Surgical Treatment of Movement Disorders: DBS, Gene Therapy, and Beyond

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8.1 INTRODUCTION

Disorders of movement represent the frontier of understanding of brain function in that the basic mechanisms underlying normal (and abnormal) movement can be ascribed to individual brain structures, but the detailed functions of these structures and their interactions are not well understood.1–7 The clinical treatment of movement disorders, particularly through neurosurgery, highlights the evolution in understanding nervous system function. In many instances, incompletely proven hypotheses, serendipity, and simple trial-and-error have led to advances in patient treatments prior to a full mechanistic understanding of the disease process or the treatment effect.

For example, the basal ganglia represented completely unknown territory in the 1930s when Russell Meyers began neurosurgical extirpation of the caudate and putamen for various movement disorders. This fascinating history extends to the present day, as radio frequency lesion generation, deep brain stimulation (DBS), and other approaches to disorders of the basal ganglia are proposed and tested in patients with movement disorders.1,6,8

Several factors profoundly influence the development and improvement of treatments for movement disorders. First, the neural systems likely to subserve motor control (basal ganglia, globus pallidus, and ventral thalamus) are still only loosely integrated into schemes that can account for normal motor control, although lesions of these structures are clearly associated with pathological disorders of movement.5 Second, one of the many critical lessons in the treatment of movement disorders is that the functional effects of particular therapeutic interventions may be far different under pathological conditions than they are under normal conditions. Therefore, the impact of many proposed therapies may be somewhat unpredictable.

This chapter provides an overview of the spectrum of movement disorders, discusses the functional connectivity of basic motor-associated circuits in the brain, and reviews current surgical treatments of movement disorders. We hypothesize that the next generation of movement disorder treatments will involve a number of new approaches including more sophisticated sensing and stimulation systems, novel medical delivery systems, new medications, and gene therapy.1,3,7,8 This chapter introduces several preclinical and clinical investigations along these lines, suggesting that clinical applicability of such therapies may potentially follow within the next few years.

8.2 SPECTRUM OF MOTOR ABNORMALITIES

Traditionally, motor disorders are classified into two main groups of abnormalities: those in which movement is hypokinetic or less than normal, and those in which movement is hyperkinetic or greater than normal. Parkinson’s disease is the classic hypokinetic disorder, with bradykinesia and rigidity as hallmarks, although pill-rolling resting tremors are also common.5 This peculiar mix of decreased capability for motion together with tremor produced the historical term paralysis agitans or shaking palsy, still used as a clinical code.
Hyperkinetic movement disorders include tremor, cerebral palsy, chorea, and hemiballismus. Interestingly, in patients with Parkinson’s disease who have been on long-term L-dopa therapy, almost all forms of hyperkinetic movement may also be observed. These treatment-related dyskinesias are relatively newly discovered phenomena, noticed only in the past 20 years when patients have remained on L-dopa therapy for longer periods. Dyskinesia includes any type of dystonic posturing or choreoathetotic movement and may be identical to the hyperkinetic features of primary and secondary dystonias or cerebral palsy. This crossover from a predominantly hypokinetic to a predominantly hyperkinetic movement disorder solely due to treatment effects has blurred the traditional distinctions among movement disorders. As understanding of the genetic basis of movement disorders increases, a more proper classification scheme for movement disorders may become available. Particularly for the dystonias, Parkinson’s disease, and parkinsonian syndromes, this evolution is already taking place.

8.2.1 Parkinsonian Syndromes and Parkinson’s Disease

James Parkinson published his observations on shaking palsy in 1817. The chief clinical symptoms of parkinsonian syndromes are tremor, rigidity, bradykinesia, postural instability, autonomic dysfunction, and frequently cognitive impairment. Parkinsonian syndromes can be the result of Parkinson’s disease or manifestations of many other nonspecific conditions collectively referred to as secondary parkinsonism. Most patients with Parkinson’s disease initially respond to L-dopa therapy; whereas many patients with parkinsonism do not. From this feature arises one initial means of classification for this group of diseases. In both Parkinson’s disease and parkinsonism, many axial symptoms such as freezing and nonmotor symptoms such as autonomic dysfunction are resistant to current medical interventions.

The pathological hallmark of Parkinson’s disease is a loss of cells within the pars compacta of the substantia nigra and the presence of Lewy bodies in a fraction of the remaining cells. The clinical features of parkinsonism arise in a wide variety of degenerative disorders including striatonigral degeneration, progressive supranuclear palsy, corticobasilar degeneration, and Shy–Drager syndrome. Classically, parkinsonism has been observed as a postinfectious manifestation of von Economo’s encephalitis, a disease that peaked in Europe and North America in the early 1920s. Parkinsonism may also result from toxins such as carbon monoxide, methanol, mercury or MPTP from stroke or from head injury.

