CLINICAL FOCUS

General CNS Disorders

INFECTIONS

Reye syndrome may develop in children following a viral infection, especially influenza or chicken pox. The use of aspirin to treat viral infections has been linked to development of the syndrome in the United States. A predisposing disorder in fat metabolism may also be present in some cases. In children affected by the syndrome, the brain cells swell, and the liver and kidneys accumulate fat. Symptoms include vomiting, lethargy, and loss of consciousness and may progress to coma and death or to permanent brain damage.

Rabies is a viral disease transmitted by the bite of an infected mammal. The rabies virus infects the brain, salivary glands (through which it is transmitted), muscles, and connective tissue. When the patient attempts to swallow, the effort can produce pharyngeal muscle spasms; sometimes even the thought of swallowing water or the sight of water can induce pharyngeal spasms. Thus, the term *hydrophobia*, fear of water, is applied to the disease. The virus also infects the brain and results in abnormal excitability, aggression, and in later stages paralysis and death.

Tabes dorsalis (tā′bēz dōr-sā′lis) is a progressive disorder occurring as a result of untreated syphilis. *Tabes* means a wasting away, and *dorsalis* refers to a degeneration of the dorsal roots and dorsal columns of the spinal cord. Symptoms include ataxia, resulting from lack of proprioceptive input; anesthesia, resulting from dorsal root damage; and eventually paralysis as the infection spreads.

OTHER DISORDERS

Tumors of the brain develop from neuroglial cells. Symptoms vary widely, depending on the location of the tumor, but include headaches, neuralgia (pain along the distribution of a peripheral nerve), paralysis, seizures, coma, and death. **Meningiomas** (mē-nin′jē-ō′māz), tumors of the meninges, account for 25% of all primary intracranial tumors.

Alzheimer disease is a severe type of mental deterioration, or dementia, usually affecting older people but occasionally affecting people younger than 60. Alzheimer disease is estimated to affect 10% of all people older than 65 and nearly half of those older than 85. Alzheimer disease involves a general decrease in brain size, resulting from a loss of neurons in the cerebral cortex. The gyri become narrower, and sulci widen. The frontal lobes and specific regions of the temporal lobes are affected most severely. Alzheimer symptoms include general intellectual deficiency, memory loss, short attention span, moodiness, disorientation, and irritability.

Alzheimer disease is characterized by the appearance of **amyloid** (am′i-loyd) **plaques** and **neurofibrillary tangles.** Amyloid plaques are localized axonal enlargements of degenerating nerve fibers, containing large amounts of β-amyloid protein, and neurofibrillary tangles are filaments inside the cell bodies of dead or dying neurons.

The gene for B-amyloid protein has been mapped to chromosome 21; however, it is thought that only the rare, inherited, early-onset (beginning before age 60) form of Alzheimer maps to chromosomes 21. The more common, late-onset form (beginning after age 65), which makes up more than three-fourths of all cases, maps to chromosome 19.

Another protein, **apolipoprotein E** (ap′ō-lip-ō-prō′tēn; **apoE**), which binds to β-amyloid protein and is known to transport cholesterol in the blood, has also been associated with Alzheimer disease. *apoE-III* is the normal protein and *apoE-IV* is an abnormal, mutant form. *apoE-IV* has been found in amyloid plaques and neurofibrillary tangles and has been mapped to the same region of chromosome 19 as the late-onset form of Alzheimer. People with two copies of the *apoE-IV* gene are eight times more likely to develop the disease than people with two copies of the *apoE-III* gene. *apoE-IV* apparently binds to β-amyloid more rapidly and more tightly than does *apoE-III*. *ApoE* also may be involved with regulating phosphorylation of another protein, called τ (tau), which in turn is involved in microtuble formation inside neurons. If τ is overphosphorylated, microtubules are not properly constructed, and the τ proteins intertwine to form neurofibrillary tangles.

Chronic mercury poisoning can cause brain disorders, such as intention tremor, exaggerated reflexes, and emotional instability. Mercury causes oxidative damage and apoptosis in several organs, including the kidneys and CNS.

Lead poisoning is a serious problem, particularly among urban children. Lead is taken into the body from contaminated air, food, and water. Flaking lead paint in older houses and soil contamination can be major sources of lead poisoning in children. Lead usually accumulates slowly in the body until toxic levels are reached.

