

**Figure 30-27**

Childhood brain tumors occur at any location within the central nervous system. The relative frequency of brain tumor histologic types and the anatomic distribution are shown. (From Kliegman RM, Behrman RE: *Nelson textbook of pediatrics*, ed 18, Philadelphia, 2007, Saunders.)

of a change. Most supratentorial astrocytomas present initially with seizures. Cerebellar astrocytomas produce typical cerebellar findings such as ataxia, and many produce symptoms of increased ICP. Tumors of the cerebral aqueduct or the fourth ventricle, such as an ependymoma or medulloblastoma, typically present at an early stage with headache, nausea, and cranial nerve palsies but also may produce long-tract signs such as hemiparesis. Hydrocephalus is a complication in patients with ependymoma and medulloblastoma, and a late manifestation of brainstem gliomas.<sup>45</sup>

### Diagnosis and Treatment

Diagnosis is by MRI or CT scan, although the CT scan may not be adequate to detect the early stages of brainstem or fourth ventricle tumors. Early treatment includes high-dose dexamethasone, emergency ventricular drainage in the case of hydrocephalus, and surgical resection. Radiation is the principal form of treatment for brainstem gliomas. Postoperative radiation is indicated for medulloblastomas and may be helpful for ependymomas and gliomas. Chemotherapy, although generally not beneficial, has been helpful for medulloblastomas.

The risks of brain radiation therapy in children are of great concern. These may include learning disabilities, hypopituitarism, occlusive disease of cerebral vessels, and radiation-induced secondary tumors. Because myelinization of the CNS is not generally complete until 2 to 3 years of age, radiation therapy performed before this age can be especially devastating and is not usually done.<sup>126</sup> Long-term effects from childhood tumors and treatment have been reported by R. J. Packer.<sup>94</sup>

Spinal cord tumors rarely occur in children. Spinal ependymoma is the most prominent primary intraspinal tumor and has a predilection for the lumbosacral spine. It is treated with resection and radiation therapy. The risks of radiation therapy in children include myelopathy and spinal deformities.

Metastatic spinal cord tumors in children arise most commonly from sarcomas and less often from neuroblastomas, lymphomas, and leukemias. Metastatic tumors in children occur principally by direct extension from an adjacent primary cancer<sup>126</sup> and can be the presenting feature of the primary cancer. This is in contrast to adult spinal tumors, in which access is by a vascular route and usually occurs in the setting of an advanced malignancy.

Because pediatric metastatic spinal cord tumors usually are not associated with extensive vertebral column destruction, they generally can be removed through a simple laminectomy. An aggressive approach to metastatic spinal tumors in children results in a more favorable outcome in children than in adults.<sup>126</sup> Approximately 96% of children have improvement or stabilization of neurologic deficits, and 60% of nonambulatory children regain the ability to walk after treatment.

### Prognosis

Seventy percent of children with brain tumors will be long-term survivors, according to data from the National Cancer Institute's SEER program.<sup>68</sup> At least half of these survivors will experience chronic problems such as focal motor and sensory abnormalities, seizures, cognitive deficits, and neuroendocrine deficiencies like hypothyroidism. Another study showed long-term sequelae in adult survivors of childhood brain tumor such as hearing losses, blindness, and coordination and motor control problems.<sup>68</sup> Rehabilitation can be of help with functional outcomes.<sup>97</sup>

### References

To enhance this text and add value for the reader, all references are included on the companion Evolve site that accompanies this textbook. The reader can view the reference source and access it on-line whenever possible. There are a total of 144 cited references and other general references for this chapter.

# CHAPTER 31

## Degenerative Diseases of the Central Nervous System

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Degenerative diseases of the central nervous system (CNS) can affect grey matter, white matter, or both. The neurodegenerative disorders are characterized by loss of functionally related groups of neurons. The pattern of neuronal loss is selective, affecting one or more groups of neurons while leaving others intact. The cause of the neuronal loss is unknown but is clearly multifactorial. The diseases appear to arise without any clear inciting event in individuals without previous neurologic deficits. The clinical symptoms produced depend on which neuronal populations are lost. Degenerative changes in grey matter diseases interfere with the function of the neuronal cell bodies and synapses. The diseases can affect the cortex, the grey matter of the spinal cord, or both. The most common factor in this group of diseases is the slow deterioration of body functions controlled by the brain and spinal cord.

The neuropathologic findings observed in the degenerative diseases reflect changes in different components. In some disorders there are intracellular abnormalities such as Lewy bodies and neurofibrillary tangles, while in others, there is primary loss of neurons.<sup>29</sup> Some degenerative diseases have prominent involvement of the cerebral cortex, such as Alzheimer's disease; others are more restricted to subcortical areas and may present with movement disorders such as tremors and dyskinesias, such as Parkinson's disease. Demyelination has the major impact on other disorders such as multiple sclerosis. Through genetic and molecular studies of these diseases it is becoming clearer that there are many shared features across the disorders.

Cellular stress is a major component of neurodegenerative disease. When the cell is stressed, the proteins that form filaments and microtubules creating the cytoskeleton can collapse and form perinuclear bundles or clumps of protein aggregates. If the stress experienced by the cell is not lethal, the cell adapts and manufactures several proteins that may restore functional activity of partially denatured proteins. If the proteins cannot be restored, then a process begins to destroy the proteins. If the proteins do not fully degrade, they become clumped together to form intracellular inclusions. The inclusions in neurodegenerative disorders are examples of such aggregates. The aggregated proteins are generally

cytotoxic, but the mechanisms by which protein aggregation is linked to cell death may be different in these various diseases. The histologic characteristics of the inclusions often form the diagnostic hallmarks of these different diseases.

Disorders of movement associated with grey matter destruction are reflected in functional loss and decreased fractionation of movement. Dementia can be present and always represents a pathologic process; dementia, despite popular belief, is not part of normal aging. The majority of the degenerative diseases that affect the basal ganglia are associated with involuntary movements. Disruption of smooth coordination of muscles can be seen in diseases affecting the cerebellum and brainstem. Many of the disorders appear later in life and mimic the normal deterioration of the nervous system that comes with aging.

The cost of care for people with degenerative neurologic disease is significant due to the protracted time of disability before death and the extent of the disability. Although medical science has made tremendous progress in the past few years, degenerative disorders continue to be a challenge to health care providers and a scourge to modern society.

### AMYOTROPHIC LATERAL SCLEROSIS

#### Overview and Definition

Amyotrophic lateral sclerosis (ALS) is a disorder that is generally recognized as an adult-onset progressive motor neuron disease but is also a complex disease process underlying a multisystem illness. It is the most physically devastating of the neurodegenerative diseases. ALS is a progressive disease of unknown cause, characterized by degeneration and scarring of the motor neurons in the lateral aspect of the spinal cord, brainstem, and cerebral cortex, giving rise to the terms *lateral* and *sclerosis* in identifying the disease. Peripheral nerve changes result in muscle fiber atrophy or amyotrophy. The resulting weakness causes profound limitation of movement.<sup>125</sup> Executive dysfunction, characterized by deficiencies in attention, language comprehension, planning, and abstract reasoning, represents cortical involvement.

## Incidence

The incidence of ALS is about 2 per 100,000, with 5000 people in the United States diagnosed each year. In the western Pacific the incidence increases to 14 to 55 per 100,000.<sup>102</sup> Electrodiagnostic equipment for testing may not be available in an area, so there may be greater numbers than are currently identified.

## Etiologic and Risk Factors

Approximately 90% of cases of ALS occur sporadically and are clinically manifest in the fifth decade or later. The cause is unknown. There have been clusters of ALS noted, where there have been three or four individuals living or working in close proximity or individuals participating in the same sport, and military service appears to hold a possible risk for ALS. Chronic intoxication with heavy metals, such as lead or mercury, has been suggested as an etiologic agent, but there still does not seem to be a clear cause. ALS occurs predominantly in men, although bulbar onset occurs more often in women. There may be an increased incidence in white males, with a lower rate reported in Mexico, Poland, and Italy.<sup>125</sup> There appears to be little evidence of active poliovirus in persons with ALS. In fact, there are very few postpolio individuals who develop ALS, and it is postulated that polio may protect against developing ALS. There is an increased incidence of cancer in individuals with motor neuron disease.<sup>26</sup>

Familial ALS (FALS) is an inherited autosomal trait. It occurs in 5% to 10% of all ALS cases. The identification of at least one additional family member with ALS in successive generations is essential for the diagnosis of FALS. Most FALS is inherited in an autosomal dominant pattern and is characterized by an early onset. Family linkage may be missed if there was a death of a family member before the usual age of onset. Copper and zinc superoxide dismutase (SOD1) gene mutation may account for about 15% of cases of FALS. SOD1 genetic testing can be used for genetic counseling in families in which SOD1 mutations are already established.

## Pathogenesis

The pathologic features are primarily degeneration of motor cells in the spinal cord, brainstem, and to a lesser extent the cerebral cortex, with secondary degeneration of pyramidal tracts. Eighty percent of FALS cases have degeneration of the spinocerebellar tract. Dementia may be due to changes in the frontotemporal cortices or in the substantia nigra (basal ganglia). Destruction of large motor neurons of the anterior horn cells is greatest in the cervical and lumbar regions of the cord and between the internal capsule and the bulbar pyramids. Critical neurons are sparse, and the dendrites are shortened, fragmented, and disorganized. Microscopic examination demonstrates a reduction in the number of anterior horn neurons throughout the length of the spinal cord, with associated reactive gliosis and loss of anterior root myelinated fibers. There are similar findings in the cranial nerve nuclei. Diffuse and patchy loss of myelin appears in all areas of the spinal cord except the posterior columns, allowing for preservation of sensation.<sup>132</sup>

Some histologic changes seen in ALS are consistent with those in other lower motor neuron diseases, but there are some changes that may be unique to ALS. Ribonucleic acid (RNA) content is reduced in the damaged and normal neurons in the area. Excessive accumulation of the pigmented lipid (lipofuscin) develops that normally is not seen until advanced age. The production of free radicals may be responsible for the changes in the lipid molecules, eventually causing cell death.<sup>21</sup> Spheroids, the axonal swelling containing packed neurofilaments found in the dendrites and axons distant from the cell body, are found more frequently in the early cases with shorter clinical courses. Spheroids are not found in FALS. The spheroids may represent the slowing of transport in the axon and the abnormal processing of neurofilaments. Inclusion bodies (see Chapter 28) of several types are found in the motor neurons and axons. The skeinlike inclusion consisting of threadlike linear or tubular structures of filaments, similar to Lewy body inclusions, may be specific to ALS. Lymphocytes indicating immunoreaction have been found in the more rapidly advancing cases. Antibodies have been found in some cases of ALS that may indicate involvement of hormones in the immune process; however, there appears to be a poor response to immunologic treatment.<sup>12</sup>

Glutamate, the principal excitatory neurotransmitter in the human motor system, can cause excitotoxic damage when the extracellular glutamate concentration increases. Plasma glutamate levels in individuals with motor neuron disease can be twice that of normal. This may be related to a defect in the transport and breakdown of excitatory amino acids predisposing the person to neurotoxicity, especially noted in males. Environmental toxins may act as excitotoxins.<sup>20,153</sup>

Oxidative damage appears to play a role in the damage to nerve cells in ALS. Calcium-mediated excitotoxicity can generate free radicals. In FALS, the mutated SOD1 appears to cause increased reactivity to hydrogen peroxide and lead to an increase in free radicals. Copper ions in a reduced state will cause this process to become harmful to the neuron. Oxidative damage and glutamate toxicity may interact or potentiate each other. They may also contribute to other mechanisms of motor neuron degeneration, including axon transport abnormalities and apoptosis.<sup>125</sup>

The death of the peripheral motor neuron in the brainstem and spinal cord leads to denervation and atrophy of the corresponding muscle fibers. In the early phases of the illness, denervated muscle may be reinnervated by sprouting of preserved nearby distal motor axon terminals, although reinnervation in this disease is less extensive than in other chronic neurologic disorders.<sup>26</sup>

There is remarkable selectivity of neuronal cell death, involving motor neurons of the brainstem and spinal cord with relative sparing of the oculomotor nuclei. There is eventual spread into the prefrontal, parietal, and temporal areas, as well as into the subthalamic nuclei and reticular formation. In persons kept breathing with ventilatory support, there may eventually be sensory system changes.

### Clinical Manifestations

Cognitive impairments are noted in up to 50% of individuals with ALS. With careful assessment, these deficiencies can be noted early on. Executive function deficits can be found in visual attention, working memory, cognitive flexibility, problem solving, and visual-perceptual skills. Verbal fluency declines before dysarthria develops. The cognitive deficits are due to changes in frontal lobe function and may be related to frontotemporal dementia. Bulbar onset is more predictive of cognitive impairment than limb onset. Pseudobulbar affect, resulting in emotional lability, emotional outbursts, and pathologic laughing or crying, is not related to a psychologic or psychiatric condition and is not a part of the frontotemporal dementia.

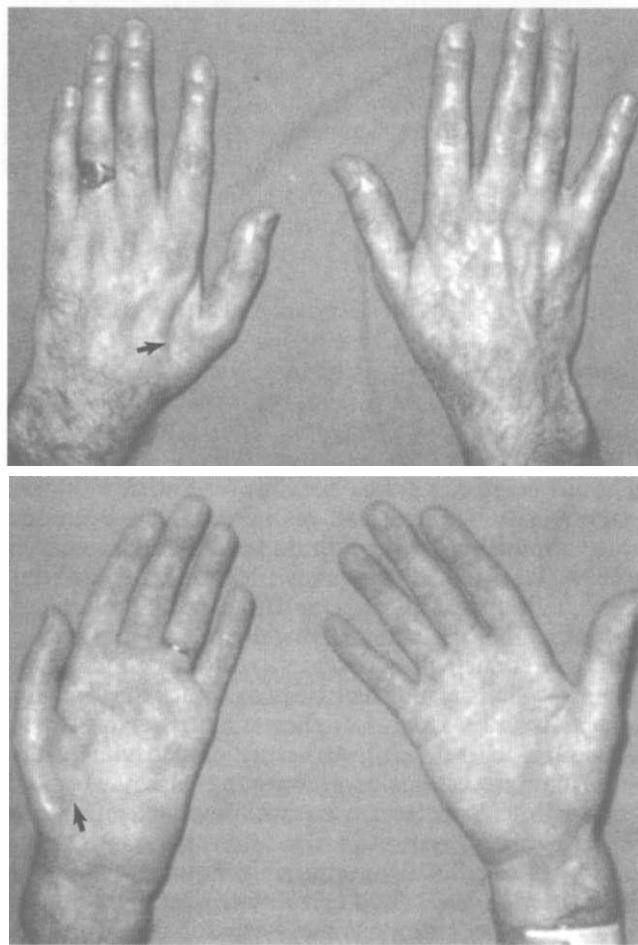
The motor control manifestations of ALS vary depending on whether upper or lower motor neurons are predominantly involved. With lower motor neuron cell death and early denervation, the first evidence of the disease typically is insidiously developing asymmetric weakness, usually of the distal aspect of one limb progressing to weakness of the contiguous muscles. Extensor muscles become weaker than flexor muscles, especially in the hands. Cervical extensor weakness develops and can lead to drooping of the head and pain associated with overstretched muscles. Increased lumbar lordosis occurs as part of the compensatory strategy to attempt to right the head and bring the eyes level.

The neurons innervating muscles controlling articulation, chewing, and swallowing originate in the medulla, or the "bulb," and any weaknesses in the muscles are considered bulbar signs. In the lower motor or flaccid component, facial muscles are affected. Inability to hold the eye closed against pressure is a standard test. Weakness around the mouth develops, and air leaks out. The movement of the tongue is decreased, and atrophy is present. Fasciculations in the tongue are present with lower motor neuron dysfunction. Dysarthria associated with lower motor neuron involvement is reflected by inability to shout or sing, a hoarse or whispering quality of the voice, and nasal tone. Manipulating food inside the mouth becomes difficult. Eventually, weak swallowing may trigger reflex coughing.

Individuals with ALS complain of drooling because of the absence of automatic swallowing, which is made worse by the forward head position. Breathing becomes difficult, and accessory breathing replaces diaphragmatic breathing. Respiratory distress can occur when sleeping, especially on the back.

Deformities of the extremities are common, especially since weakness causes shortening of the extensor muscles. Clawhand develops as the weakness of lumbricals and interossei hinders metacarpal flexion and tenodesis flexes the distal joints. Fig. 31-1 shows the hands of an individual with ALS.

Weakness caused by denervation is associated with progressive wasting and atrophy of muscles. Cramping with volitional movement in the early morning is often reported, with complaints of stiffness. Muscle cramps indicate lower motor neuron dysfunction. It may be related to hyperexcitability of distal motor axons. Early



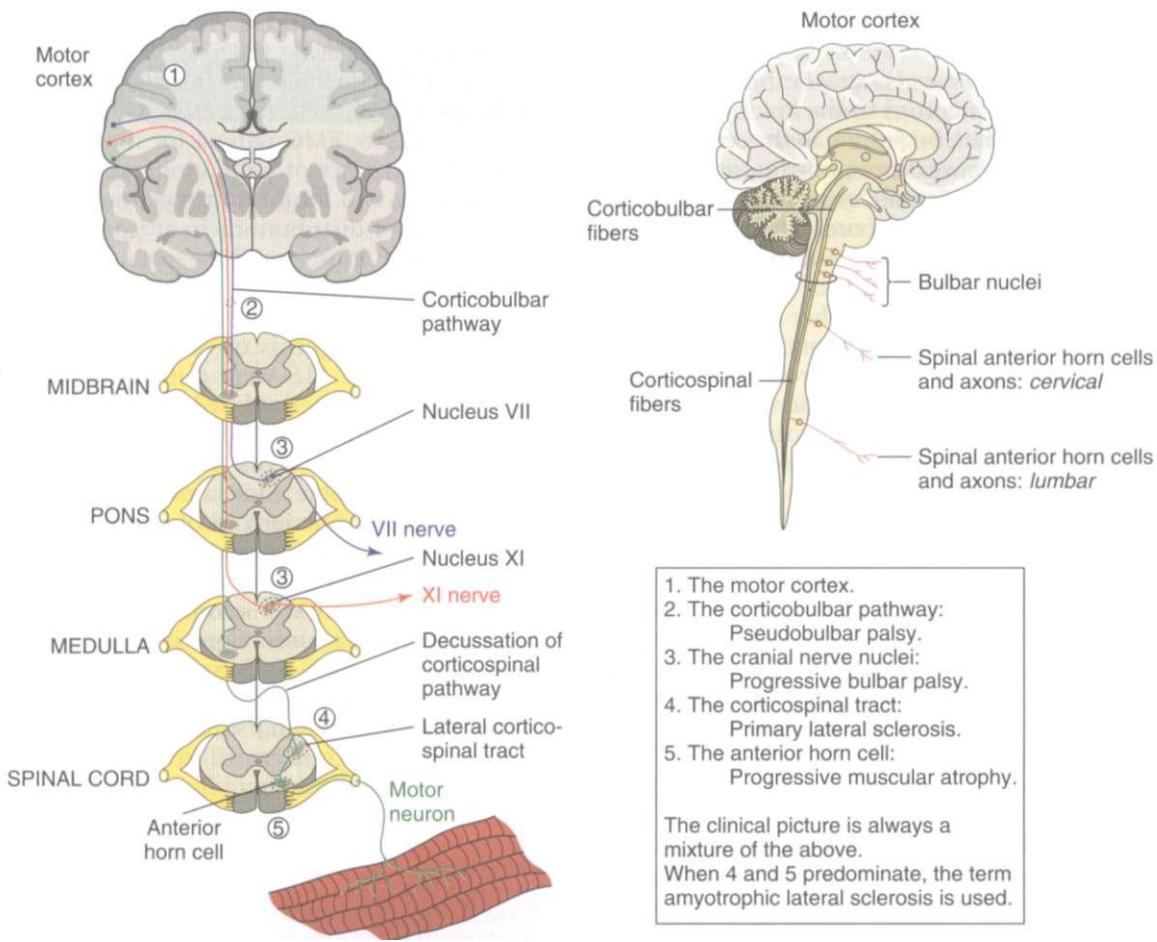
**Figure 31-1**

Wasting of hand muscles in amyotrophic lateral sclerosis. (From Parsons M: *Color atlas of clinical neurology*, London, 1993, Wolfe.)

in the disease there are fasciculations, or spontaneous twitching of muscle fibers. Fasciculations are the result of spontaneous contractions of a group of muscle fibers belonging to a single motor unit. The impulse for the fasciculation appears to arise from hyperexcitable distal motor axons. This is random in time and in muscles affected. It should be noted that both muscle cramping and fasciculations are found in healthy adults and should never be taken alone as a concern for the development of ALS.

Upper motor neuron symptoms are characterized by loss of inhibition and the resulting lack of dexterity and spasticity. Muscle strength is decreased along an upper motor neuron pattern. Extensor muscles of the upper extremity and flexor muscles of the lower extremity are weakened, since spasticity develops as the result of loss of brainstem control of the vestibulospinal and reticular formation control. As in other upper motor lesions, spasticity can limit the ability to accurately assess muscle strength.

Spastic bulbar palsy occurs when upper motor neurons and the corticobulbar fibers controlling speech, mastication, and swallowing are affected. This is termed *pseudobulbar palsy* and differs from the palsy associated with



1. The motor cortex.
2. The corticobulbar pathway: Pseudobulbar palsy.
3. The cranial nerve nuclei: Progressive bulbar palsy.
4. The corticospinal tract: Primary lateral sclerosis.
5. The anterior horn cell: Progressive muscular atrophy.

The clinical picture is always a mixture of the above.  
When 4 and 5 predominate, the term amyotrophic lateral sclerosis is used.

**Figure 31-2**

Areas of damage in the central and peripheral nervous system as a result of amyotrophic lateral sclerosis. (From Lindsay KW, Bone I, Callander R: *Neurology and neurosurgery illustrated*, New York, 1986, Churchill Livingstone. Insert from Noble J: *Textbook of primary care medicine*, ed 3, Copyright 2001, Mosby, Inc., and borrowed from Pryse-Phillips WM, Murray TJ: *Essentials of neurology: a concise textbook*, New York, 1992, Medical Examination Publisher, p 660.)

lower motor neuron loss in the brainstem. Pseudobulbar affect may manifest as inappropriate laughter, irritability, anger, and tearfulness.

The tendon, or muscle stretch, reflexes become hyperactive based on the loss of the Ia inhibitory reflex. This also extends to the development of clonus, in which manual quick stretch of a muscle induces repeated rhythmic muscle contraction. Babinski's response is positive, characterized by extension of the great toe, often accompanied by fanning of the other toes in response to stroking the outer edge of the ipsilateral sole upward from the heel with a blunt object. If there is enough wasting of the dorsiflexors, the response may appear to be flexor despite upper motor neuron involvement.

It is characteristic of ALS that, regardless of whether the initial disease involves upper or lower motor neurons, both categories are eventually implicated. In most persons with ALS, Babinski's and Hoffmann's signs are present or the tendon jerks are disproportionately active.<sup>156</sup> Throughout the course of the disease, eye movements and sensory, bowel, and bladder functions are preserved.

ALS is characterized by differing areas of CNS involvement and has been categorized in terms of four major

groups of symptoms listed below.<sup>67,110</sup> Fig. 31-2 shows the levels of dysfunction associated with the terms that describe them.

1. *Pseudobulbar palsy* reflects damage in the corticobulbar tract.
2. *Progressive bulbar palsy* is a result of cranial nerve nuclei involvement. There is weakness of the muscles involved in swallowing, chewing, and facial gestures. Fasciculations of the tongue are usually prominent. With early bulbar involvement, there can be difficulty with respiration before weakness of the limbs. Dysarthria and exaggeration of the expression of emotion, or pseudobulbar affect, indicate involvement of the corticobulbar tract. The oculomotor system is usually not involved, and eye movement remains normal.
3. *Primary lateral sclerosis* results in neuronal loss in the cortex. Signs of corticospinal tract involvement include hyperactivity of tendon reflexes with spasticity causing difficulty with active movement. Weakness and spasticity of specific muscles represent the level and progression of the disease along the corticospinal tracts. There is no muscle atrophy,

and fasciculations are not present. This form of ALS is rare.

4. In *progressive spinal muscular atrophy* there is progressive loss of motor neurons in the anterior horns of the spinal cord, often beginning in the cervical area. There is progressive weakness, wasting, and fasciculations involving the small muscles of the hands. Other levels of the spinal cord can be the site of the initial disease process, with symptoms reflecting the level involved. These areas of weakness can be present without evidence of higher-level corticospinal involvement, such as spasticity.

ALS with probable upper motor neuron signs is a condition in which there are no overt upper motor neuron signs, but involvement of the corticospinal tracts is indicated by the incongruous presence of active tendon reflexes in limbs with weak, wasted, and twitching muscles. Upper and lower limbs are usually affected first, with progression to facial symptoms and respiratory failure.

## MEDICAL MANAGEMENT

**DIAGNOSIS.** Diagnosis is predominantly made by the combination of clinical presentation and electromyogram (EMG). The time to diagnosis differs, typically according to the first presenting symptoms. With upper limb onset the time to diagnosis is approximately 15 months, with lower extremity onset it is 21 months, and with bulbar involvement as the first sign it is approximately 17 months.<sup>25</sup> Box 31-1 describes diagnostic criteria.

The symptoms are generally first reported to a primary care physician, and it appears that there is a greater delay in reaching the diagnosis in such cases than when the initial symptoms are reported to a neurologist. Often in the early cases and those that are progressing slowly, there may be minimal abnormality on the first EMG, and the changes that lead to diagnosis may not appear for 6 to 12 months. In electrodiagnosis, rapidly progressive ALS shows different changes on the EMG compared with slowly progressive ALS. It is believed that some of these differences come from the adaptation and sprouting that

occur early in the process. This adaptation cannot be sustained as the disease progresses.<sup>100</sup>

EMG studies include the muscles of the extremities and trunk and are selected based on the propensity for weakness in ALS. EMG criteria for the diagnosis of ALS include the presence of fibrillations, positive waveforms, fasciculations, and motor unit potential changes in multiple nerve root distributions in at least three limbs and the paraspinal muscles. These changes occur without change in sensory response.<sup>126</sup>

In 1990 the World Federation of Neurology El Escorial criteria for the diagnosis of ALS were established, and four categories of ALS were outlined (Box 31-2). Suspected ALS is characterized by lower motor neuron signs alone in two or more regions, to which might be added upper motor neuron signs on the basis of the clinical examination. Possible ALS is defined as upper and/or lower motor neuron signs in only one region, possibly with a grouping of upper or lower motor neuron signs in other regions. Exclusion of structural lesions would be attempted. Probable ALS is considered if there are upper and lower motor neuron signs in two regions, and the upper motor neuron signs are above the lower motor neuron signs. Structural lesions must definitely be ruled out by neuronal imaging studies. Definite ALS requires lower motor neuron signs to be present in addition to

### Box 31-1

#### ABNORMAL DIAGNOSTIC FINDINGS IN AMYOTROPHIC LATERAL SCLEROSIS (ALS)

Clinical features of weakness, atrophy, and fatigue  
 Electromyography: shows fibrillations and fasciculations  
 Unstable motor units (in rapidly progressing ALS)  
 Increased duration/amplitudes (in slowly progressing ALS)  
 Low-amplitude polyphasic motor unit potentials  
 Muscle biopsy: shows denervation atrophy  
 Muscle enzymes, such as creatine phosphokinase, elevated  
 Cerebrospinal fluid normal  
 No changes on myelogram

### Box 31-2

#### WORLD FEDERATION OF NEUROLOGY EL ESCORIAL CRITERIA FOR DIAGNOSIS OF AMYOTROPHIC LATERAL SCLEROSIS (ALS)

##### Weakness/Atrophy/Hyperreflexia/Plasticity EMG/NCV/Neuroimaging

Suspected ALS	Possible ALS	Probable ALS	Definite ALS
LMN signs in more than two regions	UMN + LMN signs in one region	UMN + LMN signs in two regions	UMN + LMN signs in three regions
UMN signs in more than one region	UMN + LMN signs in more than two regions Add LMN signs to UMN regions Add UMN signs to LMN regions Exclude structural lesions (Exclude other causes)	UMN + LMN signs in more than two regions Add LMN signs to UMN regions Add UMN signs to LMN regions Exclude structural lesions (Exclude other causes)	UMN + LMN signs in more than three regions (Discern from ALS plus, ALS LAUS, ALS mimics) Exclude structural lesions (Exclude other causes)

From Brooks BR: Introduction: defining optimal management in ALS; from first symptoms to announcement, *Neurology* 53(suppl 5):S1-S3, 1999. EMG, Electromyography; NCV, nerve conduction velocity; LMN, lower motor neuron; UMN, upper motor neuron; ( ), proposal to add this category to diagnostic criteria for ALS, WFN El Escorial Revisited; LAUS, laboratory abnormalities of uncertain significance.

**Box 31-3****DISORDERS THAT CAN MIMIC AMYOTROPHIC LATERAL SCLEROSIS**

- Myasthenia gravis
- Cervical myelopathy
- Multifocal motor neuropathy
- Hypoparathyroidism
- Inclusion body myositis
- Bulbospinal neuronopathy
- Lymphoma
- Radiation-induced effects

upper motor neuron signs in three CNS regions concomitantly with upper or lower motor neuron signs in other regions with structural lesions excluded. Definite EMG signs of lower motor neuron degeneration require the presence of evidence of acute denervation with fibrillations or positive sharp waves and chronic denervation represented by large-amplitude and long-duration motor unit potentials as well as reduced recruitment in each muscle.<sup>24</sup>

There are several disorders that resemble ALS that are treatable. ALS must be differentiated from other conditions that produce a combination of upper and lower motor neuron lesions. Lymphoma and Lyme disease can cause diffuse lower motor axonal neuropathy. Disorders of the cervical cord, such as skull base deformities, syringomyelia, cord tumors, and cervical spondylosis, must be ruled out.<sup>12</sup> Box 31-3 describes disorders that can mimic ALS.

In such cases, however, there should not be any evidence of anterior horn cell involvement in the legs or trunk, but only in the upper limbs. Cervical myelopathy can look like ALS if cord compression is combined with root involvement. The lower motor neuron findings are only in the arms, an important diagnostic feature, and this situation can be confirmed by imaging of the cervical cord and use of EMG to determine if there are fasciculations in the legs. Any signs of disease due to a lesion above the foramen magnum, such as bulbar signs or cranial nerve V or VII nerve involvement, would rule out a cervical cause. Lower motor neuron lesions may be predominant with spinal arachnoiditis (usually syphilitic) and radiculitis, cervical ribs, and peripheral nerve lesions, including the postpolio syndrome. Weakness and wasting are typical of all forms of hereditary motor neuropathy, some of which occur first in adult life, and in hereditary motor and sensory neuropathy. The same findings, although without fasciculations, are also seen in primary muscle disease, rheumatoid arthritis, and myotonic dystrophy. If there is doubt about evidence of anterior horn cell disease in the trunk or legs, EMG should be able to demonstrate that which cannot be seen clinically.