Initial therapy for a Parkinson’s disease patient can include amantadine, an antiviral agent thought to augment the release of dopamine from striatal neurons; selegiline, a monoamine oxidase inhibitor that slows the intracerebral degradation of dopamine; pergolide, a synthetic ergot derivative that stimulates dopamine receptors; and occasionally vitamin E, an antioxidant. As the disease progresses and the efficacy of these treatments wanes, L-dopa is added to the regimen. L-dopa (or levodopa), a metabolic precursor of dopamine, is the most effective agent for the treatment of Parkinson’s disease. It is typically given with the dopamine decarboxylase inhibitor carbidopa to prevent degradation of L-dopa in peripheral tissues. After 8 to 12 years of levodopa–carbidopa (Sinemet) therapy, patients may begin to
experience the long-term side effects of these medications, including dyskinesias, and may be considered for DBS.\textsuperscript{1,3,8} Stimulating electrodes are placed into the globus pallidus pars interna (GPi) or the subthalamic nucleus (STN). DBS appears to allow a long-term reduction in Sinemet dosage, reducing the severity of medication-induced dyskinesias.\textsuperscript{3,13–15}

Responses to therapies such as surgery are very different for Parkinson’s disease and the other forms of parkinsonism. As a result, the identification of patients with characteristic histories of Parkinson’s disease, including slow progression and L-dopa responsiveness, is very important to the choice of therapy. In addition, not all features of Parkinson’s disease, including eye movement abnormalities and dementia, are responsive to surgical intervention.\textsuperscript{1,7,15} Therefore, patients with predominantly treatment-resistant symptoms must be excluded from surgery.

Despite incomplete responses to therapy, the wide range of medical and surgical interventions attempted in the treatment of patients with parkinsonism or Parkinson’s disease suggests the high level of motivation for treatment present in both the patient and physician populations. Furthermore, the resistance of many symptoms to both medical and surgical therapy, including speech impairments, abnormal postures, gait and balance problems, autonomic dysfunctions, cognitive impairments, and psychiatric disturbances provides goals for the development of new forms of treatment.\textsuperscript{7}

\subsection*{8.2.2 \textbf{TREMOR}}

Tremor is defined as oscillatory movement about a joint. Normal physiologic tremor occurs in a range of 8 to 12 Hz in all muscle groups. Pathological tremor occurs in a range of 4 to 7 Hz and preferentially affects particular muscle groups, such as distal limbs. Pathological tremor may be subclassified into two main categories: action (or postural) tremor and rest tremor.\textsuperscript{5} Action tremor is present during voluntary movement and is absent when limbs are at rest. By contrast, rest tremor is present in repose and suppressed during voluntary movement.

The most common form of action tremor is essential tremor. Such tremor often arises in the second decade of life, may worsen with age, and is most pronounced during attempts to maintain a fixed posture. It typically affects the upper extremities and spares the lower extremities. The tremor is typically worsened with emotion, fatigue, or caffeine and is generally improved with alcohol. Pharmacological therapies for essential tremor include the beta-blocker propranolol and the anticonvulsant primidone. Other forms of action tremor may occur with neurological disorders such as multiple sclerosis or meningoencephalitis.

Rest tremor is commonly noted in Parkinson’s disease.\textsuperscript{5} The coarse 3- to 5-Hz tremor occurs in the distal upper extremities during rest and is absent during sleep. The tremor subsides with action such as lifting a cup, but immediately resumes when the hand is still, such as when a cup is held close to the mouth. In Parkinson’s disease, a mild tremor may be the principal manifestation for many years, with few other manifestations of the disorder. The tremor may respond to pharmacological therapy with the phenothiazine derivative ethopropazine (Parsi dol) or the anticholinergic trihexyphenidyl (Artane). Other forms of rest tremor may occur with other parkinsonian syndromes or Wilson’s disease.
For patients with either action or rest tremor, the condition may be highly disabling. Hence, many patients pursue treatment specifically for the tremor. DBS has been approved for both essential action tremor and parkinsonian rest tremor. The thalamus is the most common target of stimulation.1,3,11

8.2.3 **Generalized, Focal, and Hemi-Dystonia**

Dystonia is a tonic co-contraction of agonist and antagonist muscles in one region of the body, resulting in a transient or persistent extreme of posture.16 Dystonia may involve a focal group of muscles such as an eyelid (blepharospasm), the head and neck (spasmodic torticollis), a hand (writer’s cramp), one side of the entire body (hemi-dystonia), or the entire body (diffuse bilateral dystonia). Manifestations of dystonic conditions may be progressive, initially appearing as mannerisms, and later becoming more persistent.

Many forms of dystonia are idiopathic. However, dystonia also occurs secondary to metabolic disorders such as Wilson’s disease, degenerative disorders such as Huntington’s disease, drug toxicity such as haloperidol intoxication, or cerebral hypoxia. No clear pathologic changes are consistently associated with dystonia. A severe form of heritable, generalized dystonia has been associated with mutations of the DYT1 gene. This disorder, termed torsion dystonia of childhood, involves progression from intermittent and focal involuntary movements to persistent contortions of the entire body. In some instances, dystonia may be occupationally related, such as spasms of the hand (writers), spasms of the hand and neck (violinists), and spasms of the lip (trombonists).

