely remove the tumor or identify abnormal cells through genetic intervention. Use of gene therapy for benign tumors, and in particular pituitary adenomas, however, are more promising. Many pituitary adenomas secrete hormones and are responsive to factors that control hormone secretion and tumor growth. Thus, for example, prolactin secreting adenomas (prolactinomas) often respond to dopamine analogues, because dopamine is the inhibitory substance that controls prolactin secretion. Therefore, by introducing into the pituitary tumor directly those genes that encode enzymes responsible for dopamine production, the need for systemic use of a drug may be obviated. Ongoing studies focused on gene therapy for these tumors suggest that they may be applied within the next few years in human patients.

THE MILLENNIUM HEALTH CARE CRISIS AND THE FUTURE OF NEUROSURGERY

As managed care continues to expand and dominate health care delivery in this country, it has become clear that the dynamic and synergistic relationship between academic medical centers and health care providers is threatened. The expectation is that more care will be delivered for less money, and the providers are to disproportionately bear the burden; however, for new discoveries to occur, particularly within the field of neurosurgery, investment and time are required. As this delicate balance is threatened, so too are the enormous advances made in our country in novel approaches to neurosurgical diseases. If the current trends in our society continue, the exciting possibilities for neurosurgery that may burst into the next century with an accelerating pace of discovery may be threatened. The combination of computer technology and molecular approaches to neurosurgical diseases will offer patients better and longer lives, provided our society recognizes that this is a priority over saving money for profit-oriented health managers and companies.

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