Brain damage caused by lead poisoning in children includes edema, demyelination, and cortical neuron necrosis with astrocyte proliferation. This damage appears to be permanent and can result in reduced intelligence, learning disabilities, poor psychomotor development, and blindness. In severe cases, psychoses, seizures, coma,

or death may occur. Adults exhibit more mild PNS symptoms, including demyelination with decreased neuromuscular function. Other symptoms include abdominal pain and renal disease.

Epilepsy is a group of brain disorders that have seizure episodes in common. The seizure, a sudden massive neuronal discharge, can be either partial or complete, depending on the amount of brain involved and whether or not consciousness is impaired. A seizure involves a change in sensation, consciousness, or behavior due to brief electrical discharge in the brain.

Normally, a balance exists between excitation and inhibition in the brain. When this balance is disrupted by increased excitation or decreased inhibition, a seizure may result. The neuronal discharges may stimulate muscles innervated by the neurons involved, resulting in involuntary muscle contractions, or convulsions.

Epilepsy occurs in 1% of all people age 20 and 3% of those over age 75. A number of factors can increase the incidence of epilepsy: 2.4% of children whose fathers have epilepsy develop epilepsy and 8.7% of children whose mothers have epilepsy develop the disorder. Ten percent of children with cerebral palsy develop epilepsy, and 10% of those with mental retardation develop epilepsy. Half of children with both cerebral palsy and mental retardation develop epilepsy. Twenty-two percent of stroke patients develop epilepsy. Seventy percent of those with epilepsy will eventually experience remission.

Depression may cause more "grief and misery" than any other single disease. Although the illness has been known for over 2000 years, its medical status is still uncertain. Is depression a disease state caused by a chemical excess or deficiency, or is it a psychologic condition that a person can decide to snap out of? The answer is probably that both types of depression exist. Depression is a complex, multifaceted group of disorders. Some types of "endogenous" depression can be treated with antidepressants, of which there are five groups: tricyclic antidepressants, nontricyclic compounds, MAO inhibitors, serotonin agonists, and lithium. Many people with depression also have epilepsy. Recent research in which "pacemaker-like" stimulation of the vagus nerve to treat epilepsy has shown some promise in treating depression that does not respond to drugs.

Headaches have a variety of causes, which can be grouped into two basic classes: extracranial and intracranial. Extracranial headaches can be caused by inflammation of the sinuses, dental irritations, temporomandibular joint disorders, ophthalmologic disorders, and tension in the muscles moving the head and neck. Intracranial headaches may result from inflammation of the brain or meninges, vascular problems, mechanical damage, or tumors.

Tension headaches are extracranial muscle tension, stress headaches, consisting of a dull, steady pain in the forehead, temples, and neck or throughout the head. Tension headaches are associated with stress, fatigue, and posture.

Migraine headaches (*migraine* means half a skull) occur in only one side of the head and appear to involve the abnormal dilation and constriction of blood vessels. They often start with distorted vision, shooting spots, and blind spots. Migraines consist of severe throbbing, pulsating pain. About 80% of migraine sufferers have a family history of the disorder, and women are affected four times more often than men. Those suffering migraines are usually women younger than 35. The severity and frequency usually decrease with age.

A **concussion** is a blow to the head, producing momentary loss of consciousness without immediate detectable damage to the brain. Often, no more problems occur after the person regains consciousness; however, in some cases, **postconcussion syndrome** occurs shortly after the injury. The syndrome includes increased muscle tension or migraine headaches, reduced alcohol tolerance, difficulty in learning new things, reduction in creativity and motivation, fatigue, and personality changes. The symptoms may be gone in a month or may persist for as much as a year. In some cases, postconcussion syndrome is the result of a slowly occurring subdural hematoma, which is missed by an early examination. The blood may accumulate from small leaks in the dural sinuses.

Alexia (ā-lek′sē-ə), loss of the ability to read, may result from a lesion in the visual association cortex. **Dyslexia** (dĭs-lek′sē-ə) is a defect in which the reading level is below that expected on the basis of an individual's overall intelligence. Most people with dyslexia have normal or above-normal intelligence quotients. The term means reading deficiency and is also called partial alexia. It is three times more common in males than females. As many as 10% of males in the United States suffer from the disorder. The symptoms vary considerably from person to person and include the transposition of letters in a word, confusion between the letters *b* and *d*, and a lack of orientation in three-dimensional space. The brains of some dyslexics have abnormal cellular arrangements, including cortical disorganization and the appearance of bits of gray matter in medullary areas. Dyslexia apparently results from abnormal brain development.