Although L-dopa, bromocriptine, benzodiazepines, and other pharmacological interventions may be helpful in some cases, few dystonia patients generally respond to medical management. In many cases of focal dystonia, therapy consists of transient disruption of muscle function with botulinum toxin. In the past, stereotactic lesioning of the ventrolateral thalamus or the pallidum resulted in substantial improvements in axial symptoms for some patients.11 Recently, pallidal DBS has been applied to the treatment of generalized dystonia.16 Stimulation of the GPi has been observed to improve dystonia, presumably through effects on pallidal afferents and connections to brainstem nuclei. Interestingly, such pallidal stimulation requires a considerable period before showing treatment effects. Unlike the DBS treatment of tremor or Parkinson’s disease, in which symptoms begin to abate within seconds to minutes of DBS lead activation, the symptoms of dystonia may only begin to improve after days to weeks of pallidal stimulation. This slow onset suggests that considerable motor circuitry reorganization is required to achieve observable effects. The mechanisms and motor circuits involved remain unknown.

8.2.4 **Chorea and Choreoathetosis**

Chorea suggests dance-like rapid, involuntary, short-distance movements that vary from simple to quite elaborate. Athetosis refers to a slow, writhing motion resulting from an inability to maintain a fixed position in space. Chorea and athetosis are
observed in Huntington’s disease, post-infectious Sydenham’s chorea, kernicterus-associated basal ganglia injury, and L-dopa associated dyskinesias. Patients with choreoathetosis often attempt to incorporate the involuntary motions into voluntary movements, giving them a bizarre, dramatic character. Medical therapies for choreoathetosis are limited. Haloperidol, a dopamine antagonist, demonstrates some improvement of abnormal movements associated with Huntington’s disease. Although many stereotactic surgical lesions have been proposed as treatments, pallidal lesions and DBS have been the only effective treatments for Parkinson’s disease-associated symptoms.

8.3 BRAIN CIRCUITS CONCERNED WITH MOVEMENT

Multiple regions of the cerebral cortex, basal ganglia, thalamus, cerebellum, and brainstem are involved in the control of movement. In addition, neuronal circuits within the spinal cord contribute to complex motor control. The roles of these multiple, interacting regions to motor control have been roughly delineated, but the details of the functioning of these regions, particularly of the basal ganglia, remain highly controversial. In general, physiological studies observed the activities of various parts of the brain during the performance of specific, stereotyped two- and three-dimensional movements.

The relationship of regional neuronal activity to the initiation of movement and to the direction and type of motion was then observed across multiple trials. It became apparent that primary motor cortex (M1) activity plays a pivotal role in movement and is highly correlated with subsequent action. However, several other motor areas also contribute to movement including pre-motor cortex (Area 6), posterior parietal cortex (PP), and the supplementary motor area (SMA). Two major loops modifying the cortical control of movement include the cortex–basal ganglia–thalamus–cortex loop and the cortex–pons–cerebellum–thalamus–cortex loop reviewed next; brainstem control of axial motion is also examined.

8.3.1 CORTEX–BASAL GANGLIA–THALAMUS–CORTEX LOOP

Among the basal ganglia, the putamen is more involved in motor control than the caudate nucleus, and is tightly linked to the globus pallidus and thalamus. The circuit from cortex to putamen, pallidum, STN, substantia nigra pars reticulata, back to thalamus, and then to the cortex, is clearly involved in motor control. The circuit has an inhibitory effect upon the motor thalamus leading to the theory that the circuit tunes in certain desired actions while suppressing undesired actions. In Parkinson’s disease, the depletion of dopamine in the putamen results in altered output from this loop, significantly slowing movement.

Treatment with L-dopa leads to normalization of movement velocity by correcting the disordered control effect of this loop upon thalamic and cortical outputs. However, a lesion within the GPi for treatment of Parkinson’s disease that theoretically should block the output from this loop actually enhances motion. This
indicates that a reorganization of normal motor control circuits must occur in Parkinson’s disease so that motor output is subserved via alternative parallel pathways.

It is hypothesized that a decrease in dopaminergic input to the striatum in Parkinson’s disease results in reduced direct inhibition of the GPi. In addition, the lack of GPi inhibition of the STN leads to overexcitation of the GPi, particularly because cortical excitatory input to the STN is preserved.\(^5,15\) With less inhibition from the putamen directly upon the GPi and increased excitation of the GPi from the STN, inhibitory output from the GPi to the thalamus is markedly increased, resulting in a suppression of movement output from the thalamus. This model of basal ganglia function suggests that GPi lesions may improve parkinsonian symptoms and thalamic lesions should not. However, thalamic lesions help reduce parkinsonian tremors, suggesting that this model may be incomplete.