Weight loss may suggest carcinoma, and investigations should be undertaken to rule out underlying malignancy if there is any atypical feature on examination or investigation, such as marked slowing of motor nerve conduction velocities. Most other mimics can be excluded by

history, such as hereditary neuropathy, prior gastrectomy, polio, or electrical injury. Dyspnea may suggest chronic obstructive pulmonary disease or heart failure. Thorough examination will reveal hyperthyroidism or acromegaly. Laboratory tests will reveal lead or other metal poisoning. ALS symptoms may mimic nonneurologic diseases, and neurologic signs may be missed.<sup>25</sup> Involvement of the sensory system or conduction block with evoked potential testing may indicate other neurodegenerative disease processes.

**TREATMENT.** Multiple pathways have been implicated in the pathogenesis of ALS. A medication or combination of medications that targets more than one pathogenic pathway may slow disease progression in an additive or synergistic fashion. Such combination therapy has been successful in oncology, although there are multiple drug interactions and increased incidence of drug side effects. Drug resistance can develop with prolonged periods of medication. Specific targets for therapy are not well defined, and issues of dose, duration, and bioavailability in the diseased state are unknown. Furthermore, the timing of drug initiation is an important factor in determining the response to therapy, which is based on the ratio of reversible and irreversible injury at any time point in the disease.

Riluzole remains the only Food and Drug Administration (FDA)-approved drug for ALS based on the 3-month improvement in survival observed in two large clinical trials. Riluzole has a broad range of pharmacologic effects, including inhibition of glutamate release, postsynaptic glutamate receptor activation, and voltage-sensitive sodium channel inactivation. Riluzole appears to be neuroprotective and slows the disease course by approximately 10% to 15%, but it is not curative. There is controversy over the best time to begin therapy with riluzole.<sup>113</sup> Neuroprotective effects would be more extensive when there are more motor units intact to preserve, and this argument supports early treatment.<sup>38</sup> Asthenia and gastrointestinal side effects are common, and the long-term neurotoxic effects are unknown.

Neuroinflammation occurs in the brainstem and spinal cord of individuals with ALS, suggesting that antiinflammatory agents may be effective in treating this disease. Celastrol is a potent antiinflammatory and antioxidant that suppresses nitric oxide production. Tamoxifen may be neuroprotective in ALS because of its ability to inhibit protein kinase C, which mediates inflammation in spinal cords of individuals with ALS. The drug penetrates the CNS and is generally well tolerated.

Talamppanel is a noncompetitive modulator of ionotropic glutamate receptors primarily under development as an antiepileptic agent. The most common side effects are ataxia and sedation. The antiepileptic properties of talamppanel indicate that the drug crosses the blood-brain barrier.

Agents that decrease aggregation have been hypothesized to be neuroprotective.<sup>180</sup> Scriptaid was identified in a screen for small molecules that disrupt *in vitro* aggresome formation in cultured COS cells transfected with mutant SOD1-GFP. ONO-2506 is similar to valproate and works to restore normal astrocyte functions after

brain damage. This agent has additional antiglutamate and antiinflammatory cyclooxygenase-2 (COX-2) inhibitor properties.

The role of apoptosis in motor neuron degeneration is increasingly recognized. Minocycline is a second-generation tetracycline antibiotic that prevents microglial activation. Typical side effects include gastrointestinal upset, vertigo, and cumulative dose-dependent photosensitivity. Therapeutic manipulation of the programmed cell death pathway could represent one way of improving the disease course. However, concern has been expressed that inhibition of apoptosis could preserve viability of motor neurons that are severely injured and dysfunctional. The best approach might therefore be to combine treatment inhibiting apoptosis with other approaches that target upstream cellular pathways of motor neuron injury.

Memantine is an amino adamantine derivative licensed as a neuroprotective agent for Alzheimer's disease. The drug penetrates the CNS and is well tolerated by individuals with Alzheimer's disease; there is limited study of its use in individuals with ALS.

Myotrophin (insulin-like growth factor I [IGF-I]) appears to affect motor dysfunction by promoting the survival of motor neurons and regeneration of motor nerves.<sup>76</sup>

The high metabolic load of motor neurons and the consequent dependence of these cells on oxidative phosphorylation may make them particularly vulnerable to the loss of mitochondrial function. Coenzyme Q10 is an antioxidant and an essential mitochondrial cofactor facilitating electron transfer in the respiratory chain. This commonly used nutraceutical is being tested in neurodegenerative conditions in which mitochondrial dysfunction has been implicated, including ALS. Dosages up to 3000 mg/day are safe and well tolerated in individuals with ALS. Coenzyme Q10 is lipophilic and effectively crosses the blood-brain barrier. Use of vitamin E as an antioxidant early in the course has been advocated. The impetus for studying and treating individuals with antioxidant therapy is its role in protecting against motor neuron injury.<sup>166</sup>

A ketogenic diet similar to the one employed to control epilepsy may be of some effect as ketones have the ability to alter mitochondrial function and have a positive effect in ALS based on animal studies. However, the diet has yet to be tested in human beings. Researchers have begun studies in individuals with ALS to determine whether similar findings can be demonstrated in human beings. With the possible advent of ketone esters for oral administration, clinical trials of dietary supplements in ALS might be possible in the near future.<sup>167</sup>

Oxidative stress appears to put people at risk for ALS comparable to that found in those with Alzheimer's disease. People at risk for ALS might be identified by use of bioassays showing increased oxidative damage comparable to that in individuals with diagnosed disease. These assays could lead to early intervention and primary prevention.

Although no medication can stop the disease, much can be done in the form of symptomatic therapy. Health care providers should emphasize the value of maintaining the highest level of function throughout the course

of the disease, providing education and support to prepare for the rapid decline in function. Symptomatic measures may include the use of anticholinergic drugs to control drooling and baclofen or diazepam to control spasticity. Dextromethorphan, a drug long used for cough suppression, has been effective in controlling the tearfulness that comes with pseudobulbar involvement.<sup>168</sup>

Maintenance of nutrition is a significant problem because of the difficulty chewing and swallowing. Weakness of jaw movement, loss of tongue mobility, and difficulty in lip closure, in addition to impairment of the swallowing reflex, are common. This may lead to respiratory complications from aspiration. By modifying the consistency and texture of food and fluids, the risk of aspiration is reduced.<sup>169</sup>

There is a shift in the care of individuals with ALS toward the use of multidisciplinary ALS clinics to provide coordinated care. Survival has been found to be longer for individuals with bulbar symptoms, the use of aids and appliances was greater, and the mental quality of life was better for the individuals with ALS treated at the multidisciplinary clinics than for individuals who do not receive specialty clinic care. With focused care, up to 80% of individual with ALS can die at home.<sup>164</sup>

**PROGNOSIS.** The course of ALS is relentlessly progressive. It appears that earlier onset (less than 50 years of age) has a longer course. Death from the adult-onset sporadic type usually occurs within 2 to 5 years, resulting mainly from pneumonia caused by respiratory compromise. In general, those with bulbar palsy have a more rapid course than those with primary lateral sclerosis, in whom the prognosis is markedly better. Respiratory failure and inability to eat are part of the final stages of ALS. Nasogastric tube feeding and use of a respirator may be options to prolong the life of the client. Individual and family wishes concerning these procedures should be discussed as early as possible in the course of the disease, since some clients may experience a rapid decline in function at any time.

## SPECIAL IMPLICATIONS FOR THE THERAPIST 31-1

### ***Amyotrophic Lateral Sclerosis***

#### PREFERRED PRACTICE PATTERN

**5E:** Impaired Motor Function and Sensory Integrity Associated with Progressive Disorders of the Central Nervous System

The ALS-Specific Quality of Life Instrument (ALSSQOL) is based on the McGill Quality of Life Questionnaire (MQOL), modified by changes in format and by adding questions on religiousness and spirituality. A 59-item tool with a completion time averaging 15 minutes, it is a practical tool for the assessment of overall quality of life in individuals with ALS and appears to be valid and useful across large samples. Validation studies of a shortened version are now under way.<sup>164</sup>

The ALS Functional Rating Scale (ALSFRS-R), which can be found at and downloaded from <http://www.>

alsconnection.com/ALSFRS.asp, is a functional scale that can be used to follow the progression of ALS. Six months are needed to detect changes in the ALSFRS-R score because of variability, due principally to differing rates of progression among patients.<sup>66</sup>

The relationship between verbal associative fluency, verbal abstract reasoning, and judgment in ALS can be evaluated using a 20-minute screening evaluation. Deficiencies in these measures were found in 20% to 35% of patients with limb-onset ALS and in 37% to 60% of patients with bulbar-onset ALS. This simple screen identifies deficits that affect discussions of treatment interventions and end-of-life issues.

Muscle strength declines in an overall linear progression throughout the course of the disease. Staging of ALS helps the therapist to determine the most effective intervention based on the current functional status and on the predicted progression of the disease. Table 31-1 describes interventions associated with the various stages of the disease.

The rate of loss is stable within a broad range after the first year, but during the first year there is fluctuation of strength that may be due to the potential for adaptation within the CNS. At this point, the goal of therapy is to maintain general physical activity and muscular tone. Regular exercise in moderation can help alleviate fatigue and have a beneficial effect on the client's general well-being.<sup>17</sup> Complaints of diffuse pain will start in the early stages, related to joint stiffness and decreases in muscle control in the limbs or trunk.

Spasticity contributes to complaints of weakness. Consistent slow stretching that decreases tone may be of benefit. The Ashworth scale can be used to measure the degree of spasticity. Cramps, which can be a source of pain, also respond to a daily stretching routine.

Changes in gait are significant, and gait analysis is necessary to assess the need for assistive devices. Falls caused by weakness are a major problem. Ankle dorsiflexion is lost before loss of strength in plantar flexion. Hamstring strength appears to correlate with walking, and the decrease parallels the loss of walking ability. Isometric muscle strength as a percentage of normal shows a dramatic decrease late in the course of the disease when fewer muscle fibers are available. This is when the greatest functional losses are noted. A surprisingly small amount of muscle activity is necessary across the joints to allow normal function of a joint. Some movement and joint stability are maintained until the degeneration causes atrophy of muscle activity to less than 20% of normal. The weakness and wasting often produce painful subluxation of the scapulohumeral joint, and the arm should be supported.<sup>3</sup> Contractures should be routinely stretched, taking care to support the joints, since there is minimal control of muscle activity in the late stages. Complaints of pain may begin when the client is unable to shift weight in bed or in sitting. Changing the reclining angle of the bed or wheelchair or the position of the legs will give some relief. Caregivers need to be educated in this aspect of care.

Braces, other assistive devices, and motorized scooters or wheelchairs help to maintain mobility and freedom. Many upper extremity devices are available to maintain joint alignment at rest, to make daily activities easier to perform, and to support mobility when it is lost. Braces for the lower extremity can extend the time of upright walking, and braces for the back and neck can assist with head and trunk control. Pain is often a complaint brought to the therapist. Thermal modalities and transcutaneous electrical nerve stimulation can help the pain associated with muscle shortening, joint stiffness, and muscle cramping.

Evaluation of the home environment, providing rails, hoists, or supports; eliminating stairs where possible; and advising on helpful devices for feeding, shaving, dressing is essential as the individual becomes limited to household mobility. Posture for activities of daily living (ADLs) may be improved with a collar, a brace, or spring-loaded splints. Special beds can be leased or borrowed. Family and friends may organize a roster of people to sleep over, sparing the spouse from waking every 3 hours to turn the patient. The legs should be elevated and elastic stockings used if leg swelling is a problem. Avoid using diuretics for leg swelling.

Frustration and boredom are common. Family and volunteers can be mobilized from neighborhood groups, such as church or social groups, to visit to talk, listen, play cards, turn pages or read, or just to be there for a while.

Sexual frustration is common and is not often discussed. The clinician should do so freely and without embarrassment with both the patient and spouse; the problems are mainly matters of method. The partner may need counseling to understand that he or she needs to take the active role and to learn effective techniques that overcome weakness and muscle spasms.

Respiratory changes cause the most disability and eventually lead to death. Respiratory distress is a mechanical problem because of lack of muscle support. From the earliest stages of care of the client with ALS, prevention of respiratory complications should be emphasized. Early evidence of respiratory involvement may be shortness of breath, poor cough reflex, and headache. Some clients can be taught to use their abdominal muscles to increase inspiration and expiration when the muscles of the diaphragm and intercostal muscles become weak. Swallowing becomes difficult and should be evaluated by a speech pathologist. Pseudobulbar affect causing uncontrolled laughing or crying decreases the capacity to regulate breathing and increases risk of shortness of breath. Aspiration is common, and techniques to control this can be taught. Mechanical ventilation is an option to prolong the ability to breathe. Individuals with a relatively slow disease progression, and those with spinal onset, might benefit more from treatment with noninvasive ventilation than patients with rapid disease progression or bulbar onset. Noninvasive positive pressure ventilation (NIPPV) has been shown to improve patient

*Continued.*

**Table 31-1** Exercise and Rehabilitation Programs for Clients with Amyotrophic Lateral Sclerosis

Stage	Treatment
<b>Phase I (Independent)</b>	
<b>Stage I</b>	
Patient characteristics	
Mild weakness	Continue normal activities or increase activities if sedentary to prevent disuse atrophy
Clumsiness	Begin program of ROM exercises (stretching, yoga, tai chi)
Ambulatory	Add strengthening program of gentle resistance exercises to all musculature with caution not to cause overwork fatigue
Independent in ADLs	Provide psychologic support as needed
<b>Stage II</b>	
Patient characteristics	
Moderate, selective weakness	Continue stretching to avoid contractures
Slightly decreased independence in ADLs	Continue cautious strengthening of muscles with MMT grades above F+ (3+); monitor for overwork fatigue
Difficulty climbing stairs	Consider orthotic support (i.e., AFOs; wrist, thumb splints)
Difficulty raising arms	Use adaptive equipment to facilitate ADLs
Difficulty buttoning clothing	
Ambulatory	
<b>Stage III</b>	
Patient characteristics	
	Continue stage II program as tolerated; take caution not to fatigue to point of decreasing patient's ADL independence
	Keep patient physically independent as long as possible through pleasurable activities, walking
	Encourage deep-breathing exercises, chest stretching, postural drainage if needed
	Prescribe standard or motorized wheelchair with modifications to allow eventual reclining back with head rest, elevating legs
<b>Phase II (Practically Independent)</b>	
<b>Stage IV</b>	
Patient characteristics	
	Perform active-assisted, passive ROM exercises to the weakly supported joint—take caution to support, rotate shoulder during abduction and joint accessory motions
	Encourage isometric contractions of all musculature to tolerance
	Try arm slings, overhead slings, or wheelchair arm supports
	Motorize chair if patient wants to be independently mobile; adapt controls as needed
<b>Stage V</b>	
Patient characteristics	
Severe lower extremity weakness	Encourage family to learn proper transfer, positioning principles and turning techniques
Moderate to severe upper extremity weakness	Encourage modifications at home to aid patient's mobility and independence
Wheelchair dependent	Provide electric hospital bed with antipressure mattress
Increasingly dependent in ADLs	If patient elects HMV, adapt chair to hold respiratory unit
Possible skin breakdown secondary to poor mobility	
<b>Phase III (Dependent)</b>	
<b>Stage VI</b>	
Patient characteristics	
Bedridden	For dysphagia: provide soft diet, long spoons, tube feeding, percutaneous gastrostomy
Completely dependent in ADLs	To decrease flow of accumulated saliva: provide medication, suction, surgery
	For dysarthria: use palatal lifts, electronic speech amplification, eye pointing
	For breathing difficulty: provide airway clearance, tracheostomy, respiratory assist if HMV elected
	Provide medications to decrease impact of dyspnea

Modified from Sinaki M: Exercise and rehabilitation measures in amyotrophic lateral sclerosis. In Yase Y, Tsubaki T, eds: *Amyotrophic lateral sclerosis: recent advances in research and treatment*, Amsterdam, 1988, Elsevier.  
ADLs, Activities of daily living; ROM, range of motion; MMT, manual muscle test; AFOs, ankle-foot orthoses; HMV, home mechanical ventilation.

quality of life, despite progression of ALS, and without increasing the caregiver burden or stress.<sup>75</sup> In addition, suction, intermittent positive pressure breathing, and postural drainage appear to be useful in maintaining bronchial hygiene. Only 5% of individuals choose long-term, invasive ventilation because of the restriction of activity, caregiver involvement, and overall cost.<sup>76</sup> Communication becomes limited, again because of loss of oral muscle control and breath support. Communication strategies can be taught, and augmentative equipment is available. In all cases the individual becomes dependent over time. In the terminal stages, the comfort of the patient is the therapeutic goal.

As patients with ALS weaken, the decisions facing the patient progress from issues of morbidity to mortality. Traditionally, the neurologist and other therapeutic support staff have deferred to the wishes of the patient and family members in determining level of support in response to progressive physical decline. Impairments in judgment have potentially significant clinical implications that should be considered by health care providers and caregivers when discussing treatment interventions and end-of-life issues with these patients.<sup>60</sup>

All patients with ALS and their families have to come to grips with the many end-of-life decisions that confront them. These include the need to get the many events in life in order, come to terms with relationships, and decide how forthcoming disabilities will be handled. Decisions regarding care at home versus in a nursing facility should be made as early as possible. Information about advance directives, living wills, and power of attorney should be available. Patients may raise the question of suicide or assisted suicide, and the caregivers should be comfortable not only talking about these issues but also calling on others who may have more expertise and experience in discussing these issues. It makes things more difficult for the patient and family if the caregivers avoid these sensitive areas and talk only about the disease and medical management. Psychologic and emotional support for the individual and the family is critical. A direct and informative approach is appreciated; giving false hope should be avoided.

## ALZHEIMER'S DISEASE, ALZHEIMER'S DEMENTIA, AND VARIANTS

### Overview and Definition

The two terms *Alzheimer's disease (AD)* and *Alzheimer's dementia* are related but not synonymous. AD is the disease process that ultimately results in Alzheimer's dementia. Alzheimer's dementia has a characteristic cognitive pattern. In some individuals, early in the disease course AD may cause memory loss of insufficient severity to warrant the designation of dementia. In other individuals, AD may follow an atypical course with progressive aphasia or progressive apraxia rather than a typical

Alzheimer's dementia. Most of the time AD causes Alzheimer's dementia.

Dementia is a term for a decline in intellectual functioning severe enough to interfere with a person's relationships and ability to carry out daily activities. A significant decline in memory is a hallmark of dementia but is not the only characteristic. Age-associated memory impairment, or benign senescent forgetfulness, is a decline in short-term memory that does not progress to other mental or intellectual impairments. Other causes of dementia must be carefully ruled out, and there are syndromes that mimic AD in relationship to the dementia but have different neurologic causes. Listed here are a few of the other dementias that cause change in cognitive status.

**Pick's Disease.** Much less common and sometime clinically indistinguishable from AD, Pick's disease is characterized by cortical atrophy involving predominantly the frontal and temporal regions with sparing of the posterior two thirds. Loss of frontal inhibition of socially unacceptable and previously suppressed behavior emerges early in the disease, often overshadowing the memory disturbance. The inclusions are known as Pick bodies. The neurons balloon in the area of involved tissue, but there are not the plaques or tangles seen in AD.

**Lewy Body Dementia.** This disorder exhibits highly variable clinical and neuropathologic overlap with AD and Parkinson's disease. It is characterized by initial parkinsonism unresponsive to standard medications, progressing to deterioration of cognition. Cellular changes include presence of the Lewy bodies found in Parkinson's disease and neurofibrillary tangles, senile plaques, and granulovacuolar degeneration similar to those in AD.

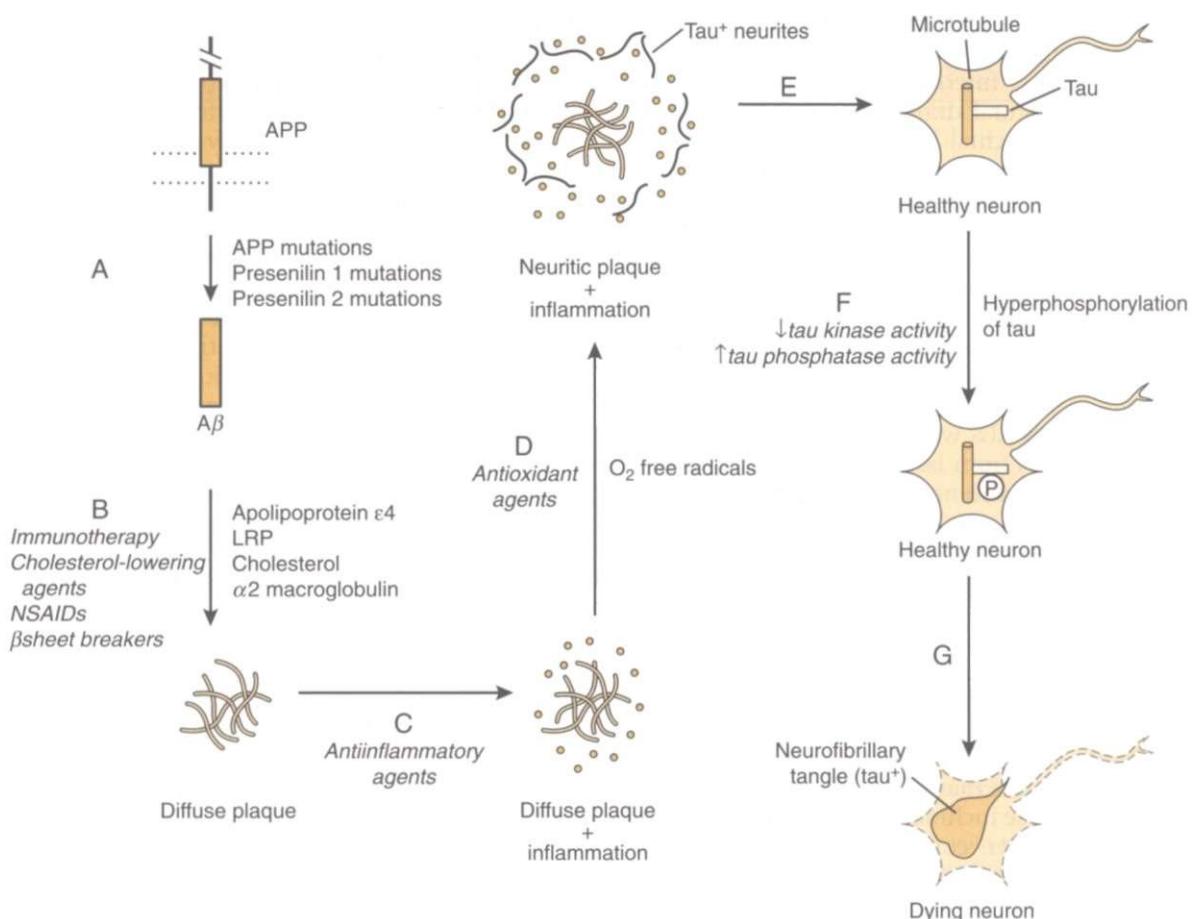
Corticobasal ganglionic degeneration is characterized by striking asymmetrical gait and speed apraxia, "alien hand" syndrome, rigidity, myoclonus, and cortical sensory loss. Dementia is usually a late manifestation of the disease.

**Frontotemporal Dementia.** This term is used to describe the various progressive disorders that have a predilection for the frontal lobes. The cellular neuropathology is variable, and in some cases it seems to be the frontal lobe manifestations of AD, Pick's disease, and Lewy body dementia.

AD is the most common cause of dementia overall. It is one of the principal causes of disability and decreased quality of life among older adults.<sup>3</sup> Progress in clinical knowledge of AD has led to more reliable diagnostic criteria and accuracy; the earliest manifestations and even the presymptomatic phases of the disease may soon be identifiable.

### Incidence and Etiologic and Risk Factors

There are approximately 4 to 4.5 million people with AD in the United States and 8 million affected around the world. Barring a cure, by 2050 this number will increase by almost threefold, to 13.2 million. The prevalence of AD rises with each decade of age. The known prevalence is 6% in people over 65 years of age, 20% in people over 80 years of age, and more than 95% in those 95 years of age.<sup>193</sup> Because life expectancy continues to rise, so does



**Figure 31-3**

The amyloid cascade hypothesis of Alzheimer's disease pathogenesis and potential therapeutic targets. (In Goetz CG: *Textbook of clinical neurology*, ed 3, Philadelphia, 2007, Saunders.)

the potential for more individuals to be afflicted. It is believed that many individuals with the symptoms go undiagnosed and untreated. The cause of AD remains unknown, but there appears to be a relationship among genetic predisposition; the abnormal processing of a normal cellular substance, amyloid; and advanced age.<sup>87</sup> Lifetime risk of developing AD is estimated to be between 12% and 17%. Twin studies show evidence that in identical twins, one may develop AD while the other remains dementia free. People with a family history of the disease are at higher than average risk for AD. Researchers are identifying important genetic factors, notably the apolipoprotein E ε4 (ApoE4) gene.

The ApoE ε2 allele (ApoE2) may be protective, and the ApoE ε4 allele (ApoE4) is associated with increased risk. The amyloid precursor protein (APP) gene is located on chromosome 21. Studies have reported the greatest deposits of β-amyloid in people with ApoE4, which is now believed to be a major risk factor for late-onset AD. Some evidence suggests that the ApoE protein removes β-amyloid but that the ApoE4 variant does so less efficiently than other ApoE types.

People inherit a copy of one type of allele from each parent, but AD is not inevitable, even in people

with two copies of the ApoE4 allele. People without ApoE4 have an estimated risk of between 9% and 20% for developing AD by age 85. In people with one copy of the gene, the risk is between 25% and 60%. In people with two copies, the risk ranges from 50% to 90%. But only 2% of the population carries two copies of the ApoE4 allele.

Genetic mutations in the genes that control APP are also being targeted as causes of early-onset AD. In the genetic disease Down syndrome, for example, β-APP, the source of β-amyloid, is overproduced, which almost always leads to early AD.

Mutations in genes known as presenilin 1 (PS1) and presenilin 2 (PS2) account for most cases of early-onset inherited AD. The defective genes appear to accelerate β-amyloid plaque formation and apoptosis, a natural process by which cells self-destruct.

Mutations of these and other genes have been identified and provide strong support for the "amyloid cascade hypothesis" of AD (Fig. 31-3). Although the amyloid cascade is currently considered by many researchers as a key contributor to the pathogenesis of AD, some researchers have challenged this assertion and have proposed that β-amyloid occurs secondary to neuron stress and func-

tions as a protective adaptation to the disease rather than causing cell death.

The same genes may have different effects depending on the ethnic population. Dietary and other cultural factors that increase the risk for hypertension and unhealthy cholesterol levels may also play a role. For example, a study of Japanese men showed that their risk increased if they emigrated to America. And the disease is much less common in West Africa than in African Americans, whose risk is the same as or higher than that of Caucasians Americans.

Some studies have reported an association between AD and systolic hypertension (the higher and first number in blood pressure measurement). Furthermore, some studies report a lower risk for AD in individuals whose blood pressure was reduced. Nevertheless, although hypertension is strongly linked to memory and mental difficulties, stronger evidence is needed to prove any causal relationship between hypertension and AD.

There has been research suggesting an association between high cholesterol levels and AD in some people. A number of recent studies support the link between AD and cholesterol by suggesting that certain cholesterol-lowering drugs known as statins may be protective against AD. The ApoE genotype is linked with both atherosclerosis and AD. The ApoE4 genotype reflects abnormal cholesterol transport.<sup>191</sup>

Box 31-4 outlines some of the key risk factors as well as possible protective factors related to AD.

### Pathogenesis

Like other degenerative conditions, AD has no single identified cause. The loss of neurons is thought to be due to the breakdown of several processes necessary for sustaining brain cells. There are several neuropathologic hallmarks of AD. There is progressive accumulation of insoluble fibrous material, amyloid. Senile plaques consisting of extracellular amyloid are found in higher concentrations in the brains of individuals with AD than in normal aging brains. The amyloid deposition appears to

have a relationship to  $\beta$ -amyloid protein, a natural substance that is required to maintain fibroblasts and cell function. Components of this protein occur typically as a by-product of neuron function. Normally, the p-amyloid dissolves and is reabsorbed by the brain tissue. When it remains in the fluid surrounding the neurons, the  $\beta$ -amyloid protein may deform its shape by folding in on itself. This abnormal protein then sticks together with other  $\beta$ -amyloid material, forming a sheet of connected proteins; the result is a plaque. The amyloid plaque also includes fragmented axons, altered glial cells, and cellular debris. This plaque triggers an inflammatory response, resulting in increased free radicals that cause damage to the nervous system. Other inflammatory factors of specific interest in Alzheimer's research are the enzyme COX and its products, called prostaglandins.

APP is a large nerve-protecting protein that is the source of  $\beta$ -amyloid. In AD certain enzymes, particularly those called  $\gamma$ -secretases, snip APP into p-amyloid pieces. This process is controlled by presenilin proteins. Genetic abnormalities that affect either APP or presenilin proteins occur in some inherited cases of early-onset AD. Another important protein in the areas of the brain affected by AD is endoplasmic reticulum-associated binding protein (ERAB), and it appears to combine with  $\beta$ -amyloid, which in turn attracts new  $\beta$ -amyloid from outside the cells. High amounts of ERAB may also enhance the toxicity of  $\beta$ -amyloid.

It appears that the amyloid plaque, when it comes in contact with a neuron, causes chemical changes that may lead to the destruction and destabilization of microtubules, the structural components of the neural cells. A protein molecule called tau normally responsible for holding the microtubules together detaches and causes the microtubule to disintegrate. This process may be due to an enzyme that escapes its normal restraints and breaks down the tau. As the microtubule disintegrates, neurofibrillary tangles form and remain in the system. The overall effects are decreased cell division and loss of axonal transport of neurotransmitters. Fig. 31-4 shows a typical neuritic plaque and neurofibrillary tangle.