Children with **attention-deficit disorder (ADD)** are easily distractible, have short attention spans, and may shift from one uncompleted task to another. Children with **attention-deficit/hyperactivity disorder (ADHD)** exhibit the characteristics of ADD, but they are also fidgety, have difficulty remaining seated and waiting their turn, engage in excessive talking, and commonly interrupt others. About 3% of all children exhibit ADHD, more boys than girls. Symptoms usually occur before age 7. The neurologic basis of both ADD and ADHD is as yet unknown.

CLINICAL FOCUS

Dyskinesias

Dyskinesias (dis-ki-nē′zē-ăs) are a group of disorders often involving the basal nuclei in which unwanted, superfluous movements occur. Defects in the basal nuclei may result in brisk, jerky, purposeless movements that resemble fragments of voluntary movements. **Sydenham chorea** (kōr-ē′ă; also called St. Vitus dance) is a disease usually associated with a toxic or an infectious disorder that apparently causes temporary dysfunction of the corpus striatum. It usually affects children. **Huntington chorea** is a dominant hereditary disorder that begins in middle life, causing mental deterioration and progressive degeneration of the corpus striatum in affected individuals.

Cerebral palsy (pawl′zē) is a general term referring to defects in motor functions or coordination resulting from several types of brain damage, which may be caused by abnormal brain development or birth-related injury. Some symptoms of cerebral palsy, such as increased muscle tension, are related to basal nuclei dysfunction. **Athetosis** (ath-ĕ-tō′sis), often one of the features of cerebral palsy, is characterized by slow, sinuous, aimless movements. When the face, neck, and tongue muscles are involved, grimacing, protrusion, and writhing of the tongue and difficulty in speaking and swallowing are characteristics.

Damage to the subthalamic nucleus can result in **hemiballismus** (hem-ĕ-bal-iz′mŭs), an uncontrolled, purposeless, and forceful throwing or flailing of the arm. Forceful twitching of the face and neck may also result from subthalamic nuclear damage.

Parkinson disease—characterized by muscular rigidity; loss of facial expression; tremor; a slow, shuffling gait; and general lack of movement—is caused by a dysfunction in the substantia nigra. The disease usually occurs after age 55 and is not contagious or inherited. A resting tremor, called "pill-rolling," is characteristic of Parkinson disease; it consists of circular movement of the opposed thumb and index fingertips. The increased muscular rigidity in Parkinson disease results from defective inhibition of some of the basal nuclei by the substantia nigra. In this disease, dopamine, an inhibitory neurotransmitter produced by the substantia nigra is deficient. The melanin-containing cells of the substantia nigra degenerate, resulting in a loss of pigment.

Parkinson disease can be treated with levodopa (lē-vō-dō′pă, L-dopa), a precursor to dopamine, or more effectively with Sinemet, a combination of L-dopa and carbidopa (kar-bi-dō′pă). Carbidopa is a decarboxylase inhibitor, which prevents the breakdown of L-dopa before it can reach the brain. Because of the long-term side effects, including dyskinesias, associated with levodopa, other dopamine agonists, such as ropinirole and pramipexole, are being examined. A protein called **glial cell line–derived neurotrophic factor (GDNF)** has been discovered that selectively promotes the survival of dopamine-secreting neurons. Chronic stimulation of the globus pallidus (part of the lentiform nucleus) with an electrical pulse generator has shown some success. Treatment of the disorder by transplanting fetal tissues, or stem cells from adult tissues, capable of producing dopamine is also under investigation.

Cerebellar lesions result in a spectrum of characteristic functional disorders. Movements tend to be **ataxic** (jerky) and **dysmetric** (overshooting—for example, pointing past or deviating from a mark that one tries to touch with the finger). Alternating movements, such as supination and pronation of the hand, are performed in a clumsy manner. **Nystagmus** (nis-tag′mŭs), which is a constant motion of the eyes, may also occur. A cerebellar tremor is an intention tremor (i.e., the more carefully one tries to control a given movement, the greater the tremor becomes). For example, when a person with a cerebellar tremor attempts to drink a glass of water, the closer the glass comes to the mouth the shakier the movement becomes. This type of tremor is in direct contrast to basal nuclei tremors, in which the resting tremor largely or completely disappears during purposeful movement.