### 8.3.2 Cortex–Pons–Cerebellum–Thalamus–Cortex Loop

Cortical efferents from multiple regions project upon ipsilateral pontine nuclei. These nuclei then project into the cerebellum. Cerebellar outputs project to the lateral and posterolateral thalamic nuclei that, in turn, project upon the primary motor cortex. This loop is thought to be important in motor control, particularly during motion. In functional MRI studies comparing real and imagined motions, the cortex and basal ganglia are active in both situations; whereas the cerebellum is only active during real motion.\(^19\)

The inputs to the cerebellum from the periphery are proprioceptive fibers, activated during motion. Many physiological studies suggest that the cerebellum stores motor learning for sequential actions and serves to compare the stored plan for intended movement with the proprioceptive evidence of actual movement. If an error or deviation from the desired action occurs, the cerebellum is proposed to help to restore the intended path by modulating the activity of the motor thalamus.

The cerebellum particularly coordinates multijoint movements. Hence, cerebellar dysfunction is associated with ataxic movement, decomposition of movement into single-joint components, and reduced correction of movement errors. No pharmacological treatments for cerebellar disorders currently exist. The neurotransmitters involved (glutamate and gamma aminobuteric acid or GABA) are highly nonspecific and serve the entire CNS. Furthermore, little improvement of function follows cerebellar injury, unlike neocortical injury. Cerebellar lesions therefore often result in permanent ataxia and gait abnormalities.

### 8.3.3 Brainstem Control of Movement

Both the basal ganglia and cerebellar loops impact motor output through motor thalamic projections to the cortex. By contrast, brainstem nuclei have much more direct effects. The motor cortex (particularly M1) has major direct efferents that project to multiple brainstem and spinal cord nuclei. These brainstem nuclei are particularly important for axial motor control. The red nucleus gives rise to the rubrospinal pathway, the reticular nuclei of the pons and midbrain give rise to the reticulospinal pathway, and the lateral vestibular nucleus gives rise to the
vestibulospinal pathway. The pedunculopontine nucleus lies in a region whose stimulation elicits walking movements. Brainstem lesions result in unwanted flexor and extensor reflex posturing. Such posturing is believed to result from unbalanced brainstem nuclei inputs to the spinal cord, without sculpting and control by the cortex. Lesions of the cortex, basal ganglia, or thalamus result in maintained extremity movement and reduce volitional movement. It appears, therefore, that the brainstem is critical to the maintenance of unconsciously maintained antigravity tone.

Due to complex interactions with the brainstem, abnormalities of axial movement such as dystonia, are more resistant to treatment. Thus, one of the current frontiers of understanding motion is defining the relationship between the cerebral cortex and the brainstem nuclei and explaining how the contributions of these two regions combine and influence spinal cord activities. Among the cortex, the globus pallidus, and the thalamus, the globus pallidus is thought to have a greater influence upon motor control. GPi therefore becomes the primary site to treat axial abnormalities associated with dystonia. However, considerable further research is required to assess whether direct interventions in brainstem areas might prove more effective for the control of axial movement.

### 8.4 CURRENT SURGICAL TREATMENTS

Surgical treatments of movement disorders have varied widely over time, offering a fascinating history of hypothesis-driven surgical therapy and the evolution of effective therapeutic targets. Early surgical treatments of movement disorders consisted of ablative procedures of the known motor system, ranging from ventral rhizotomy to precentral corticectomy. For example, beginning in 1932, Bucy performed subpial resections of the precentral cortex for the treatment of choreoathetosis and tremor. In 1939, Meyer performed a transventricular ablation of the caudate head and body to treat a patient with parkinsonian tremor. Later, Cooper, in attempting to perform a mesencephalic pedunculotomy for parkinsonian tremor, inadvertently tore the anterior choroidal artery. Although the procedure was halted, the patient awoke from anesthesia free of tremor. This led to the discovery that ablation of the medial globus pallidus could relieve parkinsonian tremor.

Along with extirpation of the ansa lenticularis, the abolition of abnormal movements through lesions of the basal ganglia represented a major advance because patients were spared the hemiparesis that accompanied corticectomy, mesencephalic pedunculotomy, lateral cordotomy, and ventral rhizotomy.

### 8.4.1 LESIONS: THALAMOTOMY AND PALLIDOTOMY

With the advent of stereotactic localization techniques in the late 1940s, lesions could be made in the basal ganglia without the risks of open craniotomy. Lesions were produced through freezing with liquid nitrogen cryoprobes or thorough heating with microwave radio frequency probes. Until the early 1950s, the globus pallidus was the stereotactic target of choice for the treatment of parkinsonian tremor. In 1954, Hassler and Riechert reported dramatic improvement of parkinsonian tremor.
following placement of a lesion in the ventrolateral thalamus.\textsuperscript{5,11} Over subsequent years, the thalamus replaced the globus pallidus as the stereotactic target of choice for Parkinson’s disease. Until the early 1990s, the primary surgery performed for any type of movement disorder was thalamotomy, the placement of a lesion in the motor thalamus.\textsuperscript{11} However, Leksell continued to place lesions in the ventral–posterior pallidum for Parkinson’s disease. Eventually these patients were studied as a group, sparking a resurgence of pallidal stereotactic surgery in the 1990s. Laitenen then recognized that the posterior aspects of the pallidum are more important in Parkinson’s disease than the anterior aspects that are more involved in cognitive and frontal lobe function.\textsuperscript{11,22}