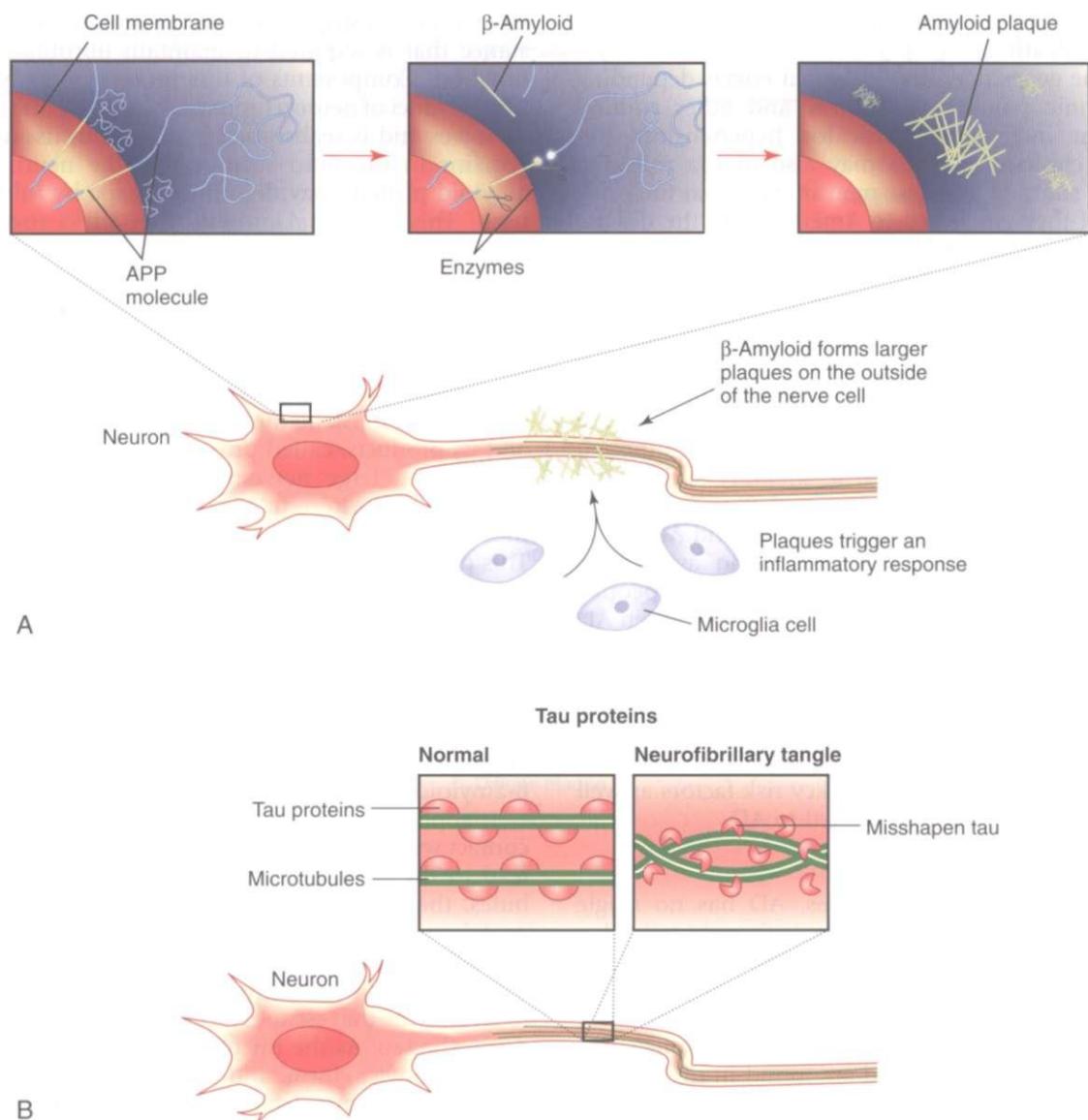
AD is characterized by disruptions in multiple major neurotransmitters, of which cholinergic abnormalities are the most prominent. Acetylcholine is an important neurotransmitter in areas of the brain involved in memory formation, and loss of acetylcholine activity correlates with the severity of AD. The reduction in the number of acetylcholine receptors precedes other pathologic changes, and these receptors are reduced significantly in late AD, particularly in the basal forebrain. There is selective loss of nicotinic receptor subtypes in the hippocampus and cortex. Presynaptic nicotinic receptors control the release of neurotransmitters important for memory and mood, such as acetylcholine, glutamate, serotonin, and norepinephrine. There is still some question whether this plays a primary role in the disease or is a secondary reaction.

Synaptic loss is the best pathologic correlate of cognitive decline, and synaptic dysfunction is evident long before synapses and neurons are lost. Once synaptic function stops, despite the number of surviving neurons, there may be little chance of changing the disease process.

#### Box 31-4

##### KEY RISK FACTORS AND PROTECTIVE FACTORS FOR ALZHEIMER'S DISEASE

- Primary risk factors: age; family history; genetic markers such as apolipoprotein E  $\epsilon 4$  gene; trisomy 21; mutations in presenilin 1 and 2; female gender after 80 years of age; cardiovascular risk factors such as hypertension, diabetes, obesity, and hypercholesterolemia
- Possible risk factors: head injury; depression; progression of Parkinson-like signs in older adults; lower thyroid-stimulating hormone (TSH) level within the normal range; hyperhomocysteinemia; folate deficiency; hyperinsulinemia; low educational attainment
- Possible protective factors: apolipoprotein E  $\epsilon 2$  gene; regular fish consumption; regular consumption of omega-3 fatty acids; high educational level; regular exercise; nonsteroidal antiinflammatory drug therapy; moderate alcohol intake; adequate intake of vitamins C, E, B6, and B12, and folate



**Figure 31-4**

Current etiologic theories for the development of Alzheimer's disease. **A**, Abnormal amounts of  $\beta$ -amyloid are cleaved from the amyloid precursor protein (APP) and released into the circulation. The  $\beta$ -amyloid fragments come together in clumps to form plaques that attach to the neuron. Microglia react to the plaque, and an inflammatory response results. **B**, Tau proteins provide structural support for the neuron microtubules. Chemical changes in the neuron produce structural changes in tau proteins. This results in twisting and tangling (neurofibrillary tangles). (From Lewis SM: *Medical-surgical nursing (single volume): assessment and management of clinical problems*, ed 7, St. Louis, 2007, Mosby Elsevier Health Science.)

Glutaminergic neurons appear to be prone to formation of neurofibrillary tangles. It appears that the most vulnerable group of cortical neurons is the pyramidal cells with corticocortical and hippocampal projections. Other subgroups of neurons are resistant to the degenerative process, such as the projections from primary sensory to adjacent secondary sensory areas. Increased excitotoxicity due to increased glutamatergic stimulation of N-methyl-D-aspartate (NMDA) receptors results in abnormally high levels of intracellular calcium and may ultimately lead to cell death.

There appears to be a hierarchy of cortical connection systems that are affected differently during the course of

AD. A progression of the neurofibrillary tangles seems to move from the entorhinal cortex and hippocampus to the limbic system to the cortex, including the frontal, temporal, parietal, and occipital cortices. One study suggests that the effect of AD on hippocampal volume equals the effect of roughly 17 years of aging.<sup>189</sup> This may correlate with the changes seen in memory, behavior, and motor skills as the disease progresses. The distribution of the lesions in the cerebral cortex may be different in AD compared with that in other disease processes that cause dementia.

Cerebral amyloid angiopathy (CAA) may predispose an individual to develop AD. CAA is an important feature of senile dementia and AD along with senile plaques,

**Table 31-2** Differences Between Normal Signs of Aging and Dementia

Normal	Dementia
<b>Early Signs of Alzheimer's Disease</b>	
<b>Memory and Concentration</b>	
Periodic minor memory lapses or forgetfulness of part of an experience.	Misplacement of important items.
Occasional lapses in attention or concentration.	Confusion about how to perform simple tasks.
	Trouble with simple arithmetic problems.
	Difficulty making routine decisions.
	Confusion about month or season.
<b>Mood and Behavior</b>	
Temporary sadness or anxiety based on appropriate and specific cause.	Unpredictable mood changes.
Changing interests.	Increasing loss of outside interests.
Increasingly cautious behavior.	Depression, anger, or confusion in response to change.
	Denial of symptoms.
<b>Later Signs of Alzheimer's Disease</b>	
<b>Language and Speech</b>	
Impaired language skills.	Difficulty completing sentences or finding the right words.
	Inability to understand the meaning of words.
	Reduced and/or irrelevant conversation.
<b>Movement/Coordination</b>	
Increasing caution in movement.	Visibly impaired movement or coordination, including slowing of movements, halting gait, and reduced sense of balance.
Slower reaction times.	
<b>Other Symptoms</b>	
Normal sense of smell. No abnormal weight changes in either men or women.	Impaired sense of smell. Severe weight loss, particularly in female patients.

Data from Junior League of the City of New York: *Alzheimer's disease: early warning signs and diagnostic resources*, New York, 1988, The League.

neurofibrillary tangles, neutrophil threads, and synapse loss. Amyloid gradually causes atrophy of the medial smooth muscle cells of the arteries of the brain that weakens them, causing predisposition to hemorrhage.<sup>135</sup> There appears to be a relationship between strokes and AD. (See Chapter 32.) Abnormalities have been reported in fibroblasts, red and white blood cells, and platelets. Alterations in blood proteins have been observed. The role of these peripheral changes is not clear.<sup>107</sup>

### Clinical Manifestations

The early symptoms of AD may be overlooked because they resemble signs of natural aging. Still, older adults who begin to notice a persistent mild memory loss for recent events may have a condition called mild cognitive impairment (MCI). MCI is now believed to be a significant sign of early-stage AD in older people. Studies now suggest that older individuals who experience such mild memory abnormalities convert to AD at a rate of about 10% to 15% per year.

Disorders of function are found in the person with AD that correlate with the level of damage in the various components of the cortex as described earlier. Visuospatial deficits are an early clinical finding. Navigating the environment, cooking, and fixing or manipulating mechanical objects in the home are all visuospatial tasks that often are impaired in the first stages of AD. Drawing is abnormal; the ability to draw a three-dimensional object is often lost. The loss of ability to solve mathemati-

cal problems and handle money is typical in the early stages of AD. Judgment is impaired, and safety in driving is diminished.

Subtle personality changes occur in AD, such as indifference, egocentricity, impulsivity, and irritability. People with AD become withdrawn and anxious. Memory is affected, and this is seen as inability to recall current events. Studies show that particular memory subsystems are relatively more or less vulnerable to diffuse cortical pathologies.<sup>11</sup> People with AD seem to retain higher capacity in implicit memory than was originally thought. AD causes loss of older memories, and recall of events from early life disappears. Language declines in a characteristic progression. Word-finding difficulty is first, followed by inability to remember names (anomia), and finally diminished comprehension. Social situations become difficult, and mood swings are common.<sup>119</sup> Between 40% and 60% of individuals with late-onset AD suffer from psychotic symptoms, which may include hallucinations, delusions, and dramatic verbal, emotional or physical outbursts. This is a severe form of AD, with a genetic basis, that has a more rapid and aggressive course. Table 31-2 describes the difference between normal aging and AD.

Major depression is uncommon, but many persons with AD have periods of depressed mood associated with feelings of inadequacy and hopelessness. AD-associated depression is often more modifiable by environmental manipulation than depressions not associated with AD.

As AD progresses, delusions, agitation, and even violence may occur.

Abnormal motor signs are common, related to the area of the brain that is involved, and perhaps due to the type of neurotransmitter dysfunction. A relationship between the motor impairments and levels of function can be seen. Presence of tremor appears to be associated with increased risk for cognitive decline, presence of bradykinesia with increased risk for functional decline, and presence of postural-gait impairments with increased risk for institutionalization and death. This may reflect need for assistance with mobility and number of falls. See Special Implications for the Therapist: Alzheimer's Disease later in the chapter.

Disorders of sleep, eating, and sexual behavior are common. The electroencephalogram (EEG) shows more awake time in bed, longer latencies to rapid eye movement sleep, and losses in slow-wave sleep.<sup>121</sup>

## MEDICAL MANAGEMENT

**DIAGNOSIS.** The most important diagnostic step in evaluating dementias is to determine whether a chronic encephalopathy results from a potentially reversible cause. Interaction of multiple medications can also trigger dementia and should be assessed.

A decline from previous levels of functioning and impairment in multiple cognitive domains beyond memory are critical in establishing dementia. Determining the rate of change is useful, since abrupt changes are not consistent with AD.<sup>122</sup> The progression is usually continuous and does not fluctuate or improve. Information obtained from family members or caregivers can provide data when there seems to be lack of insight from the client. The Functional Activities Questionnaire is a useful informant-based measure.

Clinical screening tests, such as the Short Test of Mental Status, the Mini-Mental State Examination (MMSE), and Mattis Dementia Rating Scale provide a baseline for monitoring the course of cognitive impairment over time and document multiple cognitive impairments.<sup>3</sup>

A clock drawing test is also a good test for AD. The individual is given a piece of paper with a circle on it and is first asked to write the numbers in the face of a clock and then to show "10 minutes after 11." The score is based on spacing between the numbers and the positions of the hands.

Neuropsychologic tests can accurately predict the probability of conversion to incident AD after 5 or 10 years.<sup>55,177</sup> Clues on physical examination include a variety of findings that may be common in elderly individuals but are not part of the typical picture of AD, such as ataxia, hyperreflexia, and tremulousness.

Depression can be difficult to distinguish from dementia, and it can coexist with dementia. Changes in memory, attention, and the ability to make and carry out plans suggest depression, the most common psychiatric illness in older persons. Marked visuospatial or language impairment suggests a dementing process. Depression scales can be used to determine levels of depression.

Ruling out a partially or completely reversible dementia by performing a blood count, chest radiography, and

general neurologic examination is critical in the diagnostic evaluation of a person with suspected AD. Autoimmune and paraneoplastic serologic studies may be helpful in such individuals as well.

Use of neuroimaging can be beneficial in the diagnosis of AD. Both magnetic resonance imaging (MRI) and computed tomography (CT) can identify the changes in brain size that are associated with AD. Diagnostic criteria are based on the measurement of medial temporal lobe atrophy or on the volumetric measurement of the entorhinal cortex and hippocampus.<sup>15</sup> The brain demonstrates atrophy with normal aging, so this is not the only diagnostic test.

Single-photon emission computed tomography (SPECT) can be used to determine brain activity, especially in areas where information is processed for memory functions. This may be used in the future to predict potential for development of AD.

Researchers are looking at different components of the human brain cell to identify molecular changes in deoxyribonucleic acid (DNA) and RNA seen in individuals with dementia and AD. Approaches are widespread, since it is clear that the disease is multifactorial. The National Institute on Aging (NIA) held a consensus conference in 1998 with the creation of an NIA Reagan profile that requires that neuropathologic assessment include assessment of both plaques and neurofibrillary tangles.

**TREATMENT.** There is currently no cure for AD. Current treatment focuses on establishing an early accurate clinical diagnosis, early institution of cholinesterase inhibitors and/or NMDA receptor-targeted therapy. Treating medical comorbidities and dementia-related complications, ensuring that appropriate services are provided, addressing the long-term well-being of caregivers, and treating behavioral and psychologic symptoms with appropriate nonpharmacologic and pharmacologic interventions also are important.<sup>109</sup>

Current drugs approved for treatment of AD have modest symptomatic benefits but do not have profound disease-modifying effects. Disease-modification approaches including neuroprotection are now the most active area of investigation, with focus on antiamyloid treatment. Oxidative stress and cell cycle-related abnormalities are early events in AD, occurring before any cytopathology can be identified, and together may create disease pathogenesis. Therefore, antioxidants are an AD prevention strategy under investigation. Inflammation and activation of microglia is a relatively early pathogenic event that precedes the process of neuron destruction in AD. Therefore, despite the early negative results of clinical trials with nonsteroidal antiinflammatory drugs (NSAIDs) for the treatment of AD, these and other antiinflammatory agents may still have a role in reducing the risk for AD. Modulation of cardiovascular risk factors may also reduce the risk for AD. Although hormone replacement therapy with estrogen showed no benefit and even a potential deleterious effect in individuals with AD, estrogen may still have a role in reducing the risk for AD if given early in menopause and when neurons are in a healthy state. Other neurodegenerative processes, such as excitotoxicity and apoptosis, may also have a patho-

**Box 31-5****COMMON MEDICATIONS USED IN ALZHEIMER'S DISEASE (AD)**

- **Donepezil** (Aricept) has only modest benefits, but it does help slow loss of function and reduce caregiver burden. It works equally in patients with and without apolipoprotein E ε4. It may even have some advantage for patients with moderate to severe AD.
- **Rivastigmine** (Exelon) targets two enzymes (the major one, acetylcholinesterase, and butyrylcholinesterase). This agent may be particularly beneficial for patients with rapidly progressing disease. This drug has slowed or slightly improved disease status even in patients with advanced disease. (Rivastigmine may cause significantly more side effects than donepezil, including nausea, vomiting, and headache.)
- **Galantamine** (Reminyl). Galantamine not only protects the cholinergic system but also acts on nicotine receptors, which are also depleted in AD. It improves daily living, behavior, and mental functioning, including in patients with mild to advanced-moderate AD and those with a mix of AD and vascular dementia. Some studies have suggested that the effects of galantamine may persist for a year or longer and even strengthen over time.
- **Tacrine** (Cognex) has only modest benefits and has no benefits for patients who carry the apolipoprotein E ε4 gene. In high dosages, it can also injure the liver. In general, newer cholinergic-protective drugs that do not pose as great a risk for the liver are now used for AD.
- **Memantine** (Namenda), targeted at the N-methyl-d-aspartate receptor, is used for moderate to severe AD.
- **Selegiline** (Eldepryl) is used for treatment of Parkinson's disease, and it appears to increase the time before advancement to the next stage of disability.

physiologic role in AD and are now under study. Medications currently in use are outlined in Box 31-5.

Treatment oriented at preventing the breakdown of tau, or the formation of plaques, is being tested now and shows promise. The treatment of those persons identified as at high risk may someday be protective gene therapy. Future drug therapies may be targeted at specific cognitive modules.

Management of the client with AD is a challenge to health providers and to the family who become caregivers. Manipulation of the environment can be effective. It is difficult to manage aggressive behavior in the home, and long-term care in a facility with a special Alzheimer's unit is often the most appropriate place for that client.

A management model for AD that incorporates a diagnostic protocol to identify and assess people with possible dementia and care management addressing individual function, caregiver support, medical treatment, psychosocial needs, nutritional needs, and advance directives planning is critical. To improve end-of-life care for people with AD, any treatment model should also incorporate patient-centered care and palliative care from the initial diagnosis of AD through its terminal stages. Short-term intensive counseling can significantly reduce the long-term risk for depression among those who care for spouses or partners with AD.<sup>50</sup>

In many individuals with AD, treating comorbid conditions such as depression, hearing or vision impairment, congestive heart failure, symptomatic urinary tract infection, or hypothyroidism may produce a greater benefit than focusing treatment only on AD. Cardiovascular disease may influence the expression and clinical manifestations of the disease.

There is compelling evidence for the important role of regular physical activity.<sup>115</sup> Exercise training combined with behavioral management techniques can improve physical health and depression in individuals with AD. Leisure-time physical activity at midlife is associated with a decreased risk of dementia and AD later in life. Regular physical activity may reduce the risk or delay the onset of dementia and AD, especially among genetically susceptible individuals.<sup>155</sup>

Diet in midlife shows potential for neuroprotection, and findings can be generalized to a combination of the following: consumption of a diet low in fat, high in omega-3 oils, and high in dark vegetables and fruits; use of soy (for women only); supplementation with vitamin C, coenzyme Q10, and folate; and moderate alcohol intake. It appears that no single item creates the protection, but the foods and supplements may work together to lower risk.

There is growing evidence indicating that oxidative damage caused by the p-amyloid peptide in the pathogenesis of AD may be hydrogen peroxide ( $H_2O_2$ ) mediated. Polyphenols from apple and citrus juices, such as quercetin, are able to cross the blood-brain barrier and show neuroprotection against  $H_2O_2$ . The effect of polyphenols from citrus is similar to that of vitamin C, but quercetin from apple juice gives stronger neuroprotection than vitamin C. In addition to their antioxidant properties, many polyphenols, such as quercetin, have potent antiinflammatory properties. In addition to antioxidant vitamins and polyphenols, fruit and vegetable juices also may possess other protective components, such as folate and minerals.<sup>45</sup>

The mutations in APP, presenilin 1, and presenilin 2 allow genetic screening to be used in suspected cases of familial AD with early onset and for appropriate genetic counseling and support. Although preimplantation genetic diagnosis (PGD) of the embryo, prenatal diagnosis, preimplantation embryo selection, and presymptomatic testing have been offered to families of individuals who have early-onset familial AD, complex legal and ethical issues surrounding these interventions must be addressed before these interventions can be routinely recommended.

**PROGNOSIS.** AD is the fourth leading cause of death in adults. The period from onset to death typically is 7 to 11 years. Initially, deficits in higher cortical function are the most noticeable. Motor signs may reflect higher burden or different type or more biologically detrimental localization of neuropathology. The association of different aspects of motor signs with different outcomes may reflect varying underlying neurotransmitter systems being affected. For example, in Parkinson's disease, tremor and bradykinesia have been viewed as representing more purely dopaminergic manifestations, while posture,

balance, and gait disorders may be mediated by other neurotransmitter systems in addition to dopamine. Changes caused by the dementia may advance relentlessly over many years, creating not only deep emotional and psychologic distress but also practical problems related to caregiving that can overwhelm affected families. During the middle stages of the disease, the client often develops behavioral and motor problems. Finally, the client becomes mute and unable to comprehend. Death is often secondary to dehydration or infection.

## SPECIAL IMPLICATIONS FOR THE THERAPIST 31-2

### *Alzheimer's Disease*

#### PREFERRED PRACTICE PATTERN

*5E: Impaired Motor Function and Sensory Integrity Associated with Progressive Disorders of the Central Nervous System*

Cognitive decline consistent with the diagnosis of primary degenerative dementia is a unique clinical syndrome with characteristic phenomena and progression. The Global Deterioration Scale can be used for the assessment of primary degenerative dementia and delineation of its stages.<sup>149</sup>

Use of a comprehensive cognitive stimulation program in AD patients enhances neuroplasticity, reduces cognitive loss, and helps the patient to stretch functional independence through better cognitive performance. Remarkable effects have been observed also in the areas of mood and behavior. Behavioral disturbances influence caregiver burden and institutionalization as well as being associated with patient and caregiver distress. Increase in social attention and interaction has been noted to improve mood and behavior in demented elderly. Important mood benefits have been reported from stimulation programs predominantly aimed at cognition.<sup>136</sup>

Cognitive rehabilitation programs can minimize demands on executive control systems in favor of structured tasks that are designed to exploit implicit memory. Appropriate feedback is critical, as there is increased agitation and anxiety when mistakes are recognized. Nonverbal cues can be helpful when language is the source of confusion. Moving through parts of a task with guidance can facilitate understanding and promote confidence to proceed. When the experience is more pleasurable, the response is improved, as the stress of the task may be reduced.

The client with AD has generalized weakness and abnormality of movement. Movements become more stereotyped and rigid. Postural reflexes are diminished, and the incidence of falls increases. Falls occur in approximately 30% of clients with AD, which may be attributable to their lack of perception of where their bodies are in space and their inability to move adequately around objects. Having the client move in a space that has few obstacles appears to decrease the number of falls. The use of increased lighting, especially in the early evening, will decrease the agitation often referred to as *sundowning*.<sup>195</sup>

The therapist often sees a client with AD in a structured living environment, since many people become difficult to maintain at home. Movement and exercise can provide the client with an activity that he or she can succeed in as well as maintaining mobility, good breathing patterns, and endurance. Restlessness and wandering are typical of the client with AD, and a structured exercise program appears to decrease restlessness. Daytime exercise can also help control nighttime pacing and the resulting daytime drowsiness. Some residential programs have set up areas that the client can access without wandering out of the facility. The use of these areas may decrease agitation and allow individuals to pace safely.<sup>19</sup>

Group therapy with simple exercises that use images rather than commands is most effective. Storytelling integrated into the exercise program helps to stimulate thinking as well as movement. Clients need to be able to attend to an activity for at least 5 minutes, and the group therapy session must not provide more stimulation than clients are able to tolerate. Exercises should be short and simple and done in the same order each day. Repetition and reassurance can help keep clients engaged. The exercise program should include group interaction with physical touching, such as holding hands or working in pairs. Use of exercise bands, balls to kick and throw, and light weights works well.<sup>16,111</sup>

In working with the individual with AD, knowing something about him or her may enable the therapist to use words and terms that are more familiar. Approach to the person should be slow and from the front. Always identify yourself and use the person's name before intervention begins. Identifying pain during activity is important, because pain may be involved in aggressive behavior. Use of modalities to decrease the client's pain may result in improved behavior. The Alzheimer's discomfort rating scale is useful.<sup>81</sup>

Intervention should be based on the individual's stage of progression. In the early stages, work on high-level balance and gait activities will help to maintain mobility and balance. Strength gains have been reported to be significant in older persons in a strengthening program, and strength is an important component of balance. Maintaining range of motion (ROM), especially in the trunk and distal extremities, will help to maintain function. Caregiver training is important for consistent follow-through with activities and provision of appropriate cues. When assistance is needed for mobility, caregiver training on transfers, contracture management, and assistance with gait is included in the intervention.

Choosing the appropriate orthotic, assistive device, and wheelchair can be a challenge as dementia develops. Walkers have been designed for the AD client to use on flat surfaces with appropriate support and safety.

The therapist should be familiar with the warning signs of AD. Because the disease mimics other signs of old age, the symptoms may go unreported. It is often the spouse who asks questions regarding the possibility of the client's developing AD. Information regard-

**Box 31-6****TEN WARNING SIGNS OF ALZHEIMER'S DISEASE (AD)**

1. Recent memory loss that affects job performance. People with AD will forget things often and may repeat the same question, forgetting the earlier answer.
2. Difficulty performing familiar tasks. The person may make a meal and then forget to serve it, forgetting even that he or she made it.
3. Problems with simple language: forgetting simple words or using them inappropriately.
4. Disorientation. The person with AD may get lost on his or her own block.
5. Decreased judgment, for example, the person may sometimes forget that he or she is responsible for a child's care.
6. Abstract thinking difficulties, for example, forgetting what numbers are for when balancing a checkbook.
7. Misplacing things, such as putting an iron in the freezer.
8. Changes in mood or behavior: getting angry easily and crying often.
9. Personality changes: becoming irritable, suspicious, or fearful.
10. Loss of initiative: not wanting to get involved in activities he or she previously enjoyed.

From Alzheimer's Association, 919 N. Michigan Ave., Suite 100, Chicago, IL 60611-1676.

ing the types of symptoms related to the disease can be helpful to the family in deciding whether more evaluation is needed. The Alzheimer's Association's 10 warning signs of AD are listed in Box 31-6.

## DYSTONIA

### Definition and Overview

Dystonia is a neurologic syndrome dominated by involuntary, sustained muscle contractions frequently causing twisting and repetitive movements. These abnormal postures are often exacerbated when the person performs active voluntary movements.

Traditionally, dystonia was classified according to type, including primary (idiopathic or of unknown cause) or secondary (occurring as a result of injury or other brain illness). These classifications are still reported in the literature, but the current classification scheme for dystonia now describes the disorder in each person according to three separate categories: age of onset, distribution of symptoms, and etiology. A second type of classification is by body involvement. In focal dystonia one body area is affected, in segmental dystonia two or more body areas are involved, and generalized dystonia is wider spread. There has been some confusion in the literature regarding the name *cervical dystonia*. This neurologically based movement disorder affecting the head and neck is a separate entity from spasmotic torticollis. Torticollis is a musculoskeletal phenomenon treated as an orthopedic condition (see discussion of torticollis in Chapter 23).

### Incidence

An estimated 250,000 persons are afflicted with dystonia in North America. About 1.1 in 100,000 persons per year develop dystonia, with a female to male ratio of 1.6:1.<sup>53</sup> The Mayo Clinic in Rochester found 3.4 cases of primary generalized dystonia and 29.5 cases of focal dystonia per 100,000.<sup>133</sup> Focal dystonia is estimated to be six times more common than other well-known neuromuscular disorders such as muscular dystrophy, Huntington's disease, and ALS.

The average age of onset of idiopathic dystonia is 8 years. For focal dystonias, the age of onset is between 30 and 50 years.

### Etiologic Factors

Idiopathic, or primary, dystonia is the most common diagnosis, accounting for two thirds of all cases. A genetic basis on the DYT1 gene locus is responsible for causing primary torsion dystonia.<sup>22</sup> It appears that persons with generalized dystonia carry a different gene than those with focal dystonias.<sup>56</sup> Another inherited dystonia is dopa-responsive dystonia, or Segawa's dystonia.

Secondary dystonia is the result of small areas of brain damage or scarring of the CNS. The changes have been attributed to drugs, infections, tumors, and demyelinating processes as well as acute trauma, such as caused by auto accidents. Box 31-7 lists the major causes of secondary dystonia.

Focal dystonias involving hand function are particularly common among those in certain occupational groups, such as keyboard operators and musicians. Writer's cramp is also a focal dystonia. Focal dystonia related to occupational cramps may be a result of abnormal or repetitive biomechanics. Focal dystonia involving the hand may also occur as part of a peripheral nerve disorder.

Drug-induced extrapyramidal symptoms may include dystonia as a common side effect associated with antipsychotic drugs (neuroleptics). This results in various acute and chronic manifestations of neuroleptic-induced dystonia (e.g., blepharospasm [difficulty in opening the eyelids], torticollis or retrocollis [involuntary extension of the neck]).<sup>83</sup> The fact that  $\beta$ -blocking agents are effective in reducing symptoms in these cases points to the possibility that neuroleptic drugs increase the activity of B-adrenergic transmitters.

### Pathogenesis

Descending pathways involving reciprocal inhibition of motor neurons have been identified as possible sites of pathogenesis in idiopathic dystonia. Nerve conduction velocity studies have shown that there is a failure of neural activities preparing for movement. Defective retrieval of specific motor programs in response to sensory stimuli results in co-contraction of both agonist and antagonist muscles around a joint.<sup>154,186</sup> In focal dystonia of the hand, there is somatosensory degradation in the involved hand, with graphesthesia and astereognosis.<sup>34</sup>

Inherited dystonia mapped to chromosome 9 is probably the result of a protein that affects the function of certain nerve cells. The DYT1 and DYT6 genes have been

associated with dystonia.<sup>57</sup> The exact malfunction remains unknown, but it may be that a protein is missing or is produced in excess.