The exact target coordinates of a stereotactic lesion depend on treatment purpose (tremor or rigidity) and surgeon preference.\textsuperscript{1,11} Because the radiological landmarks used in stereotactic surgery do not bear a constant relationship to the target nuclei, most surgeons employ physiological monitoring to locate targets. Although some lesion placement is guided by changes in tissue impedance or the effect of transiently cooling tissue, most surgeons monitor involuntary movements, paresthesias, and tremor suppression resulting from transient electrical stimulation.

Outcome studies demonstrate excellent results of lesion surgery in the relief of tremor.\textsuperscript{8,11} In one study, 72% of patients were nearly free of tremor. However, one quarter experienced transient or minor complications including worsening of speech (1.3%), transient contralateral hypotonia (7%), subjective finger or mouth numbness (12%), transient confusion (12%), transient neglect or ataxia of hand (5%), and transient foot dystonia (3%). Radiofrequency lesions carry a risk of hemorrhage, particularly in patients with preexisting hypertension where damage to the vessels of the basal ganglia and thalamus may exist prior to surgery. Leksell reported that stereotactically placed lesions in the posteroventral pallidum produced good long-term mitigation of tremor, bradykinesia, and rigidity in 19 of 20 parkinsonian patients (95%) followed for 1 to 5 years.\textsuperscript{20} In 1992, Laitinen reported a series of 38 patients who had undergone the Leksell posteroventral pallidotomy, monitored postoperatively for 2 to 71 months. At follow-up, 34 (89%) were improved and 92% noted relief of hypokinesia.\textsuperscript{20} Interestingly, patients experienced relief of bilateral symptoms from unilateral lesions. Adverse effects included central homonymous visual field deficits in six patients and transient facial weakness and dysphasia in one patient. Based upon these data, posteroventral (GPi) pallidotomy became the procedure of choice for Parkinson’s disease, particularly because it improved L-dopa-induced dyskinesias.\textsuperscript{11}

Intraoperative high-frequency stimulation during lesion surgery resulted in transient suppression of tremor. This inspired the development of chronic DBS for tremor and Parkinson’s disease.\textsuperscript{1–3,11,15} Enthusiasm for DBS as a treatment of movement disorders increased after the late 1990s, primarily due to perceived lower risks of placement and the possibility of reversibility, compared to the permanent lesions used in thalamotomy and pallidotomy. Despite the general trend away from lesion surgery, however, it should be noted that a randomized trial of pallidotomy versus best medical therapy was stopped early due to the higher than expected efficacy of pallidotomy in relieving Parkinson’s symptoms.\textsuperscript{21} Thus, in spite of the waning enthusiasm for pallidotomy procedures, particularly among patients, the lesions appear to provide excellent long-term relief of many Parkinson’s symptoms, and in
many instances may represent a good alternative to DBS.\textsuperscript{11,21} In addition, considerable interest exists for performing lesions instead of placing stimulating electrodes in the STN.\textsuperscript{22} A potential disadvantage of STN lesions is the hemiballismus known to arise following strokes in the region of the STN. However, this may prove to be a more theoretical concern.

In a study of subthalamotomy, only one in 21 patients experienced unmanageable dyskinesias after surgery and proceeded to DBS placement.\textsuperscript{22} Advantages of lesions over DBS include considerable reductions in surgical costs, the permanent effect of the lesion, the lack of required postoperative care, and higher patient throughput. However, side effects also tend to be permanent, and many believe that DBS therapy is likely to have fewer permanent risks. Of course, this advantage may be balanced by more problems with stimulator programming, infections, late electrical dysfunction, and the need for surgical battery replacement.

### 8.4.2 Deep Brain Stimulation: Thalamic, Pallidal, and Subthalamic

DBS for the treatment of disabling tremor and Parkinson’s disease rose to prominence in the late 1990s.\textsuperscript{1,3,13–15,23,24} Initially, Benabid attempted to suppress disabling tremor with chronic stimulation of ventral intermediate nucleus (VIM) in 26 patients suffering from Parkinson’s disease. Twenty-three patients with thalamic stimulators (67\%) experienced total suppression of tremor when assessed an average of 13 months following electrode placement.

The first commercial DBS system was FDA-approved for placement into VIM for tremor in 1999 and for placement into GPi or STN for Parkinson’s disease in 2002. Currently, practice patterns have shifted considerably with most Parkinson’s patients receiving unilateral or bilateral STN DBS stimulation,\textsuperscript{14} while tremor patients typically receive VIM stimulation. In 2003, DBS was approved for placement into GPi for dystonia.\textsuperscript{16} The mechanism by which DBS achieves its functional effect remains a topic of active research.\textsuperscript{15}

### 8.4.3 Neural Tissue Grafts

Basic mechanisms underlying the integration of embryonic tissue into the adult brain have been studied intensively for more than 30 years, particularly with a view to ameliorating parkinsonism in experimental animal models (see Chapter 2 for discussion of neural grafting for other indications).\textsuperscript{25–29} However, few procedures were performed in human patients with Parkinson’s disease until the mid-1980s. Enthusiasm for tissue grafting into the human brain rose rapidly in 1987, following a dramatic report from Mexico that adrenal medulla autografts into the caudate could improve motor performance in patients with Parkinson’s disease.\textsuperscript{30}

Although the procedure did not follow known principles on tissue preservation and little was known about the chances of survival and integration of the grafts in the brain, there was a rush to replicate the findings. The attempts were unsuccessful, confirming that the transplant conditions were nonphysiological and supporting the established literature mechanisms on transplant survival in the brain.\textsuperscript{31}
Several studies of embryonic grafting were done in the United States. Results of the first long-term studies were published recently\textsuperscript{29,32,33} and showed modest effects on parkinsonian symptoms. Several patients in each study exhibited new, unexpected side effects, particularly dyskinesias.\textsuperscript{9} Several patients required further surgery to control these otherwise untreatable side effects. The recent Swedish experience corroborated both the findings of modest symptom improvements and occurrence of side effects.\textsuperscript{26,34} It also led to considering how to alter grafting conditions and donor cells to improve the clinical outcome, but a clear dose–response relationship comparing cell survival with clinical outcome has not yet been established.\textsuperscript{28,34–36}

In addition to clinical outcome questions, many scientific and ethical issues surround the placement of embryonic human neural tissue grafts into the striatum for Parkinson’s disease.\textsuperscript{37} It is difficult to characterize donor tissue sources. Because of mixing of individual cadaveric specimens, the grafts exhibit immunological diversity, potentially low-cell recovery rates, low graft-cell survival, and lack of cellular migration. Furthermore, acquisition of embryonic tissue is difficult and ethically complex.\textsuperscript{37} No method of standardization of the dose delivered (numbers of surviving cells and their eventual location) exists. In addition, funding for such experimental surgery has been challenging because of the absence of a corporate sponsor. Furthermore, the clinical trial format usually requires a double-blind, placebo-controlled approach.\textsuperscript{38}

Because of the shortage of human embryonic allograft tissue, xenograft (particularly porcine) tissue has been suggested as an alternative.\textsuperscript{28,39,40} However, a trial of porcine embryonic cell therapy by Diacrin/Genzyme resulted in cancellation due to high cost and lack of efficacy.\textsuperscript{39} Finally, the appearance of side effects with embryonic transplants curtailed much of the enthusiasm for further trials.\textsuperscript{9} Whether this pessimism will extend to potential neural stem cell transplantation strategies remains to be seen because the technologies remain under development. Whether the current pessimistic outlook for development of neural grafts as a treatment for clinical disorders will extend also to stem cells remains a significant question.

8.4.4 GDNF: VENTRICULAR/PUTAMINAL INFUSIONS AND GENE THERAPY

Glial-derived neurotrophic factor (GDNF) has been studied extensively as a treatment for Parkinson’s disease due to its specific enhancement and support of dopaminergic neurons.\textsuperscript{41} GDNF was studied as an intraventricular infusion in nonhuman primates with MPTP-induced parkinsonism. In these model animals, striatal dopaminergic neurons demonstrated considerable regrowth, suggesting a role for GDNF in restorative therapy. The results of initial human trials for intraventricular GDNF therapy were disappointing\textsuperscript{42} due to intolerable side effects at doses below the therapeutic threshold. Side effects included intractable nausea and vomiting resulting in significant weight loss and diffuse paresthesias, likely due to GDNF stimulation effects upon sensory ganglia. No improvements in parkinsonian symptoms were noted.
Despite these initial disappointing results, investigators have adopted new approaches for delivery of GDNF to the brain and continue to express optimism that GDNF may provide benefit if delivered to appropriate regions.\textsuperscript{43,44} Results of direct putaminal GDNF infusion have been recently reported.\textsuperscript{45} In this study of five patients, no serious clinical side effects were noted and improvements occurred in both motor symptoms and activities of daily living. In addition, significant increases in dopamine storage in the putamen were observed by positron emission tomography. Both the direct infusion and gene therapy approaches for GDNF delivery to the brain have re-energized the field since considerable dopaminergic fiber regrowth may be noted following adequate GDNF therapy.\textsuperscript{41,43,44}

Direct putaminal infusion of GDNF versus placebo is currently under study in a randomized, double-blinded, multicenter study sponsored by Amgen and Medtronics. Should this study confirm the preliminary results, further pivotal studies may follow. Future studies may considerably further our understanding of long-term drug delivery within the brain and lead to improvements in drug delivery systems. Planning software based upon MRI studies of the brain that consider the relative diffusion of water and therapeutic molecules is currently under development. Such planning programs may eventually allow determination of the precise volume of distribution of a treatment molecule from a point source, taking into account tissue heterogeneity, the structural properties of the treatment molecule, and the rate of administration.