The cause of symptomatic, or secondary, dystonia is thought to be chemical dysfunction or scarring within the striatum (caudate nucleus and putamen).<sup>69</sup> Overactivity of the direct pathway within the basal ganglia loop (cortex-striatum-internal globus pallidus-thalamus-premotor/motor cortex) is speculated to result in an overflow of motor cortex activity, thus creating the dystonic movements. A defect in the body's ability to process inhibitory neurotransmitters such as  $\gamma$ -aminobutyric acid (GABA), dopamine, acetylcholine, norepinephrine, and serotonin may contribute to poor inhibition of motor control. Dysfunction of the lenticulothalamic neuronal circuit seems to be related to the development of dystonia following head trauma.<sup>108</sup>

Recent research suggests that the somatosensory cortex may also function abnormally, contributing to the altered motor output.<sup>33, 69, 90, 91, 178</sup> Both somatosensory cortex and somatotopic representation at the thalamus degrade in individuals with dystonia.<sup>111</sup>

The cerebellum has also been implicated using functional MRI. Theoretically, increased activity in the cerebellum results in the excessive movement and dystonic posturing.<sup>68, 86</sup>

### Clinical Manifestations

Cervical dystonia is the most common focal dystonia and is characterized by rotation of the neck, lateral flexion, and flexion and extension occurring in various combinations. The condition is usually painful, is disruptive to functional activity, and leads to osteoarthritis and hypertrophy of the sternocleidomastoid muscle if remission does not occur. Dystonia-induced cervical fracture has been reported.

Writer's or occupational cramp is a form of dystonia that can be particularly disabling, resulting in deterioration of handwriting or fine motor control. The fingers and wrist flex excessively, causing the hand to grasp a pen tightly and press unnecessarily hard on the paper. Another type of cramp results in extension of the fingers, making it difficult to hold a pen. Tremor or myoclonic jerks may occur while writing or trying to play a musical instrument. Lower extremity dystonia is common, including dystonic movements in the foot and toes.

Blepharospasm is uncontrolled blinking or closure of the eyelids for seconds to hours. In oromandibular dystonia, face and jaw muscles contract, causing grimaces or facial distortions, and dysphonia affects the speech muscles of the throat, causing strained, forced, or breathy speech.

Involvement of the respiratory muscles has been considered unusual but may in fact be underestimated, either because it is not conspicuous or because the problem is improperly attributed to another cause. Clinical manifestations of respiratory involvement may include involuntary deep and loud inspirations combined with dystonia, breathing arrests, or broken speech caused by deep inspirations when speaking or reading aloud.<sup>105</sup>

Dystonia usually is present continually throughout the day whenever the affected body part is used. In

### Box 31-7

#### CAUSES OF SECONDARY OR SYMPTOMATIC DYSTONIA

- Drugs, including neuroleptics, dopamine agonists, anticonvulsants, antimalarial drugs
- Intramedullary lesions of the cervical cord
- After hemiplegia: often a delayed reaction to stroke
- Focal brain lesions: vascular malformation, tumor, abscess
- Demyelinating lesions, such as with multiple sclerosis
- Traumatic brain injury with lesion to contralateral basal ganglia or thalamus
- Encephalitis
- Environmental toxins: manganese, carbon monoxide, methanol
- Hypoparathyroidism
- Degenerative disease: Parkinson's disease, Huntington's disease, Wilson's disease, progressive supranuclear palsy, multiple system atrophy
- Cerebral palsy

more severe cases, the dystonia can appear at rest. The symptoms may begin in one area only with a particular movement. For example, it may be apparent when walking forward but not when walking backward or the foot may turn under after walking or other exercise, causing the person to walk on the lateral border of the foot.

### MEDICAL MANAGEMENT

**DIAGNOSIS.** Dystonia is a clinical diagnosis except for those cases that have a genetic basis. Testing for genetic forms of dystonia appears to be most appropriate for people under the age of 26.<sup>93</sup> Otherwise, there is no definitive test for dystonia, and the diagnosis of idiopathic dystonia is often delayed 1 year or more. The clinical presentation of dystonic movements, such as head deviation or neck pain, may be the first diagnostic sign. The person usually has a normal perinatal and developmental history. EMG studies show sustained simultaneous contractions of agonists and antagonists. Determining that there is no evidence for symptomatic, or secondary, dystonia is essential in the diagnosis of idiopathic dystonia (see Box 31-7).

**TREATMENT.** Treatment remains symptomatic and includes drug therapy, including botulinum toxin type A (BTX) injections, physical and occupational therapy, and sometimes surgery.

Anticholinergics such as trihexyphenidyl (Artane) have been the most widely used medications to decrease acetylcholine and correct a cholinergic imbalance in the basal ganglia. Side effects of these drugs vary, with blurred vision, dry mouth, confusion, voiding, sleeping difficulties, and personality changes observed.

Baclofen and other muscle relaxants are used occasionally for relief.

BTX, injected intramuscularly, has emerged as a safe and effective symptomatic treatment for a number of conditions associated with excessive muscle activity, par-

ticularly focal dystonias involving a limited number of muscles. These injections are effective in improving postural deviation and pain in about 80% to 90% of people with cervical dystonias.<sup>84,85</sup> Injection directly into the actively contracting muscles blocks the neuromuscular junction by acting presynaptically to reduce the release of acetylcholine, producing a chemical denervation. Muscle weakness can result from this treatment. Response occurs in 3 to 7 days and lasts 3 to 4 months. Dysphagia is the most serious side effect but can be decreased in incidence and severity by injecting lower doses, particularly into the sternocleidomastoid. The need to continue indefinitely with repeat injections approximately every 3 months is a major drawback.

Surgery may be considered only when other treatments are no longer effective, although surgical intervention may also lose its effect over time, providing only temporary symptomatic relief. Surgeries to interrupt the pathways or foci responsible for the abnormal movements can be effective. Thalamotomy is the destruction of a portion of the thalamus. Pallidotomy is a destructive operation on the globus pallidus. Pallidus stimulation is achieved by placing an electric stimulator in the globus pallidus. Rhizotomy involves the surgical resection of the anterior cervical spinal nerve roots and is used along with selective peripheral denervation, or removal of the nerves at the point where they enter the contracting muscles.

**PROGNOSIS.** Age of onset is the best predictor of prognosis. If dystonia starts in childhood and affects other members of the family, it tends to get progressively worse over the years. If the condition starts in childhood and is secondary to cerebral palsy or other brain injury close to the time of birth, the dystonia tends to remain static for many years. In one third of cases of adult-onset focal dystonia there is progression to segmental dystonia, although there is less than a 20% chance that the disease will progress to generalized dystonia.

Spontaneous remission occurs in 30% of cases within the first year, but the majority of clients show steady progression of their focal dystonia, with maximal disability occurring after 5 years. Neck pain, occurring in 70% to 80% of clients, contributes significantly to disability. Cervical dystonia has important psychosocial consequences, since many people with this condition withdraw from their jobs and social activities.<sup>190</sup>

## SPECIAL IMPLICATIONS FOR THE THERAPIST 31-3

### Dystonia

#### PREFERRED PRACTICE PATTERN

**5E:** Impaired Motor Function and Sensory Integrity Associated with Progressive Disorders of the Central Nervous System

The Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS)<sup>44</sup> is a commonly used impairment and disability scale for rating the severity of cervical dystonia. The Barry-Albright Dystonia Scale<sup>8</sup> is used for secondary dystonia. ROM, pain, and descriptions of active motion as well as limitations in functional activities are also useful measurements. Outcomes can

be measured with life satisfaction scales, such as the SF-36.<sup>21</sup>

The therapist should address all aspects of functional ability with the client who has been affected by dystonia, including stress management, energy conservation, adaptive equipment, mobility, and splinting.<sup>32</sup>

Sensory processing abnormalities, as discussed under Pathogenesis, may be involved in the abnormal movements of dystonia. In owl monkeys who developed dystonic movements of the hand and particularly the fingers in response to a high number of repetitive movements of the forearm and hand,<sup>34</sup> the sensory cortex reorganized by decreasing the representation (dedifferentiation) of the hand and fingers. The cortical thalamic reorganization occurred after the monkeys began experiencing dystonia of the hand secondary to overuse. Later research by the same laboratory demonstrated recovery of the cortical representation and redifferentiation using sensory stimulation therapy rather than motor retraining. These studies suggest that treatment approaches should focus on sensory retraining, and particularly active interpretation of sensory stimuli. A case series using sensory retraining demonstrated success with this method in humans who had writer's cramp, a focal dystonia.<sup>35</sup> A recent literature review<sup>32</sup> of effective therapies for focal hand dystonia reported support for sensory retraining, motor sensory retuning, and limb immobilization. There was less support for modalities, stretching, and strengthening. However, Tassorelli et al<sup>17,3</sup> reported success using physical therapy of stretching, strengthening, postural control and balance exercises along with surface EMG biofeedback in a study comparing outcomes of two groups, one receiving BTX only and the other receiving BTX and physical therapy. The group given physical therapy and BTX showed significantly better outcomes than the BTX-only group. Surface EMG feedback is effective in reducing symptoms in persons with focal hand dystonia.<sup>35,94</sup> Trials using surface EMG for hand dystonia demonstrated results in as few as five sessions.<sup>47</sup> Theoretically, visual input provides an alternate, nondysfunctional route for sensory input to reach the motor output system through the surface EMG visual feedback.<sup>98</sup> The primary motor cortex, which is responsible for initiating motor tasks, receives highly processed visual information from cortical areas other than the somatosensory cortex (i.e., parietal lobe, basal ganglia). These pathways may be able to override the malfunctioning input systems.<sup>98</sup>

Task-oriented treatment, rather than more traditional strengthening and stretching exercises, has a better potential for improving function. Having clients do highly skilled tasks in treatment that are challenging and stimulating will improve learning. A combination of treatments often is most effective. For example, a client with right lower extremity dystonia of 8 years' duration used a combination of surface EMG feedback on the anterior tibialis and gastrocnemius during stepping to targets and using the foot to identify and manipulate small objects in order to normalize

*Continued.*

motion. BTX injections into the hip flexor and gastrocnemius were done later to assist in reducing the abnormal hip flexor component of walking. The outcome was a normal gait pattern.

In some cases of dystonia, splinting has been effective for improving function. In cases in which the foot or feet turn in, insoles placed in the shoes to build up the outer border of the foot may help to put the foot in a neutral position and produce a more normal gait pattern. The use of a cervical collar has been tried by some with good results, but it may be that the sensory information to the skin accounts for this success rather than the mechanical support provided. If the collar minimizes pain or provides a more functional midline position, there may be some merit in its use. Otherwise, if it only works as a sensory trick, a piece of cloth wrapped around the neck may accomplish the same effect. The person who uses a cervical collar should be taught to do task-oriented exercises outside the collar to minimize weakness in the noninvolved muscles; for example, reading letters placed on the side opposite head rotation while the body stays facing forward.

When the jaw, tongue, or lips are involved, gentle pressure on the lips or teeth may lessen spasm. Exerting slight pressure against the jaw on the side to which the head is rotated may decrease or inhibit muscle spasm, although this is an immediate and short-term reaction. Guidelines for chewing and swallowing may be helpful for the client with oromandibular dystonia.

Swimming therapy can be especially helpful in reducing discomfort and facilitating movement.

Aggressive strengthening and ROM treatments may increase the symptoms of dystonia; any treatment should be carried out within the client's tolerance and without increasing the manifestations of the dystonia. Because dystonia originates in the CNS, passive techniques such as massage provide only temporary relief from symptoms and do not affect the underlying movement disorder. Likewise, focal dystonia does not respond to facilitatory or inhibitory techniques used for modulating spasticity. When relief of spasm allows the client to assume a more normal or correct posture, underlying tight soft tissues may benefit from short-term use of physical therapy modalities and soft tissue mobilization to restore full ROM.<sup>32,173</sup>

condition with effects that are complex, management requires a multidisciplinary approach.<sup>71,198</sup>

### Incidence and Etiologic and Risk Factors

The prevalence of HD in North America ranges from 4 to 8 per 100,000. It is estimated that there are 25,000 cases in the United States. HD may begin at any time after infancy but usually starts in middle age. Twenty-five percent of persons with HD have disease of late onset, which is defined as onset of motor symptoms after age 50 years. There is almost always a history of an affected parent. There is a 50% risk in each child of an affected adult.<sup>6</sup> Transmission of the juvenile form of HD (onset before age 20 years) appears to be primarily from the father. With adult onset there is more equal transmission from both parents.

HD is an autosomal dominant disease with the IT15 or HD genetic marker found on the tip of chromosome 4. In a subset of cases, the lunctophilin 3 gene is responsible for the HD genotype. All the people who inherit the gene will develop symptoms of the disease if they do not die prematurely. Because there is no cure for HD, there is an ethical dilemma associated with testing. Studies are under way to determine the psychiatric and social problems that may result from the knowledge that one will develop HD.<sup>61</sup>

### Pathogenesis

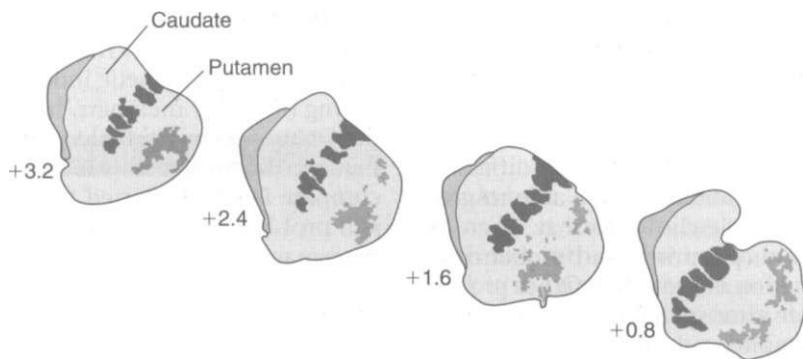
Although the cause remains unknown, pathologic findings show a consistent pattern of tissue changes in the brain. The ventricles are enlarged as a result of atrophy of the adjacent basal ganglia, specifically the caudate nucleus and putamen (collectively the striatum) (Fig. 31-5). This is due to extensive loss of small and medium-sized neurons. The volume of the brain can decrease by as much as 20%. Caudate atrophy correlates with a measured decline in Mini-Mental State Examination scores but not with the severity or duration of neurologic symptoms. It is the atrophy of the putamen that correlates with neurologic symptoms. The atrophy of the cortices appears to occur at the same rate as that of the striatum. White matter degeneration in the frontal cortex appears to be associated with the course of the disease. Slower disease progression appears to be correlated with more white matter changes. The more aggressive progressive disease is related to less white matter and more striatal damage. Other subtle changes occur in the cortex and cerebellum, including both loss of neurons and production of glial cells that inhibit neural transmission.<sup>70</sup>

As with other progressive diseases, there is selective vulnerability of neurons in a particular region with preservation of others. In the early and middle stages of HD, neurons projecting from the striatum to the substantia nigra are depleted. This reduces the amount of neurotransmitters, including GABA, acetylcholine, and metenkephalin. This leaves relatively higher concentrations of other neurotransmitters, such as dopamine and norepinephrine. The normal balance of inhibition and excitation responses in the complex organization of the basal ganglia and thalamus that allows for smooth, controlled movement is disrupted. The result is an excess of dopamine and excessive excitation of

## HUNTINGTON'S DISEASE

### Overview and Definition

Huntington's disease (HD) is a progressive hereditary disorder characterized by abnormalities of movement, personality disturbances, and dementia. Known also as Huntington's chorea, it is most often associated with choreic movement that is brief, purposeless, involuntary, and random. However, the disease course involves more than just a movement disorder, and hence the name Huntington's disease. HD is a disorder of the CNS and is classified as a neurologic disorder, but because it is a

**Figure 31-5**

Atrophy seen in the caudate and putamen in a person with Huntington's disease. As the disease progresses there is a change in the caudate at the interface with the ventricle. The outline becomes more and more concave, representing the progressive atrophy.

the thalamocortical pathway. This may explain the excessive abnormal involuntary movements described as chorea.<sup>9,147,198</sup>

In the later stages of HD, there is a loss of the direct inhibitory substance that causes more inhibition of the thalamocortical output with resultant rigidity and bradykinesia, or slowness of movement. By the late stages of HD, virtually all the caudate nucleus projection neurons are affected. The mechanism of neuronal loss is not known. One hypothesis is that an excitotoxin causes the cell death noted in the basal ganglia.<sup>146</sup>

### Clinical Manifestations

**Movement Disorders.** Many individuals with suspected early HD will show almost no neurologic abnormality on routine examination other than minor choreic movements. The movements may be suppressed during the examination since they can often be integrated into a purposeful movement, such as raising the hand to the head as if to smooth the hair. Early in the course the involuntary movements may appear to be no more than an exaggeration of normal restlessness, usually involving the upper limbs and face. The chorea is increased by mental concentration, emotional stimuli, performance of complex motor tasks, and walking. Problems with voluntary movement may be detected by asking for rapid tongue movements or finger-to-thumb tapping, or testing for dysdiadochokinesia, the inability to make rapid alternating movements.

Assessment of muscle strength will usually be normal in early cases but may be affected by any significant bradykinesia or general motor disturbance. Tone will usually be normal initially, but rigidity will become part of the clinical picture in many cases as the disease progresses. The tendon reflexes are usually normal.

Abnormalities in eye movement are common in HD. The ability to execute a saccade, a rapid movement of the eyes from one target to another in order to move the visual focus rapidly to different objects, is disturbed. There is often a decrease in the velocity of eye movement, an undershooting of the target, or latency in initiation of movement. Gaze fixation abnormalities have been noted; that is, inability to fix on a light source without the intru-

sion of small saccadic movements. Smooth pursuit, or tracking of the eye to follow a moving object, is interrupted by the same small, jerky saccadic movements. There is often an inability to suppress reflex saccades to a visual stimulus, which leads to visual distractibility.

The term *chorea* is derived from the Greek word for dance, and gait abnormalities are common in HD. When chorea is a predominant sign, persons walk with a wide-based, staggering gait. Those persons with bradykinesia and hypertonicity may walk with a slow, stiff, unsteady gait.

Dysarthria, reflected as a decrease in the rate and rhythm of speech, may be mild in the early course with an increase to the point where speech may be unintelligible. In addition to the mechanical problems, neuron loss disrupts linguistic abilities, resulting in reduced vocabulary and syntactic errors. Some persons become mute at a stage before motor disability is severe.

Abnormalities of swallowing, or dysphagia, can cause choking and asphyxia. Dysphagia may involve multiple abnormalities of ingestion, including inappropriate food choices, abnormal rate of eating, poor bolus formation, and inadequate respiratory control.

Cachexia, or the wasting of muscle with weight loss, is found despite an adequate diet. This appears to be independent of the hyperkinesia and is found in persons with rigidity as well.

Sleep disorders become a progressive problem throughout the course of HD. An increased latent period before sleep and increased periods of wakefulness are common in moderately affected persons. Sleep reversal—daytime somnolence and nighttime restlessness—is seen in severely affected persons and is probably related to the dementia. Chorea movements are reduced during the deepest part of sleep.

Urinary incontinence is often a problem. This could be related to dementia, depression, decreased mobility, or hyperreflexia of the muscles that control urine output. There can be a concomitant increase in the incidence of urinary tract infections.

**Neuropsychologic and Psychiatric Disorders.** Early mental disturbances in persons with HD include personality and behavioral changes, such as irritability, apathy,

depression, decreased work performance, violence, impulsivity, and emotional lability.<sup>129</sup> Intellectual decline usually follows the personality changes. The neuropsychologic profile characteristically includes a type of memory disturbance that suggests an impairment of information retrieval. Individuals often have difficulty recalling information on command but are able to give the correct answer in a multiple-choice format. There is difficulty with organization, planning, and sequencing, even when all the information is provided. Other prominent abnormalities include visuospatial deficits, impaired judgment, and ideomotor apraxia, the inability to perform previously learned tasks despite intact elementary motor function.

More than one third of persons with HD will develop an affective disorder. Depression is the most common psychiatric condition and does not appear to be simply a reaction to a fatal illness. Evidence for this is the fact that mood disorders are not randomly distributed but occur in subsets of families with HD.<sup>131</sup>

### MEDICAL MANAGEMENT

**DIAGNOSIS.** The clinical diagnosis of HD depends on recognition of patterns of symptoms given in the client's history and clinical signs, and the family history. Difficulties in diagnosis arise when the family history appears negative. Some families deny the presence of cognitive or psychiatric disease. Understanding of the clinical signs must take into account the fact that signs change during the course of the illness. Different patterns may be observed depending on the age of onset.<sup>71</sup>

MRI demonstrates atrophy of the striatum that is most easily appreciated as enlargement of the frontal horn of the lateral ventricles. Fig. 31-6 shows this change in brain structure. This is not of great diagnostic value unless it is very pronounced, given the normal reduction in brain mass with age and the occurrence of atrophy in other disorders that might be confused with HD. Positron emission tomography (PET) will also show atrophy, but

its value as a diagnostic tool has the same limitations as MRI.

In addition to genetic linkage analysis, which requires testing of family members, it is now possible to evaluate the DNA of an individual to identify specific components that are diagnostic for HD. This eliminates the need to compare DNA of affected family members, but there are still problems with this method, because there is a small percentage of affected individuals who do not display the characteristics on the specific gene and there are nonaffected individuals who carry the gene.

Recognition of HD in older persons is critical to establish the genetic link for future generations. Often the diagnosis is overlooked in favor of the label of senile chorea, because there are minimal changes in behavior and cognition. The differential diagnosis of HD in the older population includes various degenerative, systemic, and drug-related conditions. An individual treated with neuroleptics for a psychiatric presentation of HD, for example, may go on to develop movement disorders, and these may be confused with the typical side effects of the medication.<sup>131</sup>

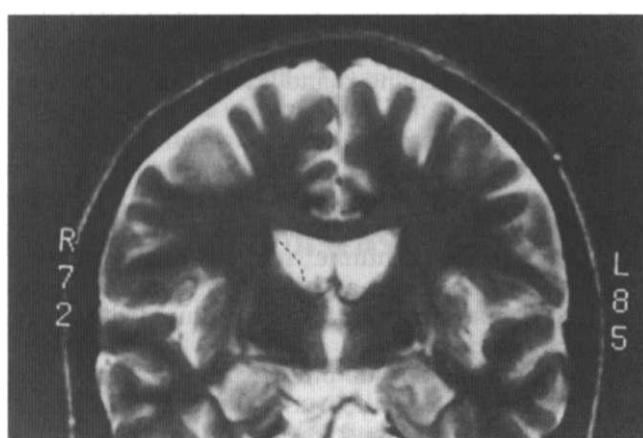
**TREATMENT.** Management of HD requires a team approach, including medical and social services. Education of clients and their families about the implications of the disease is important. Genetic, psychologic, and social counseling are started as soon as the diagnosis is confirmed. Organizations designed to help families with HD are often of great help.

Medical treatment is symptomatic. The most useful drugs for the symptomatic relief of chorea are anticonvulsants or antipsychotic agents that block dopamine neurotransmission. They can also help with the emotional outbursts, paranoia, psychosis, and irritability seen in HD. Drug therapy for chorea should be held in reserve if the abnormal movements are slight. There is a high incidence of side effects with the drugs, including acute dystonias, pseudoparkinsonism, and akathisia, which is characterized by uncontrollable physical restlessness. The most serious effect is chronic tardive dyskinesia resulting in involuntary movement of the face, tongue, and lips. Another adverse reaction is neuroleptic malignant hyperpyrexic syndrome, characterized by fever and rigidity.

Surgical procedures to remove the medial globus pallidus, thought to be overexcited by neuronal loss in the striatum, have been tried with mixed results. Implantation of adrenal medullary grafts has not been encouraging; the improvement appears to be transient.

**PROGNOSIS.** It is characteristic of the disease that younger people, with onset of symptoms at age 15 to 40 years, will experience a more severe form of the disease than older people, with onset in their fifties and sixties. The advance of the disease is slow, with death occurring on average 15 to 20 years after onset. Survival into the eighties is not uncommon, and persons living to past 90 years old have been recorded. Age at onset and age at death frequently show a familial correlation.

Increasing disability from involuntary movements and mental changes often results in death from intercurrent



**Figure 31-6**

Magnetic resonance scan showing the degeneration of the caudate in a person with Huntington's disease (HD). The dotted lines show where the tissue would be in a person without HD. (From Ramsey R: *Neurology*, Philadelphia, 1994, Saunders.)

infection. Suicide accounts for approximately 6% of deaths, and 25% of persons with HD attempt suicide at least once.

## SPECIAL IMPLICATIONS FOR THE THERAPIST 31-4

### Huntington's Disease

#### PREFERRED PRACTICE PATTERN

##### *5E: Impaired Motor Function and Sensory Integrity Associated with Progressive Disorders of the Central Nervous System*

Education of the client and family about movement disorders, including gait and safety in mobility, is the basis for therapeutic intervention. Clients with HD do fall, but it is surprising that mobility is maintained despite the seemingly precarious arrangements of the limbs and trunk. As the disease progresses, postural stability becomes impaired and axial chorea may throw the client off balance. In clients whose bradykinesia is predominant, there is a propensity to freeze, especially in confined spaces, and this may precipitate falls.

*Apraxia*, the inability to perform skilled or purposeful movements, may become severe. This impairment may lead to significant disability in performance of ADLs. The client may lose the ability to dress and do self-care activities such as grooming, regardless of cues provided by caregivers.

Positioning to prevent soft tissue deformities and safety in transfers should be taught according to the current movement disorder identified. Both the therapist and the family should understand that these techniques may need to be changed as the movement disorder progresses. The therapist should be aware that it is possible that chorea and bradykinesia are manifested in the patient at the same time owing to the progressive neuronal loss in the basal ganglia described earlier.

The ability to intervene with neurotherapeutic techniques, including motor learning, may be limited in the face of the concomitant decline in mental function as the motor system impairments progress.

## MULTIPLE SCLEROSIS

### Overview and Definition

Multiple sclerosis (MS) is a major cause of disability in young adults. The name is descriptive of the sclerotic plaques disseminated throughout the CNS that are the hallmark of the disease. There are multiple lesions found throughout the brain and spinal cord. These lesions slow or block neural transmission, resulting in weakness, sensory loss, visual dysfunction, and other symptoms. The course of MS is highly variable. Complications of MS may affect multiple body systems and require profound adjustments in lifestyle and expectations for clients and their families; therefore, a multidisciplinary approach is necessary to optimize clinical care.

MS is a chronic illness that may be manifested in multiple forms and courses. There are four generally recognized subtypes. Relapsing-remitting MS is characterized by relapses or attacks, which are periods of neurologic dysfunction lasting days to months and followed by full or partial recovery. By convention, new symptoms must last at least 24 hours and be separated from other symptoms by at least 30 days to qualify as a new attack. The hallmark is that there is a stable course between relapses. This is the most common pattern, seen in about 85% of newly diagnosed individuals. Secondary progressive MS describes an initial pattern of relapse and remission that changes into a steadily progressive pattern over time in more than 50% of the relapsing individuals. There sometimes are continued relapses during this phase. This conversion generally occurs 5 to 10 years after the initial onset of relapsing symptoms. Primary progressive MS is a steady decline in neurologic function from the outset with episodes of minimal recovery. The most common clinical presentation of primary progressive MS is myelopathy, a gradual, progressive weakening and wasting of muscles, which is typically seen in persons with onset past the age of 40 years. Progressive-relapsing MS is progressive disease from the onset with clear exacerbations. This is considered the rarest form of MS.

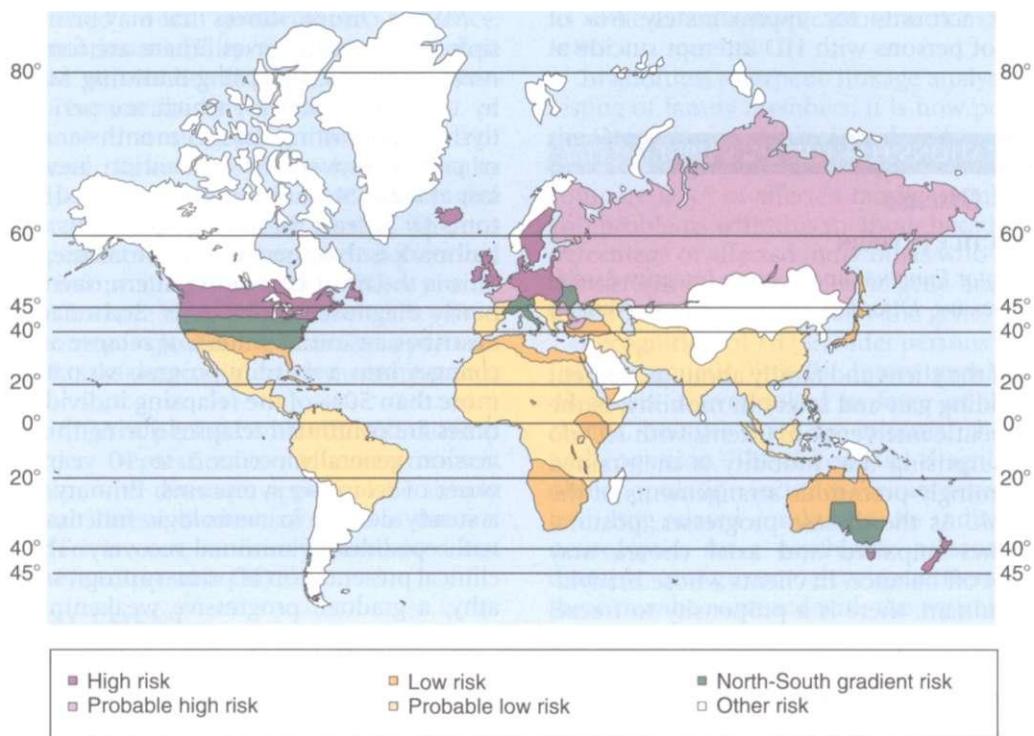
### Incidence

Marked differences in the prevalence of MS exist among different populations and ethnic groups. MS is a disease of temperate climates. Highest known prevalence occurs in the Orkney Islands, off Scotland. MS is also common in Scandinavia and elsewhere in northern Europe. There are more than 2 million persons affected worldwide; the incidence is 12 per 100,000 persons. In the United States it is estimated that 450,000 people are affected, with about 10,000 new cases per year. Caucasians of northern European descent have significantly higher rates of the disease than other racial groups. MS is extremely rare in Japan and virtually unknown in black Africa, but Japanese Americans and African Americans show an increased prevalence.<sup>151</sup> African Americans with MS have a greater likelihood of developing opticospinal MS and transverse myelitis and have a more aggressive disease course than Caucasian Americans.<sup>73</sup> Fig. 31-7 shows the incidence rates worldwide.