### 8.5 EVOLVING SURGICAL TREATMENTS

A number of new approaches are now being considered for initial human clinical trials, often following promising results from preliminary animal studies. As with many surgical interventions, the level of evidence needed to transition from animal to human feasibility trials varies considerably, depending on sponsorship and regulation. Preliminary human studies tend to be more common when considerable commercial interests are available to initiate and fund research efforts. By contrast, investigator-initiated studies tend to follow a slower pace. The ethics of experimental surgical interventions remains an issue of considerable interest and concern, particularly with regard to the amount of preclinical data required, the nature of the preclinical animal models, and the amount of time allowed to pass before suggesting human trials.\textsuperscript{1,3,8,37}

#### 8.5.1 ADVANCES IN DBS: NEW TARGETS AND STIMULATION PARADIGMS

Many manifestations of Parkinson’s disease are not routinely improved by current DBS or lesion-generating surgery.\textsuperscript{7,15} The manifestations include axial and gait abnormalities, cognitive decline, and autonomic disturbances. Because the motor symptoms of the disease can be extremely disabling, searches for new targets and stimulation paradigms for DBS are ongoing. Novel stimulation targets in the brainstem may provide potential improvements in axial symptoms. However, few studies at present suggest appropriate targets in humans. In addition, potentially important but poorly localized brainstem nuclei such as the pedunculopontine nucleus, may
be substantially more difficult to target than large prominent nuclei such as the red nucleus. Furthermore, the lower brainstem may be a difficult region in which to target and position stimulating electrodes safely. The search for additional targets of DBS may prompt further investigation of the role of brainstem nuclei in axial motor control.1,15

In addition to finding new targets for current DBS technologies, many potential improvements to the DBS device are under consideration. The number of channels and the degree of control over stimulation paradigms could be considerably increased. A large number of ongoing human studies are attempting to improve stimulation methods, for example, by using patterning. Implantation of the DBS might be made easier and more accurate with an advanced frameless stereotactic system that can decrease the time required to sample different targets. The hardware also may be improved. Advanced Bionics markets a cochlear stimulator that can be both flat and skull-mounted and intends to convert the stimulator to a new form of DBS device. Smaller devices would be easier to implant near a burr hole, for example, obviating the current need to tunnel electrode wires long distances to stimulator units in the chest or abdomen. Finally, control of motor abnormalities may become more efficient through the development of feedback-control systems that sense abnormal motions and provide corrective response stimulations (see Chapter 6 and Chapter 7). Such feedback-control systems may work particularly well for tremor control, as opposed to the current, invariant stimulation pattern. Of course, such changes would necessarily increase the complexity of the implanted DBS circuitry.

8.5.2 VIRAL THERAPY: SUBTHALAMIC GLUTAMATE TO GAD CONVERSION

A popular model of Parkinson’s disease suggests that reduced dopaminergic regulation of the striatum leads to STN overactivity. One novel approach under study is to introduce genes into the STN that will induce the production of the inhibitory neurotransmitter, GABA.46 The genes under study are GAD-65 and GAD-67 and they are introduced by viral vector to the STN. This approach demonstrates considerable promise in a rodent model of Parkinson’s disease.47 STN was effectively transformed from an excitatory to an inhibitory phenotype following GAD transfection. In addition, GAD transfection appeared to provide some neuroprotective inhibition of 6-OHDA-induced parkinsonian asymmetry. Of course, many residual questions remain regarding the mechanisms of phenotypic effects. For example, the overall impact of changing the phenotype of the STN on overall basal ganglia function is not clear. In addition, the relevance of the rodent model to human disease with respect to neuroprotection is also uncertain.

Investigators pursuing this viral approach have argued that the system is sufficiently developed in the animal model to begin human testing.46 Difficulties with viral approaches in the past have included a lack of persistent transfection over several months and toxicity due to the viral vectors. The relative absence of a strong immune response to the viral vector in rodents may not translate to humans. As in all viral and gene therapy trials, numerous theoretical safety concerns arise. Hence,
this highly innovative, promising approach not only may have applicability in the clinical setting, but also may have considerable (and unforeseen) consequences as human feasibility studies proceed.

8.5.3 STEM CELL APPROACHES

The degeneration of a specific population of neurons in Parkinson’s disease makes it an attractive target for stem cell therapeutic approaches. Many varieties of self-renewing stem cells have been described. Embryonic stem (ES) cells are pluripotent cells derived from a preimplantation blastocysts; they give rise to all cells in an organism. Multipotent stem cells, such as neural stem cells, are derived from individual organs. The adult human brain contains stem cells capable of forming new neurons and glia. Cells obtained from adults tend to have more limited capacities for development, and are often restricted to lineages for a particular region such as the hippocampus or spinal cord. Neurospheres or balls of cells that contain certain percentages of a clonal population have been derived from most brain regions of embryonic or adult individuals, and can be propagated almost indefinitely in culture. However, differentiation of the cells from neurospheres can be challenging, particularly to obtain neurons. In addition, although appropriate neurospheres have been obtained from many brain regions, cells of dopamine lineages, appropriate for Parkinson’s cell transplants, have been much more difficult to find and culture.