MS rarely will begin before adolescence; it rises steadily in incidence from the teens to age 35 years and declines gradually thereafter. Similar to many other autoimmune diseases, MS has a predilection for women, with a female to male ratio of 2.5:1. Men have a slightly later age of onset and more severe clinical outcomes than women. Men with MS transmit the disease to their children (independently of the child's sex) more often than do women who have MS.<sup>39</sup> Relapse rates may decline 70% in the third trimester of pregnancy, most likely due to circulating levels of estriol. These facts suggest a complex hormonal modulation of the immune system.

### Etiologic and Risk Factors

There is a clear genetic component in the risk of developing MS.<sup>40</sup> When one parent is affected, and especially if that parent developed MS at an early age, before 20 years,



**Figure 31-7**

World map showing the relative incidence of multiple sclerosis. Areas of greatest risk are in the northern latitudes. (Adapted from National Institute of Neurological and Communicative Disorders and Stroke: *Multiple sclerosis: hope through research*. Publication no. 79-75, Washington, DC, 1981, National Institutes of Health. In Umphred DA: *Neurological rehabilitation*, ed 5, St Louis, 2007, Mosby.)

a child has a fivefold higher risk of developing MS.<sup>158</sup> The human leukocyte antigen (HLA) region on chromosome 6 has been identified as one genetic determinant for MS, but this contributes only a small fraction to the genetic basis of MS.<sup>44</sup> Refinement of the genetic linkage map is in progress. The linkages are complex and may involve multiple weak links that are difficult to identify using current research methods. In Scotland, where risk of developing MS is high, there is an increase in the incidence of HLA-DR2 allele in the population that has a proven correlation to MS. The presence of HLA-DR2 is associated with a nearly twofold increase in the likelihood of having a second attack of MS within 5 years. The severity and course of MS may also be associated with different genes. A variety of genes have been associated with the disease, including interleukin-1 $\beta$  receptor, interleukin-1 receptor antagonist, and immunoglobulin Fc receptor.

Coexisting autoimmune disorders are seen in a majority of individuals, such as Hashimoto's thyroiditis, psoriasis, inflammatory bowel disease, and rheumatoid arthritis. Families with a history of MS have autoimmune disorders in greater than 65% of first-degree relatives. Hashimoto's thyroiditis, psoriasis, and inflammatory bowel disease are the most common disorders also occurring in family members. The presence of various immune disorders in families with several members with MS suggests that the disease might arise on a background of a generalized susceptibility to autoimmune disorders. A distinct MS phenotype, defined by its association with

other autoimmune diseases, segregates with specific genotypes that could underlie the common susceptibility.

Viral infection often precipitates an attack of MS. In fact, it is the only natural event that has been shown unequivocally to increase the risk of a new attack of MS. Less than 10% of infections are followed by relapses, but more than one third of the relapses are preceded by infection.<sup>44</sup> The possibility that infections, especially viral infections, actually may cause MS has been investigated for many years. Numerous candidate viruses and a smaller number of bacteria have been proposed and then rejected. Most recently, human herpesvirus 6 (HHV-6) and the bacterium *Chlamydia pneumoniae* have been touted as environmental triggers of MS. Research attempting to clarify these issues continues. There appears to be a protective effect of vitamin D intake on risk of developing MS.

### Pathogenesis

MS is the classic example of a primary demyelinating disorder, but demyelination alone does not account for the persistent functional disturbances that characterize the disease as it progresses. After myelin is damaged, nerve conduction properties, initially abnormal, can recover, in part related to redistribution of sodium channels. Axonal injury in MS, known from the work of Charcot in the mid-nineteenth century but subsequently associated only with late disease, was recently rediscovered as an important early pathology of considerable importance in MS.<sup>72</sup>

Myelin loss occurs initially around the small veins and venules. The spinal cord may show similar changes. There are focal abnormalities referred to as plaques disseminated throughout the cerebral hemispheres in the white matter, especially in the white matter surrounding the ventricles, the corpus callosum, the optic nerves, and the brainstem.

The pathologic conditions that occur in MS include inflammation, demyelination, and axon loss. MS is predominantly a T cell-mediated inflammatory disorder with overproduction of proinflammatory cytokines. Demyelination can result from either direct damage to neuronal myelin by inflammatory cells or indirectly because of the extracellular environment. This demyelination can cause neurons to be more susceptible to apoptosis. Although demyelination may produce the relapses that occur during the disease, long-term disability is due primarily to irreversible axon loss and cell death.<sup>62</sup>

The initial event in MS may be priming of autoreactive, peripheral T cells against myelin antigens by an infectious agent. It is believed that preexisting autoreactive T cells are activated outside the CNS by foreign microbes, self-proteins, or microbial superantigens. Activated T cells cross the blood-brain barrier through a multistep process. In this trafficking process, lymphocytes attached to endothelial cells proceed to pass through the endothelial cell cytoplasm. Chemokines, like cytokines, are secreted polypeptides that can induce increased production of integrin molecules by lymphocytes and switch these integrin molecules into a higher affinity state that allows them to transmigrate more effectively across CNS endothelium. The activated T cells secrete cytokines that stimulate microglial cells and astrocytes, recruit additional inflammatory cells, and induce antibody production by plasma cells. Antimyelin antibodies, activated macrophages or microglial cells, and tumor necrosis factor are believed to cooperate in producing demyelination. In the neurodegenerative phase of the disease, excessive amounts of glutamate are released by lymphocytes, microglia, and macrophages. The glutamate activates various glutamate receptors, causing the influx of calcium through ion channels associated with toxic damage to oligodendrocytes and axons. The oligodendrocyte is a nonneuronal component of the CNS that is directly related to the cell body or axon. The oligodendrocyte produces the myelin that wraps around the axon of the nerve cell. The myelin sheath increases the speed of the action potential and is critical for smooth and rapid movement.

Both necrosis and apoptosis play a role in the progression of MS. When necrosis occurs in MS lesions, it produces enhancing lesions caused by the substantial breakdown of the blood-brain barrier. In MS lesions, apoptosis occurs in neurons, oligodendrocytes, and leukocytes. Apoptosis occurs pathologically in MS, in part because the loss of myelin causes neurons to be much more susceptible to binding of agents that induce apoptosis rather than necrosis. Apoptosis is probably at least partially responsible for the progression that leads to permanent disability and explains why lesion activity on MRI scans can be quiescent at a time when the disability of the individual continues to increase. Apoptosis of oligodendrocytes may represent a very early stage in the

evolution of lesions that underlie acute relapses of MS. Therefore, myelin destruction in MS lesions may be caused by processes other than those mediated by macrophages.

Brain atrophy has emerged as a clinically relevant component in MS and begins early in the disease course. Progressive loss of brain tissue bulk can be identified by MRI. The caudate (part of the basal ganglia) can be smaller in volume and also have changes in shape. The demyelinated cortex contains apoptotic neurons. Cortical demyelination may influence dendrite and axon function and decrease neuronal viability, which may further activate disease progression. Axonotmesis as a result of inflammation in MS lesions can lead to retrograde neuronal degeneration and apoptosis.<sup>142</sup> In chronic lesions, demyelinated axons undergo a slow, disseminating Wallerian degeneration along neural tracts away from the initial site of injury, contributing to long-term disability.

Quantitative MRI indicates that cortical atrophy occurs early in the disease course and is related to physical disability and cognitive impairment. Besides demyelination, the cerebral cortex of individuals with MS may also be affected by tissue loss and atrophy, particularly in areas adjacent to severe white matter pathology. Neurons in such lesions may show signs of retrograde damage, including central chromatolysis. Furthermore, degeneration of cortical neurons could contribute to the depletion of neuronal metabolites in white matter that may not show MRI image changes.

New lesions frequently appear at sites of previous activity or within or at the edges of previously stable lesions. New lesions can form within or overlap shadow plaques (areas of thin remyelination) and may contribute to failed remyelination or the conversion of shadow plaques into classic demyelinated plaques.<sup>144</sup> Thus some lesions may appear to be quite large.

The plaques may be acute or chronic lesions. The acute plaques are small, circumscribed areas of hypocellularity, demyelination, and axonal loss. Astrogliosis, resulting in scar tissue formation, is more severe in MS lesions than in most other neuropathologic conditions. Periventricular infiltrates consisting of macrophages, T cells, immunoglobulins, and microglia fill the plaque.<sup>148</sup> Axons passing through may be spared, but there seems to be more and more evidence of axon loss within the plaques. New active plaques are pink with faint borders that exhibit an intense inflammatory response. Old inactive plaques are grey and firm, with sharp edges with a gliotic background crossed by axons but lacking oligodendrocytes.<sup>134</sup> Abnormal immune function in the blood and cerebrospinal fluid (CSF) is a common finding.<sup>74</sup>

A variety of pathogenic mechanisms may be involved in the development of MS plaques, which occur as a result of diversity in the sequence of events that causes the condition to arise. The features of the lesions, including the amount and nature of T cell-, macrophage-, and immunoglobulin-related damage, seem to vary from individual to individual, but there is much less variation among the active lesions within an individual. For example, the survival of oligodendrocytes varies among individuals.<sup>44</sup> In some individuals, it appears that oligo-

dendrocyte dystrophy and apoptosis are the primary cause of demyelination. In others, the presence of immunoglobulins suggests that demyelinating antibodies have a pathogenic role.<sup>104,112</sup> As with demyelination, axonal destruction could result from direct immunologic attack or inflammatory mediators or from secondary effects of chronic demyelination.<sup>182</sup>

### Clinical Manifestations

In most individuals, MS is characterized by progressive disability over time, but the amount of accumulated disability varies widely. A benign course may affect up to 20% of individuals and is characterized by an abrupt onset with one or a few relapses followed by complete or nearly complete remitting periods. These individuals experience little or no permanent disability and remain relatively symptom free. This is a designation that can only be made with certainty in retrospect, since there are no perfect prognostic markers. More recent MRI scan data suggest that even in individuals with benign MS there is likely significant progression of lesions.

Each individual's CNS appears to have a different threshold for producing symptoms and signs reflecting the affected regions of the CNS. This threshold, or the capacity of the individual's brain to adapt to the lesions, will determine the severity of the clinical manifestations.

Optic neuritis is often the first manifestation of MS. The optic nerve is an extension of the cerebral cortex, virtually a tract of the CNS, and is therefore subject to the effects of demyelination with the syndrome of optic neuritis. Optic neuritis typically presents as a unilateral, painful decrease or loss of vision. It is commonly associated with visual field defects, decreased color vision, and reduced clarity of vision.<sup>63</sup> Individuals with optic neuritis must be carefully evaluated for an ocular mobility abnormality to determine the possibility of a second anatomically distinct lesion, because the symptoms of blurring may be caused by an eye movement disorder.<sup>94</sup>

Early-onset MS is associated with lesions within the spinal cord. The spinal cord may be abnormal when the brain MRI is normal. However, an abnormal spinal cord is found more than half the time when there are nine or more brain lesions. Approximately 80% to 85% of individuals present with a relapsing-remitting course, with symptoms and signs evolving over days and typically improving over weeks.<sup>165</sup>

Sensory changes are most often the initial complaint. This is often a paresthesia or dysesthesia noted in one extremity or in the head and face. Visual blurring, diplopia, weakness, and balance problems also may be early signs. Often these symptoms are transient and not even reported. It is usually when there is a pattern or the symptoms are unchanging that the person seeks medical attention. Dorsal column symptoms include paresthesias (tingling, pricking) and hypoesthesia (diminished sensitivity). These may begin in an extremity and ascend over hours or several days to include the rest of the leg or arm, the perineum, the trunk, and perhaps other extremities. Other sensory complaints include a feeling of swelling, of wetness, or that the body part is tightly wrapped. Involvement of a cord level is diagnostically helpful in

distinguishing this attack from a peripheral neuropathologic incident. Other positive dorsal column signs are loss of vibration, position, and two-point discrimination. Sensory complaints are often not substantiated by objective findings, especially if the symptoms are mild or the remission has already begun before the individual is examined. For example, the feeling of numbness may not result in a loss of response to pinprick.

The single most common and most disabling symptom of MS is fatigue.<sup>64</sup> Fatigue is typically present in midafternoon and may take the form of increased motor weakness with effort, mental fatigue, and sleepiness. MS-related fatigue presents as an overwhelming feeling of tiredness in those who have done little and are not depressed. People who are depressed, whether they have or do not have MS, often do not sleep properly, eat properly, or feel well. They may describe this as fatigue, but the treatment revolves around the treatment of depression. Deconditioning and lack of endurance may lead to fatigue.

Neuromuscular or short-circuiting fatigue is common. The demyelinated nerve fires again and again until it shorts when it is called upon to do a repetitive task. Thus, progressive resistive exercises often result in a feeling of increased fatigue and weakness rather than a feeling of increased strength. Short breaks with energy conservation can make this fatigue less prominent.

Spasticity, velocity-dependent stiffness about a joint, is an extremely common problem with MS, occurring in 90% of all cases. It can vary from nonexistent to severe, even in the same person, and from moment to moment, making its management challenging. It seems to be the result of disequilibrium in the ascending and descending excitatory and inhibitory pathways in the brain and spinal cord. GABA and other neurotransmitters are involved. Often those who have significant spasticity use their spasticity to walk, transfer, and manage their daily living. Treatment becomes an issue only if the spasticity is causing discomfort, pain, or problems with daily living. Pain, either from an injury or from a bladder infection, exacerbates spasticity. Thus, the management of spasticity begins with the removal of noxious stimuli. In some individuals, spasticity can be intractable. The high doses of medications necessitated by this circumstance sedate and cause disability on their own. Spasms may accompany the spasticity and usually are more severe and frequent at night. They often interrupt the sleep cycle, even in those who do not recognize their awakenings. This may lead to severe fatigue the next day; thus, minimizing nocturnal spasms is important. Associated signs of upper motor neuron syndrome may include clonus, spontaneous extensor or flexor spasms, positive Babinski's sign, and loss of precise autonomic control.<sup>117,123,163</sup>

Weakness in MS usually is a result of decreased neuromuscular impulses secondary to demyelination and axonal loss. As discussed previously, progressive resistive exercises may contribute to fatigue and give the appearance of increasing weakness. Signs of muscle weakness secondary to damage of the motor cortex and tracts reflect the loss of orderly recruitment and rate modulation of motor neurons. Muscle activation patterns and agonist-antagonist relationships are disturbed.

Heat, either from increased ambient temperature or from fever, often increases weakness. This may be the result of a conduction block. Cooling often allows more efficient conduction and improved strength if there is appropriate innervation.

Involvement at the level of the brainstem reflects lesions of cranial nerves III through XII at the root, nuclear, or bulbar level. Trigeminal neuralgia (also called tic douloureux) is a shocklike pain in the face. Although not a common finding, it is highly characteristic of MS in a young person. Spasm or weakness of facial muscles can also be seen. Dysarthria, abnormal speech resulting from poor control of the muscles of speech, and dysphagia, including signs of gurgling, coughing, weight loss, pneumonia, choking, or a weak voice, can present in brainstem involvement.

There can also be gaze palsies, the loss of active control of eye movement, and nystagmus, involuntary rhythmic tremor of the eye. Intranuclear ophthalmoplegia is the most common gaze palsy, resulting in lateral gaze paralysis, and is caused by demyelination of the pontine medial longitudinal fasciculus, an area of the brain's white matter involved in the control of eye movement. Other lesions in the brainstem and reticular formation can cause other palsies, resulting in difficulty with conjugate gaze and ipsilateral gaze palsy. Idiopathic nystagmus that improves over time also can be caused by lesions in the vestibular nuclei or cerebellum.

Other abnormalities of ocular mobility, such as instability of fixation or inability to suppress the vestibuloocular response, are related to lesions involving brainstem nuclei and tracts. Vertigo, the sensation of spinning, may appear suddenly and in dramatic fashion with gait unsteadiness and vomiting. In MS this reflects a brainstem rather than end-organ vestibular disorder; a careful look at associated brainstem symptoms will help to distinguish the cause (see Chapter 38).

Coordination (ataxia) problems often accompany tremor and are among the most difficult symptoms to manage. Compensatory techniques taught via exercises can be helpful but rarely enough to satisfy. Cerebellar syndrome deficits may be symmetric, with all four limbs involved, or asymmetric, with only one side affected. Manifestations include ataxia, hypotonia, and truncal weakness, causing postural and movement disorders. Dysarthria of cerebellar origin (scanning speech, producing abnormalities in the rhythm of speech) is common. Cerebellar signs are often associated with the progressive phases of the illness.<sup>181</sup>

Pain is surprisingly common in MS, occurring in 50% of individuals. The pain usually is a burning neuropathic type. It may be disturbing, and pain medicine offers little if any relief. The distribution of the pain may not follow any recognizable neurologic distribution. It can be paroxysmal in nature but often is fairly constant, with nocturnal worsening when the body is at rest in bed. Another clinical symptom is Lhermitte's sign, a momentary electricity-like sensation evoked by neck flexion or cough.

Depression is a primary symptom of MS occurring because of actual changes in the brain and its chemistry. Depression can occur as a direct result of the MS plaques

or as a reaction to the diagnosis or disability. Depression may lead to greater disability than that caused by the level of neurologic impairment. Medication use for other symptoms may contribute to the cognitive problems with sedation and confusion; thus, these must be reviewed regularly in those who have dulled cognition. Depression may be an additive culprit and is treatable if recognized. There is no question that reactive (exogenous) depression occurs frequently in MS and is amenable to counseling and other nonpharmacologic techniques, but the brain disease seen in MS clearly leads to chemical (endogenous) depression in many. Cognitive decline is of significance in up to 50% of persons with MS.<sup>182</sup> Memory loss is the most common cognitive problem, and there commonly are a variety of slowed response types. The suicide rate for MS seems greater than that for many other neurologic diseases, some of which have a worse perceived prognosis.

Bladder and bowel symptoms are common and usually occur when the spinal cord is involved. Bladder urgency, frequency, and incontinence associated with an overactive bladder are often seen early in the disease and generally precede incontinence. Bladder issues are prominent in those who have MS. The bladder can present itself with frequency, urgency, hesitancy, and incontinence with differing mechanisms. Most frequent is the small, failure-to-store bladder characterized by a low postvoid residual. This can be measured by catheterization or ultrasound. It often has uncontrollable contractions.

More problematic from a management point of view is the large, failure-to-empty bladder. It overfills with residuals from 200 to 900 ml and presents with the same symptomatology despite looking different anatomically and physiologically. Frequently, there is a dyssynergia between the bladder and the urinary sphincter, causing similar symptoms from yet another mechanism. Residual urine after emptying, with subsequent overflow incontinence and heightened risk of urinary tract infections, is a problem for 50% of persons with MS, especially later in the course of the disease. This may require intermittent or chronic catheterization, or use of the Crede method (manual pressure on the bladder to express urine).<sup>14</sup> Neurogenic disorders may also impair bowel function, resulting in incontinence or constipation.

Bowel function is affected less than bladder function but can be problematic. Irritable bowel is a common associated problem, and regulating the bowel often means changing treatments, depending on the circumstances. It is better to be slightly constipated than slightly loose.<sup>163</sup>

Sexual expression may require special attention in MS. Relationships remain of utmost importance and need to be stressed, without diminishing the importance of the actual sexual performance in the face of disability. In men, erectile dysfunction is frequent. Occasionally, penile prostheses may be placed. This is less common today because of alternative treatment options. Female sexual expression may be diminished by vaginal dryness or decreased or altered sensation in the vaginal area.

Unique symptoms in MS are called paroxysmal because they come in bouts. Sometimes they are sensory in nature and may be painful. Trigeminal neuralgia is a common

example of this type of painful, paroxysmal symptom. This lancinating, electrical sensation along the distribution of a branch of the trigeminal nerve can be terribly disabling. It may be a stand-alone problem in some individuals but also is a symptom associated with MS. Periodic electrical sensation down the spine with the bending of the neck is called Lhermitte's sign, another paroxysmal sensory symptom. These types of sensations occasionally may be felt in other parts of the body. Often the paroxysmal symptoms are motor in nature. They may be twitching of an eyelid or myokymia in the facial muscles. They may manifest as a true spasm of an arm in an extended or, occasionally, flexed position lasting for seconds. They can occur frequently, several times an hour. The spasm may occur with speech, a paroxysmal dysarthria or speech arrest. All of these can be disconcerting to the individual and the clinician.

The aggressive use of immune-modulating agents to slow down the actual disease process has contributed to the development of a whole new set of symptoms that the clinician must recognize and manage. Interferon initiation often brings about a fever reaction, which may be disabling to the person who has MS. It often is recommended that interferon be administered in the evening before going to bed. This allows for the impact of the fever during the night, when it may be less disabling to activities of living. Antipyretic medications (ibuprofen or acetaminophen) may be administered 4 hours before the injection, at the time of injection, and then, if necessary, 4 hours after the injection.

Subcutaneous injections can lead to immune reactions within the skin, with inflammation, redness, and significant irritation. Good injection technique is essential. This may involve icing the area before injecting. A common error is injecting too shallowly. Injection devices use improved techniques and have decreased many of these side effects but may contribute to the problem if they are set to deliver the medication too shallowly within the skin rather than beneath it. It is important to allow the air bubble in the syringe to remain to push the medication through the skin and it is recommended that the needle be free of lingering medication as it pierces the skin. Rotation of the injection sites is an absolute necessity to preserve as much skin area as possible and allow healing between injections. For some individuals, the addition of a cortisone cream or a local anesthetic cream may be helpful. With some treatments, pain can linger after the injection. Applying cooling can offer symptomatic relief. Understanding the issues often is helpful in the development of compensatory strategies.

Glatiramer acetate occasionally induces a systemic reaction. This rare, but real, symptom complex presents with a feeling of panic, chest discomfort, shortness of breath, and a feeling of doom and gloom. It usually lasts for 20 minutes and then clears rapidly, but if panic sets in and an emergency is called, the issue may be magnified and complicated. The treatment is to realize that the problem is associated with the medication and requires resting for the duration of the symptoms to allow them to abate on their own. This usually is not a recurrent problem but occasionally can repeat.

## MEDICAL MANAGEMENT

**DIAGNOSIS.** No clinical sign or diagnostic test is unique to MS, but a typical clinical syndrome with typical MRI of the brain or spinal cord and exclusion of other similar illnesses can result in a correct diagnosis very rapidly. MRI of the brain and spinal cord is critical to the diagnosis of MS. It is, however, important to first exclude other potentially treatable causes of the presenting symptoms before making a diagnosis of MS. Box 31-8 show some examples of differential diseases for which screening should be done. The corpus callosum is usually involved in MS, whereas this is not as common in hypoxic-ischemic diseases. This is because this structure receives a unique double blood supply, and with short arterioles, perfusion deficits may be less likely to result in injury.

The whole spinal cord can be imaged with high resolution and phased-array coils, showing abnormalities in 80% to 90% of individuals with MS, usually without accompanying neurologic symptoms or signs. Hypoxic-ischemic disease does not present with spinal cord abnormalities. Incidental spinal cord lesions do not occur with aging and are rarely reported in other immune-mediated disorders. Most individuals with early MS have lesions within the spinal cord. But imaging may not be performed, so they may not be isolated. Spinal cord lesions tend to increase as the number of brain lesions rises; this is associated with higher risk for a second attack and a diagnosis of clinical MS. Ultimately, abnormal brain MRI scans are present in more than 90% of individuals with clinically definite MS. Normal brain MRI scans may represent disease that is relatively restricted to the spinal cord. Reductions in nerve fiber density are seen in the spinal cord, including in otherwise normal-appearing tissue, and are likely related to permanent disability. Axonal loss can be profound in later stages of disease.

Fig. 31-8 shows the plaques seen on MRI. The lesions do not always correlate with the clinical signs, and there can be evidence of focal lesions in the absence of disease. In fact, the vast majority of enhancing lesions are considered to be asymptomatic when they first appear on the brain scan. However, there is a correlation between periods of clinical worsening of the disease and increases in the total number of lesions, the number of new lesions, and the total area of enhancement on MRI.<sup>23</sup> Thus, a single brain MRI scan after a first event is highly prognostic of development of clinically definite MS.<sup>137</sup> Fig. 31-9 shows an example of aggressive MS over 2 years revealed in MRI imaging.

Contrast enhancement in CT and MRI suggests inflammation but is more accurately a measure of leakage of moderate-size molecules across the damaged tight junctions of the CNS endothelium. The enhancement pattern (size, shape, solid versus ring) may be variable within and more so between individuals, which reflects a heterogeneous pathology. Ring enhancement, for example, may suggest a more severe pathology. Fig. 31-10 demonstrates the development of a T2-weighted hyperintense lesion by serial MRI. The correlation between the pattern of enhancement, the underlying pathology, and the clinical course in given individuals may not be straightforward.

**Box 31-8****DIFFERENTIAL DIAGNOSIS OF MULTIPLE SCLEROSIS****Other Inflammatory Demyelinating Central Nervous System Conditions**

- Acute disseminated encephalomyelitis
- Neuromyelitis optica

**Systemic or Organ-Specific Inflammatory Diseases**

- Systemic lupus erythematosus
- Sjögren's syndrome

**Inflammatory Bowel Disease**

- Vasculitis
- Periarteritis nodosa
- Primary central nervous system angiitis
- Susac's syndrome
- Eales' disease
- Granulomatous diseases
- Sarcoidosis

**Infectious Disorders**

- Lyme neuroborreliosis
- Syphilis
- Viral myelitis
- Progressive multifocal leukoencephalitis
- Subacute sclerosing panencephalitis

**Cerebrovascular Disorders**

- Multiple emboli
- Hypercoagulable states
- Sneddon's syndrome
- Neoplasms
- Metastasis
- Lymphoma
- Paraneoplastic syndromes

**Metabolic Disorders**

- Vitamin B12 deficiency
- Vitamin E deficiency
- Central (or extra) pontine myelinolysis
- Leukodystrophies (especially adrenomyeloneuropathy)
- Leber's hereditary optic neuropathy

**Structural Lesions**

- Spinal cord compression
- Chiari malformation
- Syringomyelia/syringobulbia
- Foramen magnum lesions
- Spinal arteriovenous malformation/dural fistula

**Degenerative Diseases**

- Hereditary spastic paraparesis
- Spinocerebellar degeneration
- Olivopontocerebellar atrophy

**Psychiatric Disorders**

- Conversion reactions
- Malingering

From Goetz CG: *Textbook of clinical neurology*, ed 2, Philadelphia, 2003, Saunders.

Monitoring serial MRI studies with enhancement helps to identify agents that may be active against the early inflammatory stage of MS.<sup>170</sup>

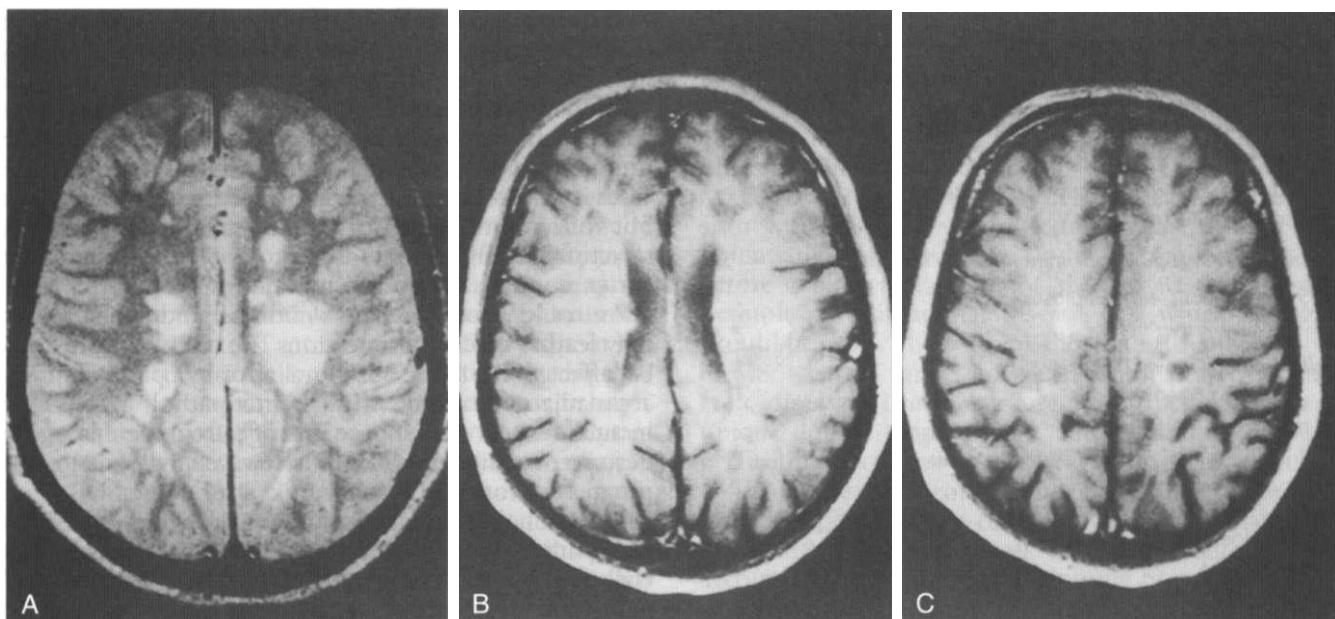
Individuals with MS have significant atrophy of both white matter and grey matter. Atrophy is considered an important measure in MS because it likely reflects in most cases irreversible injury, much of which is from axon loss, but with additional contributions from myelin loss and structural changes from astrogliosis. The demyelinated cortex contains apoptotic neurons. Cortical demyelination could affect neurons, dendrites, and axons, which may lead to disease progression. The cerebral cortex may be affected by tissue loss and atrophy, particularly in areas adjacent to severe white matter pathology. Neurons in such lesions may show signs of retrograde damage as described earlier. Fig. 31-11 shows changes related to progressive forms of MS.

Functional MRI maps the brain areas activated using a task paradigm. Functional disturbances have been the basis for hypotheses suggesting that compensatory mechanisms develop in early MS, which initially may mask injury and delay the appearance of dysfunction. Functional disturbance may only become apparent after exhaustion of these adaptive mechanisms. Fatigue severity is correlated with the reduction in thalamic and cerebellar activation. Although abnormal functional MRI patterns may be observed in given individuals with MS, their interpretation may not be straightforward. Functional MRI findings reflect functional adaptation, they do not necessarily serve as direct evidence for grey matter pathology.

Functional MRI appears to identify sensorimotor and cognitive disturbances in MS. The most consistent finding by functional MRI studies in populations of individuals with MS is impairment in sensorimotor activation indicated by abnormally increased contralateral blood oxygenation level and ipsilateral supplementary motor activation. Sensorimotor functional MRI is sensitive even in the early stages of disease.

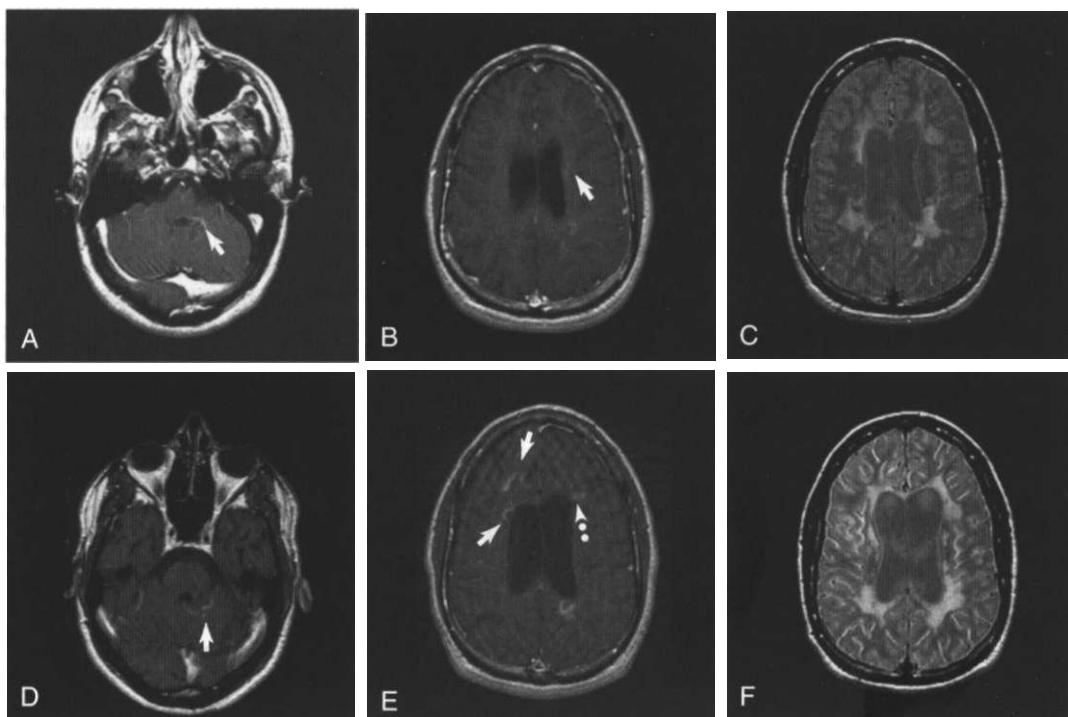
Measures of regional brain atrophy are useful to determine neuropsychologic dysfunction. Imaging data suggest that neuropsychologic impairment in MS is related, in part, to atrophy of grey matter regions and in the juxta-cortical areas. Grey matter atrophy has been associated with impairments in verbal memory, euphoria, and disinhibition.

Whole-brain atrophy reflects the destructive aspects of the disease. The data linking brain atrophy to clinical impairments suggest that irreversible tissue destruction is a major determinant of disease progression, whereas white matter lesion activity has less correlation. The strongest correlations between MRI measures and disability may be those provided by atrophy measures. Confounding factors must be considered when assessing whether loss of brain volume directly indicates tissue atrophy. Secondary progressive disease causes significantly more atrophy of both white matter and grey matter and a significantly higher lesion load than relapsing-remitting disease.<sup>174</sup> Primary progressive disorders show decreased numbers and volume of enhancing lesions, related to the less intense inflammation. Spinal cord



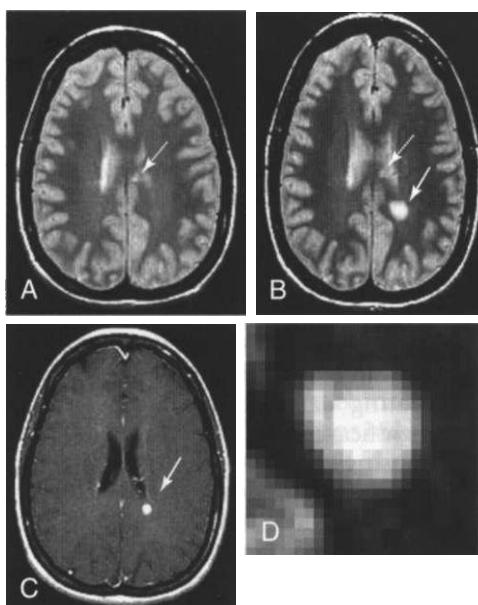
**Figure 31-8**

**A**, Typical scattered, variably sized plaques in the brain associated with the diagnosis of multiple sclerosis (MS). **B**, Contrast-enhanced magnetic resonance imaging reveals scattered area of solid and ring-shaped enhancement. **C**, Note the atrophy, greater than would be expected for the person's age, a common finding in MS. (From Ramsey R: *Neuroradiology*, Philadelphia, 1994, Saunders.)



**Figure 31-9**

Aggressive multiple sclerosis over 2 years. Disease was initially relapsing-remitting but converted relatively quickly to secondary progressive MS. Top row: Contrast-enhanced left pons (**A**) and left frontal-parietal white matter (**B**), both showing a relatively rare edge enhancement pattern (arrows). Typical confluent T2 hyperintensities and mild-moderate volume loss based on lateral ventricle size (**C**). Bottom row: Two years later magnetic resonance image shows different edge-enhancing lesions (arrows) in posterior fossa (**D**) and both edge enhancement (arrows) and ring enhancement (dotted arrow) in deep white matter along the lateral ventricles (**E**). Progressive volume loss based on moderately large lateral ventricles and more extensive confluent T2 hyperintensity is seen in (**F**). (From Radiologic Clinics of North America, Volume 44, Number [1], January 2006. Copyright © 2006 WB Saunders Company.)



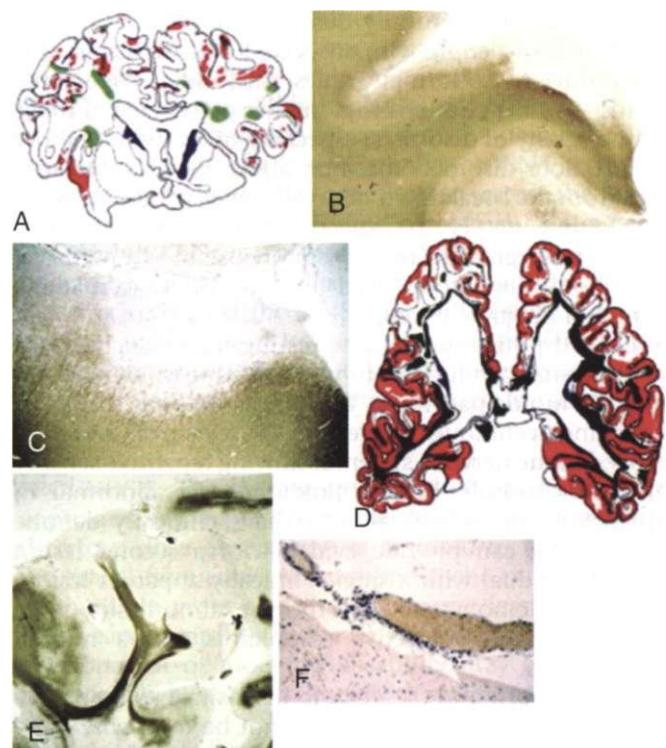
**Figure 31-10**

Development of a T2 hyperintense lesion by serial magnetic resonance imaging. **A**, Case of relapsing multiple sclerosis with low T2 hyperintense lesion burden, including chronic lesions in the corpus callosum (arrow). **B**, One month later, a new T2 hyperintense lesion develops in the left parietal-occipital white matter (solid arrow), whereas the corpus callosum lesions remain stable (dotted arrow). **C**, Corresponding enhancement in acute lesion (arrow) from blood-brain barrier breakdown and concurrent inflammation. **D**, Exploded view of the new lesion showing the complex structure, centrally hyperintense, most likely from mixed pathology including demyelination, matrix including glial change, and, importantly, axonal degeneration. The intermediate black ring may be a zone of macrophage infiltration, and the outer ring is likely from edema. (From Radiologic Clinics of North America Volume 44, Number 1, January 2006 Copyright © 2006 WB Saunders Company.)

pathology has been hypothesized to be an important factor in disease progression in primary progressive MS but is not always predictive (see Fig. 31-11).

Cellular imaging based on superparamagnetic iron oxide-tagged cells is a more specific probe of the migration occurring at the level of the blood-brain barrier basic to the inflammatory process. The superparamagnetic iron oxide particles are used to follow macrophages as they pass into the CNS. The particles exert a strong influence on the local magnetic field, which is detected as signal loss on T2-weighted and T2-weighted pulse sequences. The location of lesions and their time course based on superparamagnetic iron oxide imaging does not correlate strongly with that based on conventional contrast-enhanced MRI, suggesting that it provides different quantitative and qualitative information. Studies of fiber degeneration and connections between lesions and fiber pathways are becoming feasible in the clinical imaging environment through diffusion tensor MRI.

Although the mechanisms that contribute to brain atrophy are unclear, degenerative processes that underlie brain atrophy will hopefully provide novel therapeutic targets to help individuals. Several initiatives are under way to define criteria for successful or acceptable treatment versus treatment failure, based on both clinical



**Figure 31-11**

Cortical plaques in progressive forms of multiple sclerosis (MS). Cortical demyelination and diffuse white matter inflammation are hallmarks of primary progressive MS (PPMS) and secondary progressive MS (SPMS). **A** and **D**, Schematic lesion maps based on whole hemispheric sections from two archival cases of progressive MS. Case A (PPMS): A 37-year-old man with a history of gradually progressive hemiparesis (left greater than right), sphincter dysfunction, and dysarthria, requiring use of a wheelchair within 6 years of disease onset. Patient died at age 72 of aspiration pneumonia and acute myocardial infarction. Case D (SPMS): A 33-year-old woman initially presenting with diplopia and hemiataxia that partially resolved following short course of corticosteroids. Subsequent course characterized by gradually progressive dysarthria, dysphagia, ophthalmoplegia, and limb and gait ataxia, requiring use of a wheelchair within 7 years of disease onset. She also developed a focal seizure disorder 4 years prior to death and died at age 46 of aspiration pneumonia. **B** and **C**, Subpial cortical demyelination is demonstrated in case A at low (**B**) and high (**C**) magnification. **E**, Extensive subpial demyelination involving multiple gyri is illustrated in case D at low magnification. **F**, Meningeal inflammation may be prominent, often in close proximity to areas with subpial cortical demyelination. Proteolipid protein immunocytochemistry; green = focal demyelinated plaques in the white matter; orange = cortical demyelination; blue = demyelinated lesions in the deep grey matter. (From Palko I: Gray matter involvement in multiple sclerosis, *Neurology* 68[9]:634-642, 2007.)

and MRI activity. MRI monitoring may increase confidence in a clinical impression of stable disease or help discount borderline symptoms or signs, supporting maintenance of the current therapy. MRI activity may support a clinical impression or uncover a need to initiate aggressive and more risky therapy with immunosuppressive agents.

CSF analysis often shows increased mononuclear cell pleocytosis, an elevation in total immunoglobulins, and the presence of oligoclonal bands. These responses suggest an inflammatory response in the CNS. In 85% to 95% of

individuals with clinically definite MS, these values are abnormal. In people with suspected MS, the number is much lower. Abnormal values, including oligoclonal bands, also may be seen in a smaller percentage of those with a variety of disorders, especially other inflammatory or infectious disorders that may affect the CNS. Metabolites from the breakdown of myelin may also be detected in CSF but are very nonspecific. Measurement of these myelin basic proteins in CSF is more useful as a predictor of response to steroids used during acute exacerbations than as a diagnostic tool.

Evoked potential response testing may detect slowed or abnormal conduction in visual, auditory, somatosensory, or motor pathways. These tests employ computer averaging techniques to record the electrical response evoked in the nervous system following repetitive sensory or motor stimuli. Evoked potentials are abnormal in up to 90% of individuals who have clinically definite MS. Testing can provide evidence of a second lesion in an individual with a single clinically apparent lesion, or it can demonstrate an objective abnormality in an individual with subjective complaints and a normal examination.

Myelography and CT are both insensitive to the pathologic changes in MS and should not be used where the diagnosis of MS is a possibility. Both may still be used to rule out other disorders that mimic MS symptoms.

**TREATMENT.** Keeping an activated immune system from getting to the central myelinated fibers slows the process of demyelination in MS. Therefore, the principle of treatment in MS today revolves around immune modulation. Different steps of the pathologic cascade in MS may eventually be targeted therapeutically for optimal treatment of MS. Understanding the inflammatory process in MS is important, because it is becoming clear that inflammation includes destructive components that should be targeted for inactivation and potentially beneficial mechanisms that should be enhanced or not disturbed by treatment. Despite earnest research efforts, there is no cure for or immunization against MS.

Current drug therapy can diminish approximately one third of the attacks in the actively affected MS population 2 years beyond onset. The "ABC" drugs are used. A is for interferon beta-1a (Avonex, Biogen Idee), and B is for interferon beta-1b (Betaseron, Berlex Laboratories). The higher the dose of interferon, the more potent is the response. Rebif, another interferon beta-1a drug, is used in higher doses. Rebif is given subcutaneously at a 46% higher dose three times weekly, for a total of 4.4 times as much drug as Avonex. The potent antiinflammatory effects of interferons have a dramatic effect on the MRI scans, with a decrease in contrast-enhancing lesions.<sup>101,106</sup> Interferon beta-1a also has been shown in relapsing individuals to slow progression of disability, brain atrophy, and cognitive dysfunction.<sup>108</sup> The treatment effect can be delayed by at least several months. This delay might indicate the fact that the atrophy occurring in the first months is the culmination of a cascade of events that began before the onset of therapy. Alternatively, the ongoing loss of brain volume might be the result of "pseudoatrophy," such as that due to treatment-related resolution of

brain edema and inflammation. Proposed mechanisms by which interferon might limit brain atrophy include increasing nerve growth factors, limiting immune-mediated destructive inflammation, and limiting toxic mechanisms such as pathologic iron deposition.<sup>122</sup> Thus, the question remains as to whether controlling acute relapses and inflammation will ultimately be adequate. Other factors may have an influence on demyelination and axon injury.<sup>134</sup>

The C drug, glatiramer acetate (Copaxone, Teva Pharmaceutical Industries) is a polypeptide that appears to fool the immune system. It seems to decrease the attack by blocking immune cells headed toward myelin and thereby preventing damage. It also has a partial and delayed but significant effect of limiting the rate of brain atrophy in relapsing-remitting MS. Glatiramer acetate has gained wide acceptance as one option for the treatment of relapsing-remitting MS as there is less occurrence of the flulike symptoms that are associated with the interferons. Although its precise immunologic mechanisms continue to be investigated, current views suggest that its principal effect may be mediated by a shift from a proinflammatory cell bias to an antiinflammatory cell bias. Ongoing studies are exploring the possibility that glatiramer acetate confers neuroprotection and are seeking novel ways to use the agent alone or in combination with other medications.<sup>120</sup> Localized panniculitis or inflammation of lipid stores at the sites of subcutaneous injections seems to be a rare but characteristic side effect.

Mitoxantrone (Novantrone, Immunex) is used to modify relapsing and secondary progressive MS. Mitoxantrone is the only drug approved for treatment of secondary progressive MS. It presumably works by depression of T-cell counts and removal of activated T cells from the immune repertoire. Because of potential side effects, its use is being limited at present to individuals whose MS is clearly advancing in spite of aggressive ABC therapy or who already are in a secondary progressive phase. The ABC drugs have not yet been found conclusively to be helpful in secondary progressive disease, and no drugs have been found effective in primary progressive disease.<sup>169</sup>

Natalizumab (Tysabri) is a monoclonal antibody that prevents immune cells from moving from the blood to the CNS. It was originally approved by the FDA based on a dramatic lowering of relapse rate and a 50% reduction in the development of a sustained increase in disability. This treatment is a once-monthly intravenous infusion. Unfortunately, shortly after approval of the treatment by the FDA, there were two fatal cases of progressive multifocal leukoencephalopathy (PML) when it was used in conjunction with interferon beta-1a. As a result, the distribution of natalizumab was halted, pending further evaluation. Studies continue, and it may emerge again for use in treating MS, perhaps as a monotherapy.<sup>187</sup>

Fingolimod (FTY720) is a new oral immunomodulating agent under evaluation for the treatment of relapsing MS. Its final effect is also to reduce the normal circulation and trafficking of leukocytes. It also nears the 50% mark for decreasing the mean cumulative number of lesions. A phase III trial is under way to definitively assess clinical efficacy. Encephalopathy is a risk, and fin-

golimod is also associated with an initial reduction in the heart rate.<sup>92</sup>

Despite the time and effort given to slow the disease, the bulk of current intervention is devoted to symptomatic management. Improvement in the ability to control symptoms through therapy and medications can enhance quality of life in the individual with MS. Amantadine, pemoline, modafinil, and other medicines can reduce fatigue. Depression and sleep disorders may contribute to fatigue and must be recognized and treated appropriately. Centrally acting and peripherally acting muscle relaxants, such as baclofen (Lioresal), tizanidine, and dantrolene, decrease hypertonicity and leg spasms. Anticonvulsants and antidepressant medicines are used to treat pain. Intrathecal baclofen pumps reduce severe spasticity. Oxybutynin and tolterodine diminish bladder hyperactivity. Focal injections of BTX can be helpful in decreasing muscle spasticity.<sup>1</sup> Repetitive transcranial magnetic stimulation may improve spasticity in MS. The antiepileptic agents and antidepressant treatments often are effective in modulating the painful symptoms. Gabapentin in relatively high doses often is necessary for the desired effect. Spasms occurring during the day usually are handled best by the addition of the antiepileptic medications, including gabapentin and topiramate.

Amitriptyline is helpful, especially at night as it can sedate and provide pain relief. Clonazepam, given at bedtime, can aid in sleep initiation and decrease spasms with minimum side effects. Diazepam has a similar effect. Dose escalation should be avoided. Dopamine agonists and dopamine itself also decrease nocturnal spasms reasonably effectively at low dosages.

All of these treatments require adjustment from time to time to maintain some relief. All medications currently available to control symptoms of MS have potential side effects and therefore must be used judiciously. Careful monitoring of systems affected by MS is essential to medical management.<sup>157</sup>

Both corticosteroids (prednisone, cortisone, methylprednisolone) and adrenocorticotropic hormone (ACTH) are known to shorten the recovery period after an acute MS attack. There appears to be no consensus about the optimal form, dosage, route, or duration of corticosteroid therapy, but there is now a consensus statement from the American Academy of Neurology regarding treatment of acute optic neuritis with methylprednisolone. Oral prednisone should not be used. Corticosteroids can alter almost every aspect of the immune system. Corticosteroid-induced restoration of the blood-brain barrier, which becomes less effective during active demyelination or plaque formation, has an anti-edema benefit and may prevent circulating toxins, viruses, or immunoactive cells from entering the CNS. Decreased activity of the macrophages and lymphocytes results in less damage to the myelin in response to steroid therapy.<sup>61</sup> Individuals with severe demyelination who do not respond to corticosteroids may improve with plasma exchange.<sup>93-94</sup>

Based on the rapid advances in our understanding of the immunopathogenesis of MS, a variety of experimental approaches presently are under study. These include the hormonal agent estriol, matrix metalloproteinase

inhibitors, statin drugs, adhesion molecule antibodies, T-cell peptides, combination therapies (especially ABC drugs with other types of agents), intravenous immunoglobulin, and stem cell transplantation. All these are preventive, not restorative of previously damaged CNS function. Growth factors that enhance CNS remyelination are being studied as a method to restore the loss of oligodendrocytes in MS.<sup>139</sup> Findings of neural stem cells in the adult CNS and the potential of blood-derived stem cells to become neural cells offer the possibility of transplanting cells into the CNS that will restore function. Studies on intense immunosuppression with bone marrow transplantation (autologous and stem cell) continue, but results are not positive enough to recommend its use.

**PROGNOSIS.** The average frequency of attacks of MS is approximately 1 per year. The attacks vary in severity; therefore close observation is required to reliably track the attack frequency. Attacks tend to be most common in the early years of MS and become less frequent in later years, regardless of the disability. The risk for rapid development of moderate disability may be greater in persons in whom the frequency of attacks is higher than average.

Multiple factors may predict a severe course, such as motor and cerebellar symptoms, disability after the first attack, and short time interval between attacks. Numerous relapses within the first year negatively influence the clinical course. Conversely, sensory symptoms, infrequent attacks, full neurologic recovery after a relapse, and a low level of disability after 5 to 7 years may be associated with an improved prognosis.

Burden of disease on MRI scans may be the strongest predictor of clinical outcomes. Over 14 years, there was no significant disability accrued in individuals with normal MRI findings at the time of diagnosis, whereas MRI scans with greater than 10 lesions predicted that individuals would require a cane for walking within that same time frame. A change in lesion load within the first year also is a negative predictor of outcome. Late-onset MS is not necessarily associated with a worse outcome. Progression of primary progressive and relapsing MS differed little between late-onset and early-adult-onset disease. The individuals with late-onset disease were older when reaching an Expanded Disability Status Scale score of 6.<sup>183</sup>

Because disability is often significant in individuals with MS, lifestyle changes are frequently necessary. Movement impairment is frequently associated with MS, and difficulty in walking is a major disability. If MS is untreated, 15 years after diagnosis 50% of individuals with MS will require the use of an assistive device to walk, and at 20 years 50% will be wheelchair bound. About one fourth of persons with MS will require human assistance with ADLs.<sup>94</sup>

It is the coexistence of physical and cognitive impairments together with emotional and social issues in a disease with an uncertain course that makes MS rehabilitation unique and challenging. Individual rehabilitation improves functional independence but has only limited success in improving the level of neurologic impairment.

Severely disabled people derive as much as or more benefit than those who are less disabled, but cognitive problems and ataxia tend to be refractory. Cost and utility are significantly correlated with functional capacity.<sup>97</sup> There is now good evidence that exercise can improve fitness and function for those with mild MS and helps to maintain function for those with moderate to severe disability. Several different forms of exercise have been investigated. For most individuals, aerobic exercise that incorporates a degree of balance training and socialization is most effective. Time constraints, access, impairment level, personal preferences, motivations, and funding sources influence the prescription for exercise and other components of rehabilitation. Just as immunomodulatory drugs must be taken on a continual basis and be adjusted as the disease progresses, so should rehabilitation be viewed as an ongoing process to maintain and restore maximum function and quality of life.<sup>27</sup>

Life expectancy is reduced by a modest amount in MS; the risk of dying of MS is strongly associated with severe disability. The death rate in persons who are unable to stand or walk is more than four times that in persons the same age without MS. In mildly disabled individuals, the death rate is approximately 1.5 times that of the age-matched population. Persons with more frequent initial episodes with rapidly developing disability have a poorer long-term outcome. Individuals with primary progressive disease also have decreased life expectancy. Suicide is more than seven times more common than in age-matched controls, and depression must be treated aggressively.

The replacement of oral spasticity medications with intrathecal baclofen has become more routine, and the therapist should be involved in the dosing and management. Any spasticity the individual is using for ADLs may be altered. Thus, transferring techniques may require a different approach. The perception of strength that may be given by stiffness may disappear, giving the perception of weakness. Determining the appropriate muscle for use of BTX should also be done with the therapist who is most familiar with the individual's movement disorder and functional status.

In establishing a training program for endurance and strengthening, careful consideration of the neurologic changes is critical.<sup>75</sup> Careful monitoring of exercise appears to be necessary because of impaired cardiopulmonary systems. Individuals with MS have poor exercise tolerance as a result of respiratory muscle dysfunction.<sup>37</sup> Repetitive submaximal strength training appears to be of benefit to most people, with an increase in both peak torque generated and a decrease in the reported perception of fatigue.<sup>172</sup> Changes achieved in strength and endurance are probably the result of the normal physiologic changes that are associated with this type of training. Clients demonstrating increased reflex activity with exertion will need a longer time to recover after fatigue and may notice increased extensor tone and difficulty with flexion. Use of cooling vests to lower core temperature during exercise can be beneficial to those who have heat intolerance. It is important to realize that for most people with MS, fatigue will exacerbate symptoms.<sup>38</sup>

Establishing individually designed fitness programs is an important role of the physical therapist. Models for such programs can lead the therapist in the appropriate direction and provide protocols taking into consideration the common concerns associated with MS.<sup>96</sup>

Understanding movement disorders common to lesions in specific brain regions and the spinal column is essential for the therapist. Analysis of movement is the most critical skill necessary to determine sensory and motor deficits that may be contributing to loss of postural control and mobility. The therapist must be able to identify the specific impairments to establish the appropriate stretching and strengthening exercises. A successful exercise program depends on a number of factors essential to motor learning, including practice, adequate feedback, and knowledge of results. The client with MS is often restricted in practice by neurologic fatigue and by impairments that disrupt sensory feedback, attention, memory, and motivation. The therapist will need to carefully identify the client's resources and abilities and capitalize on them to minimize the level of disability.<sup>138</sup>

A common disability scale used by rehabilitation professionals and researchers working with patients with MS is the Kurtzke Expanded Disability Status Scale (Box 31-9). It is used to monitor changes in disability levels and has value in determining prognosis. Therapists working with this patient population should become adept at using this tool.<sup>72</sup>

## SPECIAL IMPLICATIONS FOR THE THERAPIST 31-5

### **Multiple Sclerosis**

#### PREFERRED PRACTICE PATTERN

**SE: Impaired Motor Function and Sensory Integrity Associated with Progressive Disorders of the Central Nervous System**

Because MS is typically progressive, it is expected that individuals will need to access the medical community with greater needs over time. Maintaining function in the household and community is a typical rehabilitation goal. Although people with MS are advised to be as active as possible in all ways of life, there is no consensus on the best method to attain that goal. Activity carried out in accordance with individual strength and abilities, avoiding exhaustion, will help to prevent or diminish the complications leading to disability. Skin breakdown following sensory loss and immobility is a common problem that can be controlled by appropriate skin care and positioning.

Fatigue and weakness are the complaints most often taken to a therapist. The Modified Fatigue Index is a self-report scale to monitor changes in the level of fatigue. This can be helpful for therapists to measure changes associated with interventions or to describe changes in function following a relapse.

**Box 31-9****KURTZKE EXPANDED DISABILITY STATUS SCALE**

0.0	Normal neurologic examination
1.0	No disability, minimal symptoms
1.5	No disability, minimal signs in more than one functional level
2.0	Slightly greater disability in one functional system
2.5	Slightly greater disability in two functional systems
3.0	Moderate disability in one functional system; fully ambulatory
3.5	Fully ambulatory but with moderate disability in one functional system and more than minimal disability in several others
4.0	Fully ambulatory without aid, self-sufficient, up and about 12 hr/day despite relatively severe disability; able to walk about 500 m without aid or rest
4.5	Fully ambulatory without aid, up and about much of the day, able to work a full day; may otherwise have some limitation of full activity or require minimal assistance; characterized by relatively severe disability; able to walk about 300 m without aid or rest
5.0	Ambulatory for about 200 m without aid or rest; disability severe enough to impair full daily activities (e.g., to work a full day without special provisions)
5.5	Ambulatory for about 100 m without aid or rest; disability severe enough to preclude full daily activities
6.0	Intermittent or unilateral constant assistance (cane, crutch, brace) required to walk about 100 m with or without resting
6.5	Constant bilateral assistance (canes, crutches, braces) required to walk about 20 m without resting
7.0	Unable to walk beyond approximately 5 m with aid; essentially restricted to a wheelchair; wheels self in standard wheelchair and transfers alone; up and about in wheelchair 12 hr/day
7.5	Unable to take more than a few steps; restricted to wheelchair; may need aid in transfer; wheels self but cannot carry on in standard wheelchair a full day; may require motorized wheelchair
8.0	Essentially restricted to bed or chair or perambulated in wheelchair but may be out of bed itself much of the day; retains many self-care functions; generally has effective use of arms
8.5	Essentially restricted to bed much of the day; has some effective use of arm or arms; retains some self-care functions
9.0	Helpless bed patient; can communicate and eat
9.5	Totally helpless bed patient; unable to communicate effectively, eat, or swallow
10.0	Death from multiple sclerosis

Modified from Kurtzke J: Rating neurological impairment in multiple sclerosis: an expanded disability status scale (EDSS), *Neurology* 33:1444, 1983.

The day-to-day variation in MS makes determination of an appropriate training program challenging. Use of both impairment and disability scales will assist in monitoring changes. The scales show the relative improvement after intervention or overall decline regardless of intervention. The scales are useful in tracking the disease process for both the client and the health care provider. Therapists making decisions regarding the need for adaptive equipment can use the scales to establish trends in the course of the disease.

of the CNS, characterized by rigidity, tremor, and bradykinesia and postural instability. The disease is thought to result from a complex interaction between multiple predisposing genes and environmental effects, although these interactions are still poorly understood. PD is still regarded as a sporadic neurodegenerative disorder, characterized by the loss of midbrain dopamine neurons and presence of Lewy body inclusions.

### Incidence

Parkinsonism, including PD, affects more than 800,000 adults in the United States, with prevalence rates of 350 per 100,000. Approximately 42% of parkinsonism is related to PD. The lifetime risk of developing parkinsonism is 7.5% according to a Mayo study. There appears to be a higher rate among white Americans and Europeans compared with black Africans. Black persons in America and Chinese in Taiwan have higher rates of disease than their counterparts in West Africa or China.<sup>13</sup> PD becomes increasingly common with advancing age, affecting more than 1 person in every 100 over the age of 75 years. A possible explanation of the correlation between age and prevalence may be the age-related neuronal vulnerability. Because of the increase in life expectancy, the aging of the baby boomers, and the precision of diagnosis, the incidence of PD is expected to rise. It is estimated that there will be more than 1.5 million persons living with PD in the United States and close to 40 million worldwide by the year 2020. The majority of cases begin between the

## PARKINSONISM AND PARKINSON'S DISEASE

### Overview and Definition

Atrophy of the brain leading to degeneration of neurons in the basal ganglia can be caused by a variety of disorders that are not well understood. These include striatonigral degeneration, Shy-Drager syndrome, progressive supranuclear palsy, olivopontocerebellar atrophy, corticobasal ganglionic degeneration, and diffuse Lewy body disease. Parkinsonian features can be manifested as a part of other diseases affecting the CNS, such as atherosclerosis, ALS, and HD.<sup>192</sup>

Parkinson's disease (PD), or idiopathic parkinsonism, is a chronic progressive disease of the motor component

ages of 50 and 79 years. Approximately 10% will develop initial symptoms before the age of 40 years.<sup>104</sup>

### Etiologic and Risk Factors

An increasing number of chromosomal features linked to familial parkinsonism have been found, notably PARK1 to PARK11. Among these, seven genes have been identified, four causing autosomal dominant parkinsonism (synuclein, UCHL1, NURR1, LRRK2) and three causing autosomal recessive disease (DJ1, PINK1, parkin). These provide insights into the molecular pathogenesis of the disease, but genetic testing for these mutations is of little clinical relevance. The chance of identifying parkin mutations is less than 5% in sporadic cases with onset at younger than 45 years. The probability is much greater in those with onset at younger than 30 years and in those with an affected sibling. Confirmation of this recessive form of disease might be helpful in genetic counseling, because it renders transmission to the subsequent generation very unlikely.<sup>49</sup> Given the late onset of typical PD, it is likely that by the time individuals become symptomatic, many first-degree relatives are deceased from other causes.