Stem cell approaches have shown some promise in the treatment of Parkinson’s disease, but are accompanied by considerable technical, political, and commercial difficulties. ES cells have been shown to differentiate into functional dopaminergic neurons after transplantation in a rat model of Parkinson’s disease. However, transplanted stem cells may have high teratogenic potential. A patient with Parkinson’s disease died of ventricular obstruction and brainstem compression following transplantation with embryonic mesencephalic dopamine neurons. An autopsy demonstrated teratomas throughout the ventricular system.

Further impediments to progress in stem cell approaches arise from a lack of availability of stem cells for study, highly variable definitions, the different and often proprietary methods to produce stem cells, the political climate against human ES cell research, and the difficulty of producing differentiated cells from undifferentiated precursors. In addition, many of the proprietary stem cell lines propagated in culture are accompanied by specific and severe legal restrictions upon their use, further inhibiting developments in neural grafting. Stem cell neural grafts therefore remain promising future tools, but a decade or more may be required before a clinically effective treatment regimen becomes available.

8.5.4 NOVEL DRUG DELIVERY METHODS

Medications to treat movement disorders are often limited by oral dosing schedules and systemic fluctuations that can lead to considerable motor variability. Although new medications are in development, most act upon dopaminergic signaling. In addition to dopamine agonists and inhibitors of dopamine degradation, new classes of drugs may include dopamine uptake inhibitors, neuroprotective medica-
tions, and opioid or nicotinic receptor modulators. Other approaches may include
direct intracerebral infusion of drugs that are not absorbed orally or are unable to
cross the blood–brain barrier, similar to the system implemented for GDNF delivery
into the brain.45

An advantage of local drug delivery into the brain is that the regional concen-
tration may be maintained at a high level, reducing nonspecific remote actions or
systemic side effects. The development of an effective intracerebral infusion system
and an accurate pharmacological modeling program to guide device placement could
yield substantial therapeutic benefits. In contrast to other schemes, drug infusions
could be easily halted if side effects developed. However, the FDA has not approved
any drugs for direct, intracerebral infusion, although several (e.g., morphine,
baclofen) have been approved for intrathecal infusion into CSF. Pharmaceutical
firms will have to demonstrate significant benefits to obtain such approval, partic-
ularly compared to traditional oral medications, because of the high degree of
invasiveness. Such systems will require direct catheter placement into the brain,
usually performed stereotactically, as well as permanent implantation of one or more
programmable pumps.

8.5.5 Neuroprosthetic Approaches

No effective treatments to reverse the abnormality or improve the motor output
scheme currently exist for many movement disorders. In cerebral palsy, for example,
extensive damage to the basal ganglia and motor system defies medical and surgical
correction even with more sophisticated DBS and other treatment modalities. How-
ever, in many instances, the cortex remains normally functional. In such scenarios,
a neuroprosthetic approach that obtains motor signals directly from the cortex or
from subcortical structures and bypasses damaged regions of the brain may be highly
effective (see Chapter 7 for further examples and discussion).

A neuroprosthetic may be able to drive external actuators to perform desired
tasks that a patient is unable to perform alone (see Chapter 7). The signals obtained
from the cortex might be direct neuronal recordings or local field potential recordings
that may require a large number of neurons to produce a signal with sufficient
information bandwidth for device control. Such approaches currently work for the
control of robotic arms, for example, in nonhuman primates.

8.6 Conclusions

The surgical treatment of movement disorders and Parkinson’s syndrome and disease
in general has developed in concert with clinical and basic science knowledge about
the roles of various motor structures.1,3,6,15 In many cases, treatments have been
performed first, driving further insight into the structures and their functions, par-
ticularly with precentral corticectomy, mesencephalic pedunculotomy and pyrami-
dotomy, and later with basal ganglia and thalamic lesions.11,21 As the use of lesions
has waned, neural tissue transplants have demonstrated the possibility of true restor-
avative surgery, to be further developed along with various types of growth factor
enhancements and stem cell transplants.50
DBS is currently the most frequently performed type of movement disorder surgery, and further development may include additional targets and improved designs, particularly with intermittent demand systems rather than constant stimulation. Further surgical treatments are in development to more radically prevent cell loss in the early stages of Parkinson’s disease, for example, or to switch phenotypes to alter function. It is likely that the fascinating history of surgical treatments and availability driving basic research developments in motor systems will continue for some time, with neurosurgeons potentially leading many advances, due to patient demands for improved treatments.

REFERENCES