Many potential exposures have been cited as possible risk factors for PD. Three major groups include toxic exposures, infection exposures, and a heterogenic group of miscellaneous exposures. Some toxic agents such as carbon monoxide, manganese, cyanide, and methanol can damage the basal ganglia and produce parkinsonian symptoms. A rapidly developing Parkinson-like disease has been linked to the use of MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), a synthetic narcotic related to heroin. Some neuroleptics can produce a parkinsonian syndrome. In drug-induced parkinsonism, the symptoms can usually be reversed by withdrawal of the drug.

The link to infection exposure remains unresolved, despite years of study. There may still be a possibility that infection plays a role, based on observations of serum antibody titers for measles virus, rubella virus, herpes simplex virus types 1 and 2, and cytomegalovirus in persons with PD. Pesticides and herbicides may be environmental causes and are likely to produce between 2% and 25% increased risk. If some individuals are determined to be particularly susceptible to low environmental exposure, then pesticides may pose a more serious risk. In every age group, men are more likely than women to develop parkinsonism. This finding is not completely understood, but perhaps hormones may protect women, whereas men may be exposed to more environmental toxins according to their occupational choices. Long-term exposure to either manganese or copper has been linked to an increased incidence of parkinsonism.

More years of formal education appear to increase the risk of PD. Physicians are at significantly increased risk of PD when occupational data are used. By contrast, four occupational groups show a significantly decreased risk of PD according to one source: construction and extractive workers (miners, oil well drillers), production workers (machine operators, fabricators), metalworkers, and engineers.<sup>65</sup>

There is a relatively well established relationship between PD and a history of smoking. Individuals with

a history of smoking seem to have a lower risk of developing PD.

High levels of physical exercise may lower PD risk. The risk of PD appears to be lower among women who report strenuous exercise during early adulthood. Physical exercise can promote secretion of growth factors in the CNS that in turn may contribute to the survival and neuroplasticity of dopaminergic neurons. Moreover, exercise decreases the ratio between dopamine transporter and vesicular monoamine transporter; a decrease in this ratio may lower the susceptibility of dopaminergic neurons to neurotoxins and reduce dopamine oxidation. Finally, physical exercise may activate the dopaminergic system and increase dopamine availability in the striatum. Any of these or other mechanisms may be responsible for the beneficial effects of forced exercise in animal experiments; however, the relevance of these short-term animal findings to possible neuroprotective effects of leisure physical exercise in human PD pathogenesis remains to be established. In the rat model of PD, forced exercise prior to chemically induced parkinsonism caused a significant increase of glial-derived neurotrophic factor that has neuroprotective effects for dopaminergic neurons.<sup>51</sup>

### Pathogenesis

Parkinsonian symptoms come primarily from dysfunction within the subcortical grey matter in the basal ganglia. Physiologic studies have shown the basal ganglia to be actively involved in almost all types of movement, including postural responses, alternating movements, and spontaneously occurring movements. The basal ganglia are active prior to recorded EMG activity in the muscles involved in a movement. Lesions do not produce paralysis or weakness but rather change the character of movement, leading to loss of adaptive control, slowing of movement, and poor coordination. The motor loop that determines the initiation and scaling of motor activity derives its input from the premotor, motor, and somatosensory cortices. This is the process of preparation for forthcoming movement, and when disrupted it can cause a reduction in size and speed of the movement.

Basal ganglia-cerebral cortex interactions are disrupted by the abnormal function of the basal ganglia. This reflects a delay in motor programming related to the unconscious initiation of motor preparation, or lack of "response set" or readiness to move. The complex loop that includes the basal ganglia is involved in motivation and in planning global aspects of behavior.<sup>101</sup> The basal ganglia interact with the frontal cortex and with the limbic system, including the hippocampus and amygdala, and therefore have a role in cognitive and emotional function. The basal ganglia, in association with the frontal lobe, appear to play an important role in the integration of sensory information. It is now recognized that diffuse neuronal loss in the cerebral cortex may also contribute to changes observed in PD.

The basal ganglia are large subcortical structures that are interconnected and functionally interposed between the cortex and the thalamus. They also have direct connections to the limbic lobe, frontal cortex, and brainstem. It is likely that the fundamental principles that will be

described here in relationship to the cortex-basal ganglia-thalamus-cortex system can also explain the disorders related to the connections between the basal ganglia and the frontal cortex, limbic lobe, and brainstem. The failure to facilitate desired behaviors and simultaneously inhibit unwanted behaviors may be responsible for the cognitive, emotional, and memory problems that coexist with movement disorders.

The signs and symptoms of parkinsonism are neurochemical in origin. The pathologic hallmark is the degeneration of a nucleus that is part of the basal ganglia, the substantia nigra. It loses its ability to produce dopamine, a neurotransmitter necessary to normal function of basal ganglia neurons. A depletion of 70% to 80% of the dopamine is estimated to occur before clinical signs of the disease are noted.<sup>39,85</sup> Initially, the system adapts, and there is increased efficiency in the pathways that depend on dopamine, but over time, as the dopamine depletion continues, function declines.

Abnormal protein breakdown, which may occur spontaneously or in relationship to a gene mutation, contributes to the neurodegeneration of PD. It appears that there are many possible triggers for the programmed cell death that results in mitochondrial dysfunction and oxidative stress. Despite significant research in this area, many observations are correlative in nature, and a precise process has not been identified. The inherited, early-onset forms of the disease may have a mutation which causes degradation of protein that may mimic the changes found in those individuals with sporadic, later-onset disorder. The changes in neurochemistry and protein are both consistent with aging. There is some overlap of degeneration that is similar to the processes seen in the dementias, including AD.

Free radical or oxidative stress appears to also have a role in the dysfunction of the basal ganglia.<sup>16</sup> Compared to the rest of the brain, the substantia nigra is exposed to higher levels of oxidative stress. This is not a direct response and may be the result of dying cells.

Evidence of inflammation is typically found in the area of the substantia nigra pars compacta in conjunction with programmed cell death. It is proposed that neuroinflammation does not initiate PD but can promote progression and add to the worsening of symptoms.

The motor pattern generators, thoughts and behaviors, and processes for memory are all initiated through the cerebral cortex. The parietal-occipital-temporal lobes, prefrontal areas, thalamic nuclei, limbic lobe, amygdala, and hippocampus use glutamate projections into the striatum (caudate and putamen). The input into the striatum comes in a topographic organization that is maintained to some degree throughout the basal ganglia.

Dopamine is produced in the substantia nigra pars compacta. Dopamine has more than one configuration, and the D1 configuration either increases the efficiency or decreases the effect of cortical input to the striatum depending on the context of the desired movement. The D2 family primarily decreases the effect of cortical input to the striatum. The striatum (caudate and putamen) has medium spiny neurons that project outside of the striatum. Dopamine input to the striatum terminates largely

on the shafts of these dendritic spines and is able to modulate transmission from the cerebral cortex to the striatum. Cholinergic interneurons and GABA interneurons also synapse on these dendrites. Although there are fewer GABA interneurons, they have a powerful inhibitory effect. Through long-term potentiation and long-term depression, dopamine may be involved in the neural mechanism of habit learning. Depletion of dopamine in the striatum impairs the learning of new movement sequences.

D1 dopamine goes from the striatum primarily to the internal globus pallidus and substantia nigra pars reticulata. (These two groups of neurons are functionally related and often grouped together.) The second population contains GABA and enkephalin and expresses D2 dopamine receptors. These neurons project to the external globus pallidus. The external globus pallidus sends inhibitory input via GABA receptors to the internal globus pallidus.

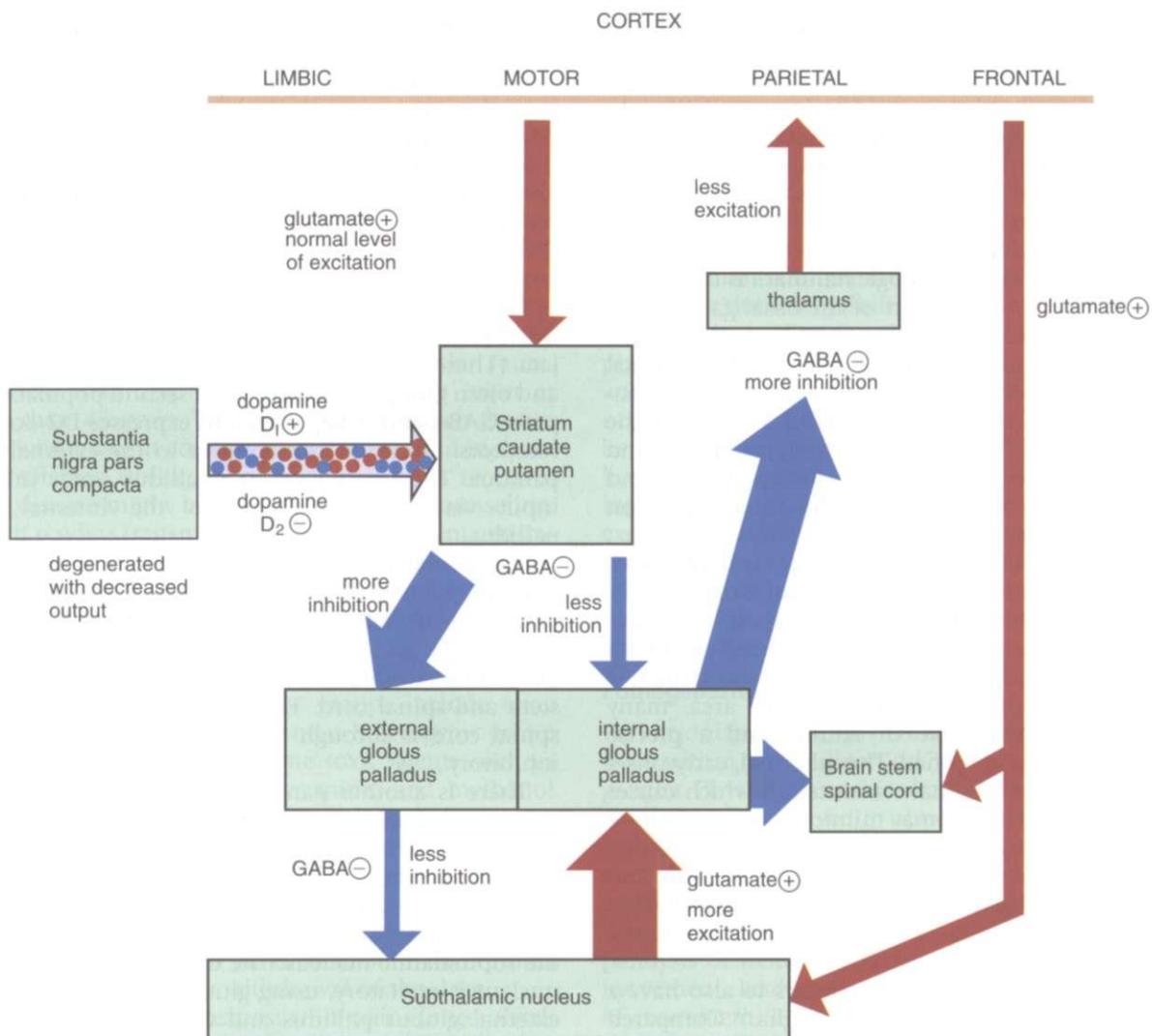
The primary basal ganglia output comes from the internal globus pallidus, representing the body below the neck, and the substantia nigra pars reticulata, representing the head and eyes. The output is to the thalamus and, via several additional pathways, eventually to the brainstem and spinal cord. The output to the brainstem and spinal cord is through GABA neurotransmitters and is inhibitory.

There is another parallel circuit via the subthalamic nucleus. Excitatory input using glutamate via the hyperdirect pathway comes from the frontal lobe and motor areas and goes directly to the subthalamic nucleus, forming a somatotopic organization. There also appears to be a topographic separation of motor and cognitive inputs to the subthalamic nucleus. The output of the subthalamic nucleus is excitatory, using glutamate, and facilitates the external globus pallidus and the substantia nigra pars reticulata, producing a GABA inhibition to the thalamus.

The subthalamic nucleus also participates in a third or indirect pathway. This pathway involves signaling from the striatum (caudate and putamen) to the external globus pallidus to the subthalamic nucleus to the basal ganglia outputs.

The basal ganglia intrinsic circuitry is complex, with the direct pathway through the striatum (caudate and putamen) and a hyperdirect pathway through the subthalamic nucleus to the basal ganglia outputs. The hyperdirect pathway through the subthalamic nucleus is excitatory and fast, and the direct pathway through the striatum (caudate and putamen) is slower and inhibitory but more powerful.<sup>124</sup>

The cumulative inhibitory output of the basal ganglia acts as a brake on the motor pattern generators in the cerebral cortex and brainstem. The interaction among these pathways allows for a planned movement to be executed while competing movements are prevented, thereby increasing the precision of the movement without losing the power necessary to perform an activity. This is thought also to allow one part of a movement sequence to be activated in order for another sequence to begin. Through these mechanisms, movement and thought can be adapted quickly when the environment requires a different response.



**Figure 31-12**

How the loss of dopamine production in the substantia nigra causes the eventual decrease in excitation of the cortex in the motor loop that involves the basal ganglia. Glutamate (positive transmission) is red and GABA (negative transmission) is blue. The decreased dopamine causes less than normal inhibition of the striatum (caudate/putamen), so there is more output to the internal globus pallidus. This output is inhibitory, so the cycle of inhibition is already started. Because the internal globus pallidus has been inhibited, there is less output, resulting in less inhibition of the subthalamic nucleus. This results in increased output of the subthalamic nucleus, this time causing more facilitation of the external globus pallidus. The increased output of the external globus pallidus, because it is inhibitory, causes greater inhibition of the thalamus, and the final end result is decreased excitation of the frontal or motor cortex. So the movement coming out of the cortex is less forceful than intended.

Note the other available pathway from the frontal cortex directly to the subthalamic nucleus. The subthalamic nucleus then facilitates the external globus pallidus, and the output of the external globus pallidus is inhibitory to the internal globus pallidus. The output of the internal globus pallidus is inhibitory to the thalamus as well as the brainstem and spinal cord. In this case, because of the double inhibition (sometimes referred to as disinhibition) the final output is excitatory. This pathway is not dependent on dopamine, but because it sends signals to the same nuclei that have already been affected by the decreases in dopamine, the system gets out of balance and the result is loss of normal modulation. Note also the pathway out of the basal ganglia to the brainstem and spinal cord.

When dopamine stimulation is decreased or withdrawn from the cycle, the overall effect is increased inhibition of input into the thalamus. The final effect of increased inhibition of the thalamus decreases the ability of the thalamus to send excitatory input back to the frontal cortex. So the ultimate outcome is less activity in the cortex, resulting in slowed movement and less power generated through the musculoskeletal system (Fig. 31-12).

These abnormal responses also influence the pathways to the brainstem that travel through the superior collicu-

lus to the nucleus raphe magnus. Abnormalities in facial expression, blinking, and eye and eyelid movements result. Although less clearly understood, abnormal firing or sequencing to the pedunculopontine tegmental nucleus can influence locomotion, sleep cycle regulation, attention, arousal, and startle.

Although the relationship of the substantia nigra and the striatum (caudate and putamen) are foremost in the disorder of parkinsonism, neuropathologic findings can be found in many other dopaminergic and non-dopaminergic cell groups. The pathway responsible for

postural stability may be affected outside of the basal ganglia.

### Clinical Manifestations

Movement disorder is the hallmark of parkinsonism, although other symptoms are evident and may actually precede the impairment of movement. The ability to move is not lost, but there is a problem with movement activation and loss of reflexive or automatic movement. Movement becomes reliant on cortical control. The ability to perform known tasks, such as walking, changing direction, writing, and basic ADLs, is diminished. The considerable variation among individuals in the clinical manifestations and the level of deterioration in movement over time can be explained by the complex mechanism of dysfunction defined in the Pathogenesis section.<sup>32</sup>

The tremor of PD, the most common initial manifestation, often appears unilaterally and may be confined to one upper limb for months or even years. It is first seen as a rhythmic, back-and-forth motion of the thumb and finger, referred to as the pill-rolling tremor. It is most obvious when the arm is at rest or during stressful periods. The tremor starts unilaterally but can eventually spread to all four limbs as well as neck and facial muscles. Tension or exertion will cause the tremor to increase, and it will disappear during sleep. Tremor does not usually impact the functioning of the individual.

Rigidity is an increased response to muscle stretch that appears in both antagonist and agonist muscle groups. Rigidity, like tremor, usually appears unilaterally and proximally in an upper limb and then spreads to the other extremities and trunk. One of the earliest signs of rigidity is the loss of associated movements of the arms when walking. Rigidity is identified when another person is trying to passively move the extremity and there is a jerky response, known as cogwheel rigidity, or a slow and sustained resistance, known as lead-pipe rigidity. Rigidity does not appear to have a direct effect on volitional movement. Axial rigidity usually limits rotation and extension of the trunk and spine. Reduced variability and less adaptation of movement between thoracic rotation and pelvic motion appears early in the onset of PD. This rigidity can decrease the ability to make adjustments of the extremities during functional tasks, such as transfers, reaching, and bed mobility as well as gait.

Bradykinesia is the slowness of movement seen in parkinsonism. Impairment of the normal mechanisms that scale the output of agonist muscles causes the inability to produce, modulate, and terminate quick movements. Persons diagnosed with PD show relatively small EMG bursts in agonist muscles and move the legs in a series of small steps rather than in a single movement. Bradykinesia results from disruption of the neurotransmitter from the internal globus pallidus to the motor cortical regions known as the supplementary motor area and the primary motor cortex.

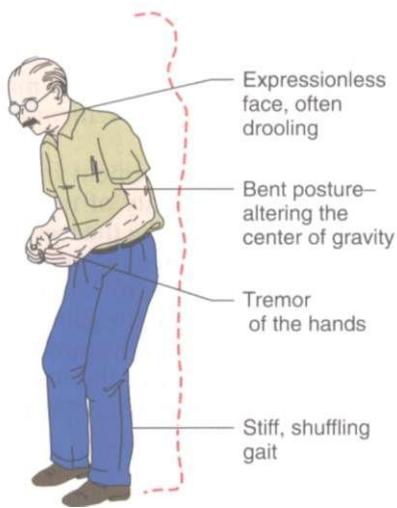
The slowing of lip and tongue movements during talking causes a garbled speech pattern. There is loss of fine motor skills with the gradual development of small, cramped writing, or micrographia. Parkinsonism is accompanied often by diminished efficiency of pursuit

eye movements, so that small accelerations of eye movement (saccades) are required to catch up with a moving target, which causes smooth pursuit eye movements to be jerky instead of smooth. Eye movement in the vertical plane may be reduced.

Akinesia is a disorder of movement initiation and is seen in parkinsonism as a paucity of natural and automatic movements, such as crossing the legs or folding the arms. Small gestures associated with expression are reduced. The face is masklike, with infrequent blinking and lack of expression. Freezing, or gait akinesia, is the sudden cessation of movement in the middle of an action sequence, as if the foot is stuck to the floor. Sometimes it is the environment that seems to trigger freezing, such as when the individual walks through a doorway or over a change in surface like stepping from a carpet to a hard floor. Freezing most often affects walking, but it can affect speech, arm movements, and blinking. Freezing is uncommon in the early phase but increases over time.<sup>58,128</sup>

The gait pattern in parkinsonism is highly stereotyped and characterized by impoverished movement. ROM in the joints of the lower extremity is often limited. Trunk and pelvic movement is diminished, resulting in a decreased step length and reciprocal arm swing. The gait is narrow based and shuffling. The speed is decreased. Persons with plantar flexion contractures will toe-walk, and this further narrows the available base of support. In gait there is a loss of heel strike, reduced toe elevation, reduced movement at the knee joints, loss of dynamic vertical force, reversal of ankle flexion-extension movement, and loss of backward-directed shear force.<sup>148</sup> Festination is common when attempting to stop or change direction; the stride becomes smaller but more rapid, and instead of stopping, the individual actually increases speed and is usually stopped by running into something or by falling. Preparatory postural responses to move from a bipedal to single-limb stance are frequently absent for induced steps, which may increase instability during first step.<sup>152</sup> There is reduced ability to adapt to changes of environments or to perform new tasks.

The posture in PD is characterized by flexion of the neck, trunk, hips, and knees (Fig. 31-13). Kyphosis, or extensive flexion of the spine, is the most common postural deformity. Scoliosis, an abnormal lateral curvature of the spine, can result from the unequal distribution of rigidity in posture. Persistent posturing of a forward head and trunk tends to pull the center of gravity forward. This may result in a tendency to keep weight shifted posteriorly in order to compensate. Postural instability is also associated with abnormal patterns of postural responses, including excessive antagonist activity that results in coactivation of distal and proximal muscles. Adapting to changing support conditions is less efficient in individuals with PD.<sup>127</sup> The ability to sequence motor activity appears to have an impact on postural correction. Abnormal control of center of mass results in decreased limits of stability.<sup>79</sup> Lateral postural stability is compromised by lack of trunk flexibility. During posterior perturbations, lack of stability appears to be the result of lack of appropriate knee flexion. Box 31-10 outlines some of the contributions to imbalance seen in individuals with parkinsonism.

**Figure 31-13**

Typical posture that results from Parkinson's disease.

**Box 31-10**
**CAUSES OF BALANCE IMPAIRMENT IN PARKINSON'S DISEASE**

- Loss of postural reflexes
- Visuospatial deficits
- Retropulsion
- Start hesitation
- Freezing
- Festinating gait
- Orthostatic hypotension
- True vertigo

Performing dual tasks causes more slowing in individuals who have parkinsonism. Smooth performance of sequential motor tasks is broken down into distinct components. Changing the "set" for an activity is more difficult for the individual with parkinsonism when the context or environment requires a sudden change in activity.

Olfactory function is diminished along with impaired color vision and visual perception.<sup>185</sup> Spatial organization is often disturbed, resulting in difficulty with orientation to the environment. The inability to distinguish self-movement from movement in the environment can contribute to abnormal balance reactions.<sup>24</sup> There is an increased dependence on visual information for motor control. There is strong visual dependency for balance, resulting in the inability to choose a balance strategy based on vestibular information even when the visual surround is unavailable for visual stability.<sup>19</sup>

Most people with PD experience weakness and fatigue once the disease becomes generalized. The person has difficulty sustaining activity and experiences increasing weakness and lethargy as the day progresses. Repetitive motor acts may start out strong but decrease in strength as the activity progresses. This compounds bradykinesia and increases immobility.

Nonmotor symptoms, such as those related to autonomic dysfunction, are common and potentially dis-

abling manifestations of the disease. Loss of neurons in the sympathetic ganglia may cause autonomic dysfunction. This results in excessive sweating, excessive salivation, incontinence, and disabling orthostatic hypotension.<sup>51</sup> There is a greasy appearance to the skin of the face and occasional drooling because of loss of the swallowing movements that normally dispose of saliva. Olfactory dysfunction is an early sign of PD in most individuals, and overlaps with multiple system atrophy and progressive supranuclear palsy.

Rapid eye movement sleep behavior disorders result in lack of the normal muscle atonia and jerking of body and limbs causing disrupted sleep. Restless leg syndrome appears to be associated, mostly because of the similarities in treatment response. Abnormal sleep patterns may also contribute to the daily fatigue.

Fatigue is related to other nonmotor features such as depression and excessive daytime sleepiness. In more than half of the individuals mental fatigue is persistent and seems to be an independent symptom that develops parallel to the progressive neurodegenerative disorder of PD.<sup>4</sup>

Many persons with PD experience pain that is poorly localized but is generally described as cramping in the axial muscles or the limbs. Paresthesias are reported by many persons, including tingling, numbness, and abnormal temperature sensation.

Dementia and intellectual changes occur in almost 50% of persons with PD. Development of dementia is associated with more rapid progression of disability and potential for need for assisted living. Bradyphrenia, a slowing of thought processes, with lack of concentration and attention may also occur. Coexisting AD, organic brain disease, and vascular compromise may also contribute to the dementia.<sup>143</sup>

Depression is common and is probably related to the dopamine depletion. Loss of serotonin in the brainstem and limbic lobes has been found using PET studies. Behavioral changes, such as apathy, lack of ambition, indecisiveness, and anhedonia, are common and may be related to depression. Depressive episodes or panic attacks can precede onset of motor symptoms.

Although reduced motor activity by itself would not seem to be a functional disorder, many of the small automatic muscular adjustments are important for successfully carrying out functional activities. For example, in attempting to rise from a chair a person may fail to make the small initial adjustments of legs that are crucial to standing up and fail to be able to get from sitting to standing without assist.

The person with PD typically becomes deconditioned. Rapid heart rate and difficulty breathing are common. Vital capacity is reduced as the kyphosis increases and the intercostal muscles develop rigidity.<sup>145</sup> Respiratory complications are the leading cause of death. The Hoehn and Yahr classification (Table 31-3) is a common scale used to define the level of disability associated with PD.

## MEDICAL MANAGEMENT

**DIAGNOSIS.** The classic triad of major signs of PD is made up of tremor, rigidity, and akinesia.<sup>179</sup> The combination of asymmetry of symptoms and signs, the presence of a

**Table 31-3** Hoehn and Yahr Classification of Disability

Stage	Character of Disability
I	Minimal or absent; unilateral if present
II	Minimal bilateral or midline involvement; balance not impaired
III	Impaired righting reflexes; unsteadiness when turning or rising from chair; some activities restricted, but patient can live independently and continue some forms of employment
IV	All symptoms present and severe; standing and walking possible only with assistance
V	Confined to bed or wheelchair

Modified from Hoehn MM, Yahr MD: Parkinsonism: onset, progression and mortality, *Neurology* 17:427, 1967.

resting tremor, and a good response to levodopa best differentiates PD from parkinsonism due to other causes. Diagnostic problems may occur in mild cases. Other movement disorders that do not fall under the category of parkinsonism need to be recognized by clinicians to establish a differential diagnosis. See Box 31-11 for features of parkinsonism due to causes other than PD.

Depression, with its associated expressionless face, poorly modulated voice, and reduction in voluntary activity, may be difficult to distinguish from mild parkinsonism. Olfaction is frequently impaired in PD, suggesting that deficiencies in smell may be a potentially useful test to distinguish PD from related disorders.

CT or MRI is not helpful in diagnosis of PD but can identify other causes of symptoms, such as Wilson's disease, or mass effects causing disruption of the basal ganglia function, such as stroke or hydrocephalus.

Functional imaging through PET is highly sensitive to regional changes in brain metabolism and receptor binding associated with movement disorders. SPECT shows differences in the posterior putamen, contralateral to the predominantly affected limb. Asymmetric scan findings have been observed in individuals with mild, newly recognized symptoms. Unilateral disease produces a significant difference in striatal uptake between the ipsilateral and contralateral sides in both the caudate and putamen nuclei. One explanation is that there is a preceding unequal functional reactivity of the basal ganglia, which results in an asymmetrical clinical response.

Altropine (a close cousin of cocaine), a component of radioactive technetium 99m, is a compound that can measure the concentration of dopamine transporters imaged by SPECT. This may lead to diagnosis of PD based on identifying decreasing levels in the brains of persons when only mild symptoms appear.

Assessing progression of PD using clinical rating scales such as the United Parkinson's Disease Rating Scale (UPDRS) is a common way to track progression. However, the progression may be masked by medication, and because of the multitude of symptoms that may change at different rates, it is hard to determine a change in the course of the disease.

**TREATMENT.** The current therapeutic approach to PD is symptomatic; major studies to determine possible thera-

**Box 31-11****PARKINSONISM VERSUS PARKINSON'S DISEASE****Multisystem Atrophy: Striatonigral Degeneration, Sporadic Olivopontocerebellar Atrophy, Shy-Drager Syndrome**

- Orthostatic hypotension, sexual impotence, bladder dysfunction
- Cerebellar dysfunction
- Myoclonus of face and hands
- Neck flexion
- Mottled, cold hands
- Dysarthria
- Good response to levodopa initially for a small percentage; dyskinesia and cranial dystonia associated with use of levodopa

**Progressive Supranuclear Palsy**

- Vertical ophthalmoplegia
- Oculomotor dysfunction
- Axial rigidity greater than limb rigidity
- Early falls
- Speech and swallowing disturbances
- Cognitive or behavioral changes
- Hypertension
- Poor response to levodopa

**Corticobasal Degeneration**

- Apraxia, cortical sensory changes, alien limb phenomenon
- Asymmetric rigidity
- Limb dystonia
- Myoclonus
- Negligible response to levodopa

**Vascular Parkinsonism**

- Dysfunction in lower extremities
- Gait disturbances
- Additional focal signs of midbrain lesion
- Poor response to levodopa

**Dementia with Lewy Bodies**

- Early dementia
- Rigidity more prominent than bradykinesia or tremor
- Hallucination
- Fluctuating cognitive status
- Falls
- Motor features may respond to levodopa but with psychiatric side effects

From Lang AE, Lozano AM: Parkinson's disease, *N Engl J Med* 339(15):1044-1053, 1998.

peutic neuroprotection are under way, but no single intervention has proven to be disease modifying. Drug therapy is adapted to the person's needs, which may vary with the stage of the disease and the predominant manifestations.<sup>5</sup> When mobility becomes affected to the degree that walking and self-care activities become difficult, medications improve the control of movement. As the disease progresses over time, the effectiveness of medication changes, leaving the individual with a shorter "on" time during which symptoms are reduced and more rigidity during "off" times when symptoms are active. Long-term use of medication can also increase the dyskinesia or chorea-like movement resulting from the change

in activity in the basal ganglia. Side effects can become more problematic as the dosages needed to control symptoms are increased. The management of these medications becomes the focus of intervention.<sup>59</sup>

Levodopa (1-dopa), which is taken up by remaining dopaminergic neurons in the basal ganglia and converted to dopamine, improves most of the major features of parkinsonism, including bradykinesia. Initially it leads to nearly complete reversal of symptoms, with effects lasting up to 2 weeks, known as long-duration levodopa response. As the disease progresses, the length of the effect becomes shorter, it takes longer for the effect to be noticed after dosing, and symptoms increase during the end of the dose period. Eventually there is dose failure or lack of any effect at all. Levodopa can cause dyskinesias that produce chorea, athetosis, dystonia, tics, and myoclonus. Predictable fluctuations include a wearing-off effect and early-morning akinesia. The duration of effect of each dose becomes shorter and will often match the drug's half-life of less than 2 hours. Although levodopa is the most effective drug for PD, the time to start taking it is controversial. Early use may contribute to greater activity levels and employability but cause more disability at later stages when the effect fluctuates and ultimately decreases. Protein in food uses the same mechanism as levodopa for crossing the blood-brain barrier. When levodopa is given with protein, the protein blocks the ability of the levodopa to cross the blood-brain barrier. This is usually managed by having the individual eat most of the daily protein in the evening, when immobility will cause the least inconvenience. Caffeine administered before levodopa may improve its pharmacokinetics in some individuals with parkinsonian symptoms.<sup>48</sup> Infusion of levodopa directly into the intestines gives a more stable response but is expensive and invasive. Levodopa should be avoided in persons with malignant melanoma and in persons with active peptic ulcers, which may bleed.

Carbidopa inhibits the breakdown of levodopa and is often used in combination with levodopa. Carbidopa reduces the amount of levodopa required daily for beneficial effects and is often combined with levodopa in a single preparation (Sinemet).

Catechol-O-methyl transferase (COMT) inhibitors are reported to provide smoother and more sustained levels of levodopa to the brain. Of these, entacapone and tolcapone reduce the off time, and allow for decreased dosing of levodopa.<sup>141</sup> Liver function must be monitored regularly with the use of tolcapone. Tolcapone must be used with levodopa but can decrease the amount of levodopa needed.

Dopamine agonists act directly on dopamine receptors. Bromocriptine seems to be the best tolerated, and its use in parkinsonism is associated with a lower incidence of response fluctuations. It is often given in combination with levodopa and carbidopa. Pramipexole or ropinirole can be used either to delay starting levodopa or to decrease the amount needed. Transdermal application of dopamine agonists can be provided with rotigotine and lisuride.

Selegiline (Eldepryl) and rasagiline have been used to inhibit monoamine oxydase type B (MAO-B) enzyme in

the basal ganglia (MAO-B inactivates dopamine). It was thought that selegiline also may be able to delay the neuronal degeneration, but studies do not support that claim.<sup>42</sup>

Persons with mild symptoms but no disability may be helped by amantadine. Amantadine is also effective for the dyskinesia that develops later in the course of the disease. Coadministration of levodopa and amantadine controls dyskinesia without disrupting the effect of levodopa.

In the striatum the low level of dopamine is accompanied by increased cholinergic transmission. Accordingly, motor functions in individuals are improved by anticholinergic drugs. The side effects of the anticholinergic medications, including sedation, confusion, and psychosis, limit their usefulness, especially with advancing age. MAO-B inhibitors have replaced the use of anticholinergics in treatment of PD.<sup>36</sup>

Antioxidants have been studied for neuroprotection, such as coenzyme Q10, which helps stabilize mitochondria and appears to decrease the worsening of symptoms. Trophic factors, antiinflammatories, antiapoptotics, and antioxidants have been identified by the National Institutes of Health for further study for control of neuronal death.

Deep brain stimulation uses a pacemaker-like device surgically implanted with electrodes in the nuclei of choice and a pulse generator implanted in the chest. The generator is controlled externally through a magnetic field. When a tremor begins, the client activates the low-voltage, high-frequency generator by passing a magnet over it. Stimulation through the electrodes can be applied to the internal globus pallidus and the subthalamic nucleus or thalamus. Thalamic stimulation is most effective for tremor, with less effect on dyskinesia and rigidity. Electrode implantation in the globus pallidus appears to have good initial effect; however, there is a chance of psychosis and punding activity over time. Most centers are now stimulating the subthalamic nucleus bilaterally, but the individual's profile leads the decision. Preoperative response to levodopa predicts better outcome after deep brain stimulation of the subthalamic nucleus. The ability to perform ADLs is improved, and there is typically improved sleep time. Apathy and abulia can occur over time; this may be related to withdrawal of levodopa. There can be an increase in sadness or the opposite response with excessive hilarity that may be related to stimulation of the surrounding area or change in subthalamic limbic activity. Edema around the electrode may contribute to the psychotropic effects. The implant is believed to last approximately 5 years and can be removed if another more effective type of treatment is found.<sup>8</sup> Bilateral subthalamic stimulation, alone or in combination with levodopa, causes improvement in axial signs for posture and postural stability.

While there is little evidence for drug effect on postural stability and gait disorders, researchers in motor control are making progress in identifying the nature of the abnormal responses both inside and outside of the basal ganglia.<sup>161</sup> (See Special Implications for the Therapist: Parkinson's Disease later in the chapter.) Based on the strong evidence that relates prior exercise and activity

status to risk of PD, and the recent knowledge gained about neuroplasticity in the brain, it is likely that changes in postural control may come through interventions that drive neuroplastic changes.

Although orthostatic hypotension affects less than 20% of individuals with parkinsonism, it can limit activity. Use of midodrine, fludrocortisone, and etilefrine can be helpful in maintaining normal blood pressure. Supine hypertension may result and must be monitored. Urinary dysfunction is treated via antimuscarinic agents or antagonists. Anticholinergics or scopolamine patches may be helpful for drooling, and use of intraparotid injection of BTX can help. Constipation is common and may precede the motor symptoms in PD; it is usually managed by fluids, fiber, stool softeners and exercise.

Depression is found in over 40% of individuals with PD. Medication interactions must be looked at carefully. Use of serotonin uptake inhibitors may interact with selegiline. Tricyclics can be useful, but the central effects must be monitored more carefully than in the healthy younger population.

Respiratory complications, which are the leading cause of death, can be prevented to some extent with an early aggressive aerobic exercise program, followed by regular moderate activity as the disease progresses. Control of breathing can be facilitated using verbal and tactile stimuli and should be integrated into any intervention.

Behavioral abnormalities can be associated with high doses of dopaminergic replacement therapy, including the phenomenon of punding, characterized by fascination with technical equipment and excessive sorting of objects, grooming, hoarding, or use of a computer. This may be related to the impaired frontal lobe function and a result of psychomotor stimulation. Other abnormalities in reward-seeking behavior related to dopamine are hypersexuality and excessive gambling. Reducing the level of medication is helpful, and some neuroleptics such as clozapine will lessen symptoms of psychosis.

Experimental therapeutics targeted at improving dopaminergic drugs to increase selectivity for various receptor subtypes and at controlling the uptake of dopamine are currently under study. Improved plasma stability is achieved through transdermal application, which bypasses the fluctuations in gastric release. Studies are aimed at potential substances that evoke antiparkinsonism through neurotransmitter systems outside of dopamine. Pharmacologic manipulation of glutamate and GABA neurotransmission includes the drug istradefylline, which is currently undergoing phase III study.<sup>13</sup> Opiate, serotonin, and histamine receptors are possible sites for intervention. A more careful look at the cholinergic system may help to manage the issues of dementia and find possibilities for reducing the apparent dysfunction at the level of the brainstem that affects sleep wake cycles and orthostasis.

Cell transplantation of grafted dopaminergic neurons in PD continues to hold promise. The striatum (caudate and putamen) are primary targets for the implants. Individual selection, cell-handling variation in surgical techniques, and immunosuppression currently make it difficult to determine success. Graft-induced dyskinesia much like that associated with long-term levodopa use appears in some recipients. It is not clear which individ-

ual will develop the dyskinesia, and at this time there is not any medication to control the abnormal movements. Fetal stem cells remain the most successful; however, alternative types are being studied. There is hope for cells derived from the individual's own body, but the response has been less than hoped for and the current graft survival is low. Rejection of the graft continues to limit effects, and immunosuppression has to be considered as a possible long-term adjunctive therapy with grafts.<sup>184</sup>

**PROGNOSIS.** In general, all the clinical manifestations in PD worsen progressively, although not to the same extent. Tremor as a presenting symptom may be used to predict a more benign course and longer therapeutic benefit to levodopa. In individuals with newly diagnosed PD, older age at onset and rigidity/hypokinesia as an initial symptom can be used to predict more rapid rate of motor progression.<sup>171</sup>

The presence of associated comorbidities, stroke, auditory deficits, and visual impairments as well as male sex may be used to predict faster rate of motor progression. Older age at onset and initial hypokinesia/rigidity may be used to predict earlier development of cognitive decline and dementia. Older age at onset, dementia, and decreased dopamine responsiveness may be used to predict earlier nursing home placement as well as decreased survival. Lack of mobility, loss of balance reactions, and weakness result in more falls than in an age-matched normal population. Osteoporosis can result from prolonged inactivity and may be present secondary to advanced age at onset. Falls more often lead to fractures owing to the prevalence of osteoporosis. Fracture healing may be delayed. Posture and gait abnormalities are the most difficult to control in advanced cases.

PD does not significantly reduce life span in most persons who develop the generalized form between 50 and 60 years of age. However, since there is progressive neuronal loss despite the response to treatment, deterioration continues until death occurs, often from infection or other conditions associated with debilitation.

Since the onset of disease is typically in the fifth or sixth decade of life and is progressive despite medication, the economic cost of the disease can be quite high because of loss of income, cost of drugs, assistive devices, and assisted living. Pain, fatigue, and depression also adversely affect the quality of life compared with that of age-matched normal subjects.<sup>159</sup>

## SPECIAL IMPLICATIONS FOR THE THERAPIST

31-6

### *Parkinson's Disease*

#### PREFERRED PRACTICE PATTERN

*5E: Impaired Motor Function and Sensory Integrity Associated with Progressive Disorders of the Central Nervous System*

There are clearly various and separate components of the movement disorders related to parkinsonism, especially in PD. As we become better able to identify the relationship between specific impairment and the

*Continued.*

resulting function, intervention by the therapist will have more impact on ability to participate in typical activities. Each individual's needs and goals must be addressed and programs modified as the movement disorders change as the disease progresses.<sup>27,47,50,150</sup> Skills are learned most effectively when they are practiced repeatedly in relation to meaningful goals.

Spinal flexibility or axial mobility contributes to function. It can impact ability to perform many of the components of tasks, including functional reach.<sup>11,159</sup>

External temporal constraints and input can provide individuals with PD a means of organizing the timing and speed of their movements that compensates for their loss of internal cueing. Speed of arm movement in persons with PD can be increased by external cues that require faster movement to reach a moving target compared with self-selected fastest speed to reach a nonmoving target.<sup>114</sup>

Cognitive impairment may impact the ability of individuals with PD to learn new motor skills.<sup>10,77</sup> Pathways leading to and from the frontal cortex, limbic lobe, and hippocampus are affected in PD. Learning strategies and environments that best eliminate stress need to be identified.

Tasks involving a similar movement of each hand do not appear to pose as many problems for individuals with PD as those that require different movements for each hand.<sup>89</sup> The ability to sequence the muscles in the upper extremity when it is necessary to perform complex movements with disparate postures appears to be under the control of the basal ganglia. The ability to perform tasks under this constraint may be appropriate as a screening tool to determine progression of disease in persons with PD.<sup>54</sup> Therapy that incorporates cueing and feedback appears to have most effect.<sup>70</sup> Dual task performance and motor planning in general diminishes with the complexity of the task. Studies are now under way looking at the training of breaking tasks down into manageable steps.

The movement disorders resulting in postural instability predispose people with PD to increased falls. Strategies to improve postural stability show promise, with better understanding of the control mechanisms within and parallel to basal ganglia function.<sup>50</sup> The changes that occur over time related to both the disease process and aging can affect the ability to respond to interventions addressing postural control and balance.<sup>130</sup> Integration of sensory input through the thalamus and basal ganglia has been identified, and better understanding of the mechanisms and pathways implicated will no doubt provide new interventions.<sup>77,127</sup>

The use of rhythmic auditory stimulation in persons with PD leads to an increase in gait velocity, cadence, and stride length associated with an increase in the EMG activity around the ankle.<sup>175</sup> Complexity of task appears to be related to gait. Individuals with moderate disability associated with PD experience considerable difficulty when they are required to walk while attending to complex visuomotor tasks involving the upper limbs.<sup>18</sup> Visual cueing for improved gait appears

to have the most effect on stride length and decreases time spent in double stance during walking.<sup>7</sup> Walking speed, arm swing amplitude, and step length can be increased by verbal instructional sets, using cognitive strategies.<sup>7</sup> Gait training strategies and goals will vary according to the progression of the disease.<sup>128</sup>

Managing the home environment is critical, since most falls occur at home. The training of a caregiver to give the appropriate verbal and visual cues can be beneficial.<sup>82</sup> Use of grab bars can be valuable, especially if there is a bathtub, since stepping over the edge requires significant weight shift. Recognizing areas that may induce freezing (doorways, narrow spaces) may decrease the fall risk in those areas. Keeping a diary of falls can be helpful.

Strategies mentioned earlier can work by means of bypassing the basal ganglia and making use of the supplementary motor area. External feedback can be effective in improving movement when it cannot be controlled from internal organization. Use of virtual reality has been shown to be effective in persons with parkinsonism. Until the time that it is readily available, techniques employed by persons with PD to trigger movement or to "unfreeze" are used by most individuals with PD. Typical tactics are included in Box 31-12.

Intervention strategies have been established and can be used to establish programs. Clinical trials with randomized approaches are under way to provide evidence of interventions addressing the movement disorders discussed here. This will assist therapists the most when the components studied can be extrapolated into functional tasks.

Disease-modifying aspects of exercise shows strong promise. Future research may look at the complexity of the motor skills and degree of protection. With evidence for exercise benefit within this population, it should also be recognized by the therapist that submaximal responses to exercise testing occur in PD, with higher heart rate and increased oxygen consumption.<sup>89</sup>

#### Box 31-12

##### METHODS TO IMPROVE MOVEMENT NOTED BY INDIVIDUALS WITH PARKINSONISM

- Walking sideways
- Rocking the body to generate weight shift
- Stamping feet, shaking legs
- Self-talk
- Stepping over objects, such as the handle of a cane, lines on the floor, or laser pointer
- Quick head movements
- Music
- Clapping
- Snapping fingers
- Virtual reality

From Stern GM, Lander CM, Lees AJ: Akinetic freezing and trick movements in Parkinson's disease, *J Neural Transm Suppl* 16: 137-141, 1980.

## Secondary Parkinson's Syndrome

Parkinsonian syndromes, also called *atypical parkinsonism* or *Parkinson's plus syndromes*, are a family of neurodegenerative disorders that result from neuronal loss in different components of the basal ganglia, the brain system of which the dopaminergic midbrain neurons affected in PD are a part. All of these disorders can be difficult to differentiate from PD early in the course of the illness. These disorders have distinctive clinical features, which may emerge only after the onset of parkinsonism. Important clinical clues that one of these disorders is present are symmetric onset of parkinsonism, absence of typical resting tremor, early autonomic dysfunction, prominent dystonia, significant early cognitive impairment, and prominent early falls.<sup>2</sup>

Iatrogenic parkinsonism or drug-induced parkinsonism results from the use of pharmacologic agents that block dopamine effects or interfere with dopamine metabolism. The most common causes of drug-induced parkinsonism are dopamine antagonist antipsychotic medications. The risk of drug-induced parkinsonism is reduced significantly with newer atypical antipsychotic agents. Another group of drugs that can cause drug-induced parkinsonism is older (non-serotonin antagonist) dopamine antagonist antiemetics. Agents interfering with dopamine production or synaptic vesicular storage can cause drug-induced parkinsonism. These include methyl-para-tyrosine, methyldopa, and reserpine. Flunarizine and cinnarizine, when they are used as vestibular suppressants or cerebral vasodilators, can cause parkinsonism. Sodium valproate may cause tremor that can progress to parkinsonism. Features of iatrogenic parkinsonism are bilateral onset and predominant bradykinesia with increased involvement in the arm compared to the legs in the younger population, but more consistent with PD in older individuals. If drug-induced parkinsonism is suspected, the suspected offending agent is withdrawn, and the individual should improve. With dopamine antagonists or reserpine, improvements can occur within days to weeks after medication withdrawal, but there is sometimes a prolonged latency of months before marked improvement occurs.

Vascular parkinsonism involves primarily the lower extremities. It is associated with lacunar infarcts (see Chapter 32) and probably represents small infarcts in the basal ganglia or corticobasilar pathways. A stroke in the region of the striatum (caudate and putamen) and hemiparesis of the arm is common. Systemic lupus erythematosus may also cause cerebral vasculitis. Vascular parkinsonism presents typically with start hesitation, a broad-based shuffling gait (rather than the narrow-based gait associated with PD), and frequent falls. Depending on the level of damage and the cause, the response to levodopa will vary.

Infectious causes of parkinsonism are suspected when the symptoms develop during the acute or recovery phase of an illness with fever. Cases of parkinsonism have been reported as a result of West Nile virus infection and have historically been associated with encephalitis. Human immunodeficiency virus (HIV) infection can cause par-

kinsonism via the viral damage in encephalopathy or opportunistic infections.

Toxicity, often related to manganese accumulation in the substantia nigra, can cause parkinsonism and dystonia, seen in miners, factory workers making dry cell batteries, and those exposed to some fungicides.

## Disorders with Parkinsonian Characteristics

### Benign Essential Tremor

Benign essential tremor is not associated with any underlying cause, is common after the age of 50 years, and is usually hereditary. This tremor is of a different character, and there is a lack of other neurologic signs.

### Progressive Supranuclear Palsy

Progressive supranuclear palsy has symptoms of bradykinesia, rigidity, and postural instability similar to those of PD and is frequently misdiagnosed as PD. Neurofibrillary tangles are the main pathology in progressive supranuclear palsy; oligodendrocytes are also affected. Postural instability is the most pronounced symptom, with falls that are not associated with obstacles or change in surface. Gait freezing and apraxia are common. Dysarthria and dysphagia are on a continuum, with dysphagia typically occurring later than 2 years after onset. Loss of upward gaze, saccades, and smooth pursuit eye tracking progresses over time. Inhibition of eyelid opening and closure, or blepharospasm, can cause functional blindness. Inability to perform vestibulo-ocular reflex cancellation is lost. Apathy, intellectual slowing, and impairment of executive function progress, and there can be pseudobulbar laughter or crying. The autonomic nervous system maintains near-normal function.

Levodopa and deep brain stimulation are effective for the movement disorder, and BTX can help to improve blepharospasm.

### Multiple System Atrophy

There is extreme clinical variability within the multiple system atrophy group of disorders that is primarily familial but can be sporadic. Neuronal atrophy is seen to a variable degree in the brainstem, cerebellum, spinal cord, and peripheral nerves. The differential pathology is associated with gliosis and cytoplasmic inclusion in the glia. Multiple system atrophy typically has its onset in the fifth to seventh decade, and parkinsonism is the primary condition; however, there is more evidence of cerebellar involvement, and autonomic dysfunction is greater and more disabling than that found in PD. Levodopa is used in the treatment, but with less success than when it is used in PD. Cerebellar and autonomic nervous system dysfunction respond poorly to anticholinergics. Large European studies are under way to examine pathogenesis and intervention strategies.

### Olivopontocerebellar Atrophy

Olivopontocerebellar atrophy is one of the most common and variable of the non-PD parkinsonian conditions.

Neuronal loss with gross atrophy is concentrated in the pons, medullary olives, and cerebellum. Ataxia, rigidity, spasticity, and oculomotor movement disturbances are present in variable degrees and combinations. The intracytoplasmic inclusions are predominantly oligodendrocytic, and there is modest tau and synuclein immunoreactivity.

### Wilson's Disease

Wilson's disease, or progressive hepatolenticular degeneration, is rare but also represents degeneration of the basal ganglia and is related to excess deposition of copper. Cysts or cavities form in the basal ganglia with necrosis. The lateral ventricles can be enlarged with associated brain atrophy. This can be imaged using MRI, PET, or SPECT studies. Cerebellar and brainstem damage is common, and there can be spheroid bodies in the cerebral cortex. The symptoms of Wilson's disease go far beyond movement disorder mimicking PD and include profound affective disorders. Ophthalmologic signs of brownish or greenish rings in the periphery of the cornea are a hallmark sign. The disorder is treated via copper chelating.

### Restless Leg Syndrome

Restless leg syndrome is reported as the desire to move the extremities associated with paresthesia, motor restlessness with worsening of symptoms at rest (typically at night), and relief with activity or sensory stimulation. It is familial in 60% of cases, and the effect is related to reduced iron stores in the substantia nigra. There is no loss of dopaminergic neurons as is seen in PD, but the dysfunction lies within the presynaptic and postsynaptic junction of dopaminergic neurons. Levodopa is the traditional treatment, and it is effective when movement is the most problematic symptom. Opioids such as methadone can help when dopamine agents are not effective. For the individual with pain or dysesthesia, neuroleptics can be of benefit.

### References

To enhance this text and add value for the reader, all references are included on the companion Evolve site that accompanies this textbook. The reader can view the reference source and access it on-line whenever possible. There are a total of 198 cited references and other general references for this chapter.

# CHAPTER 32

## Stroke

KENDA S. FULLER

### STROKE

#### Overview and Definition

Stroke, or cerebral vascular accident, often occurs in well-appearing adults as a sudden, devastating vascular event that results in destruction of surrounding brain tissue. Stroke is a leading cause of serious long-term disability, with estimated direct and indirect costs totaling \$62.7 billion annually. Stroke is primarily a consequence of changes in both the function of the heart and in the integrity of the vessels providing blood to the brain.

Transient ischemic attack (TIA) has been the term used for focal neurologic symptoms that completely resolve within 24 hours. However, because the etiology is the same as stroke, and it is becoming more common for the symptoms to be regarded and named as stroke, resulting in hospitalization, closer observation and early use of imaging to determine level of brain damage are warranted. Because there is less microvascular bleeding in TIA than stroke, early management often includes blood thinners.

Cerebrovascular disease, the primary cause of stroke, is caused by one of several pathologic processes involving the blood vessels of the brain. The damage may be intrinsic to the vessel, or the stroke may originate remotely, such as when an embolus from the heart or extracranial circulation lodges in an intracranial vessel. The stroke may result from the rupture of a vessel in the subarachnoid space or intracerebral tissue. Fig. 32-1 shows the effects of different types of stroke on brain tissue.<sup>98</sup>

#### Incidence

The average incidence rate of first strokes is 114 per 100,000 persons, which accounts for 750,000 first strokes each year in the United States. First strokes account for about 75% of acute events, and recurrent strokes account for about 25%. An estimated 700,000 persons in the United States will have a stroke, and approximately 160,000 will die from stroke. Currently close to 4 million stroke survivors are alive. Two thirds of strokes occur in low-income and middle-income countries, where the average age of stroke onset is 15 years below that in high-income countries.

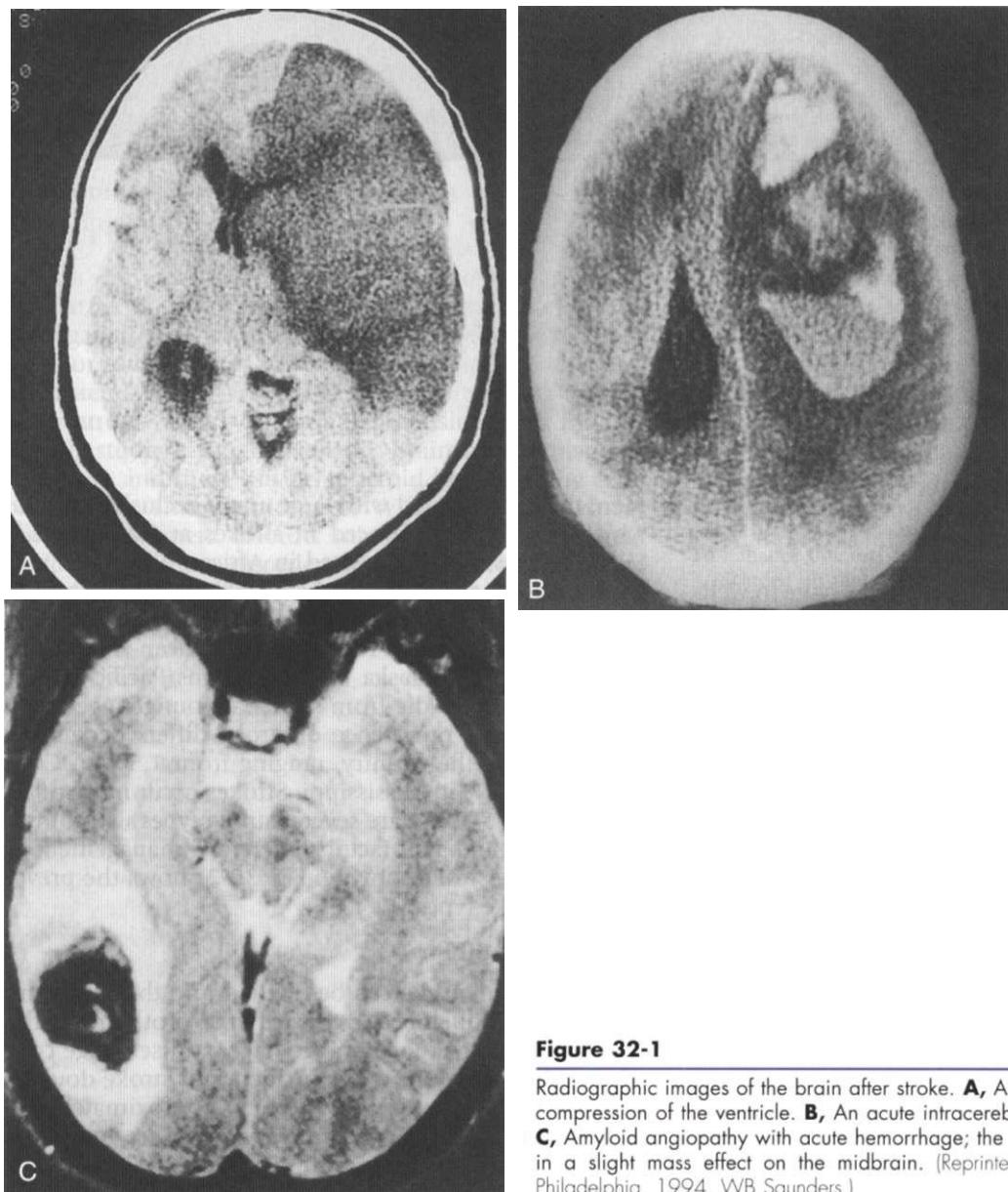
Mexican-American and African-American men have a 50% higher chance of having a stroke than do Caucasian

men; this is associated with large artery occlusive disease, which is most pronounced in strokes at earlier ages.<sup>32</sup> Sickle cell disease is increased in African-Americans and leads to a higher incidence of stroke.<sup>61</sup> Stroke death rates are higher in the southeastern United States compared with other regions of the country; African-Americans, American Indians/Alaska Natives, Asians/Pacific Islanders, and Hispanics die from stroke at younger ages than Caucasians. The prevalence of stroke differs depending on the area of the country, ranging from 1.5% in Connecticut to 4.3% in Mississippi. Strokes occur more often in the spring.<sup>69</sup> There are several stroke types with different etiology and risk factors; therefore management is driven by the stroke subtype. Fig. 32-2 shows the prevalence of stroke types.

#### Risk Factors

Risk factors for stroke can be divided into those that are potentially modifiable and those that are not. Among the nonmodifiable risk factors (age, race, and sex), age constitutes the greatest risk. The incidence of stroke doubles with every decade after age 55 years. Approximately 5% of men aged 65 to 69 years have had stroke compared with the 10% of men aged 80 to 84 years. Women have a 20% less chance of stroke than men, but age increases the risk just as with men. Incidence of stroke is increased with a family history of stroke, with both paternal and maternal influence.<sup>52</sup> Cognitive function and incident cognitive decline appear to be associated with increased risk for stroke. Additional studies are needed to determine whether modification of stroke risk factors can reduce the cognitive decline that is often attributed to normal aging.

Stroke is a heterogeneous multifactorial disorder, but epidemiologic data provide substantial evidence for a genetic component to the disease and the extent of predisposition is unknown. The identification of *NOTCH3* mutations has been found in individuals with cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy. Studies of sickle cell disease have drawn attention to the importance of modifier genes and of gene-gene interactions in determining stroke risk. There are probably many alleles with small effect sizes associated with multifactorial stroke. Genetic association studies on a wide range of candidate path-



**Figure 32-1**

Radiographic images of the brain after stroke. **A**, An acute infarct with mass effect and compression of the ventricle. **B**, An acute intracerebral hemorrhage in the hemisphere. **C**, Amyloid angiopathy with acute hemorrhage; the edema surrounding the area results in a slight mass effect on the midbrain. (Reprinted from Ramsey R: *Neuroradiology*, Philadelphia, 1994, WB Saunders.)

ways are currently underway. Fig. 32-3 shows the interaction of genetics, disease, and environment.<sup>16</sup>

Hypertension (blood pressure above 160/95 mm Hg) is the most prevalent and modifiable risk factor for stroke. Decreasing diastolic blood pressure by 5 to 6 mm Hg decreases risk of stroke by up to 40%.<sup>17</sup> Prehypertension describes blood pressure at the upper end of normal range (between 120/80 and 129/89 mm Hg), which in combination with other risk factors as described below may increase the risk of cardiovascular disease and stroke.

Various cardiac diseases have been shown to increase risk of stroke, including coronary heart disease, left ventricular hypertrophy, and cardiac failure. The stroke risk increases with the degree of stenosis. Death is more often from fatal coronary artery disease than stroke. The risk of stroke after myocardial infarction (MI) is 30% in the first month.<sup>18</sup> If cerebral microembolism occurs after stroke,

there is increased risk of an embolic event.<sup>19</sup> Development of neurologic deficits preceded by brief symptoms of focal symptoms in the same vascular territory usually suggests atherosclerosis as the vascular mechanism. Cardiac valve abnormalities such as mitral stenosis and mitral annular calcification are moderate risk factors. Structural abnormalities of the heart, such as patent foramen ovale and atrial septal aneurysm increase risk. Atrial fibrillation is an important risk factor for stroke.<sup>20</sup> It increases the stroke risk by a factor of six, and 8% of individuals over the age of 80 years have atrial fibrillation. See Chapter 12 for cardiac structure and function and related pathogenesis.<sup>11</sup>

Fibrinogen is a coagulation factor that has been demonstrated to be associated with increased stroke risk. Fibrinogen plays a crucial role in platelet aggregation. Platelets initiate thrombosis by attracting fibrin and other clot-forming substances. Conditions associated with