

# Brain Facts

## NEURAL DISORDERS: ADVANCES AND CHALLENGES

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### Addiction

Drug abuse is one of the nation's most serious health problems. Indeed, 9 percent of Americans, more than 22 million people, abuse drugs on a regular basis. Recent estimates show that the abuse of drugs, including alcohol and nicotine, costs the nation more than \$276 billion each year.

If continued long enough, *drug abuse* — often defined as harmful drug use — can eventually alter the very structure and chemical makeup of the brain, producing a true brain disorder. This disorder is called *drug addiction* or *drug dependence*. Drug addiction is characterized by a pathological desire for drugs, such that drug-seeking and drug-taking behaviors occupy an inordinate amount of an individual's time and thoughts, at the expense of other activities, and these behaviors persist despite many adverse consequences. Addiction is also characterized by difficulty controlling frequency of use and terminating use, despite a stated desire to do so.

People initially experiment with drugs for many different reasons, one of which is that most drugs of abuse produce feelings of pleasure or remove feelings of stress and emotional pain. Neuroscientists have found that almost all abused drugs produce pleasure by activating a specific network of neurons called the *brain reward system*. The circuit is normally involved in an important type of learning that helps us to stay alive. It evolved to mediate the pleasurable and motivating effects of natural rewards, such as eating when we are hungry or drinking when we are thirsty. Indeed, when a reward produces feelings of pleasure, we learn to repeat the actions that got us the reward in the first place. Drugs can activate this same system and therefore can also promote continued drug use.

Neuroscientists have learned a great deal about how drugs of abuse affect neurons to exert their influence. Abused drugs alter the ways neurotransmitters carry their messages from neuron to neuron. Some drugs mimic neurotransmitters, whereas others block them. Still others alter the way neurotransmitters are released or inactivated. Ultimately, in all cases, the brain reward system is activated inappropriately because drugs alter the chemical messages sent among neurons in this circuit.

Finally, neuroscientists have learned that addiction requires more than the activation of the brain reward system. Over the past 20 years or so, research has indicated that the drugs themselves change the brain of susceptible individuals in complex ways, leading

to symptoms of addiction. The brain regions that are changed by drugs include the brain reward system as well as brain regions involved in executive functions and judgment. These latter brain systems are important in inhibiting behavior and in decision-making.

The process of becoming addicted is influenced by many factors that scientists are only beginning to understand. Motivation for drug use is an important one. For example, people who take opioids to get high may get addicted, but people who use them properly to relieve pain rarely do. Genetic susceptibility and environmental factors, such as stress, also alter the way that people respond to drugs. The characteristics of the drugs themselves, such as how quickly they enter the brain, also play a role in addiction. In addition, the development of *tolerance* — the progressive need for a higher drug dose to achieve the same effect — varies in different people, as does *drug dependence* — the adaptive physiological state that results in withdrawal symptoms when drug use stops. Tolerance and dependence are standard responses of the brain and body to the presence of drugs. However, addiction requires that these occur while a *motivational form of dependence* — the feeling that a person can't live without a drug — also is developing.

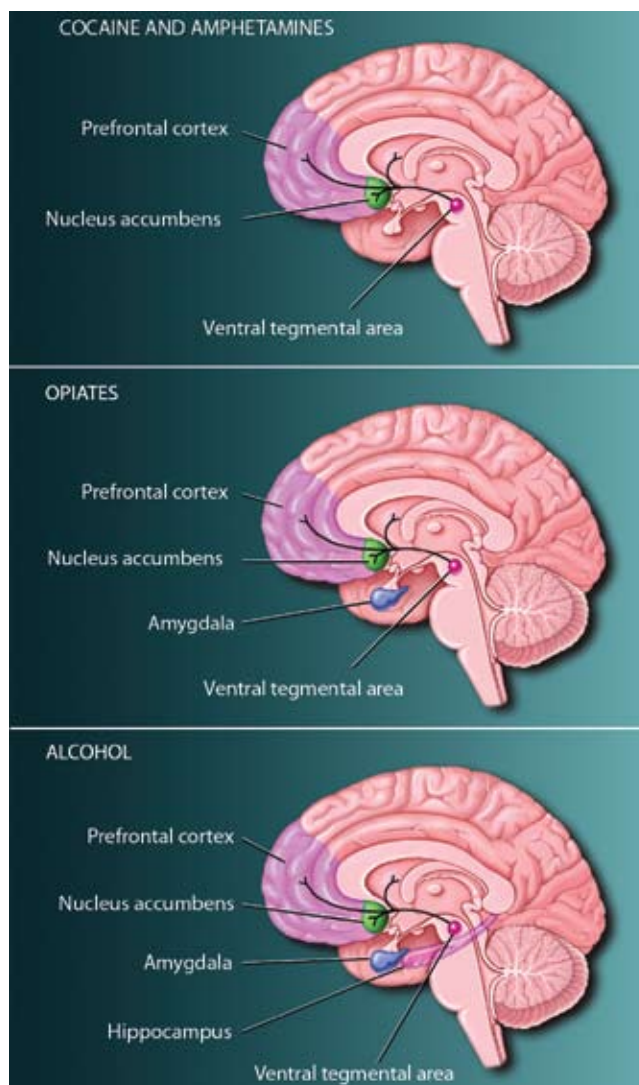
An important question for addiction research is to understand how these many factors interact to predispose individuals to addiction and, conversely, how to protect them. The knowledge and insight into abuse and addiction arising from this research will lead to new therapies.

**Alcohol** Although legal, alcohol is addictive. Alcohol abuse and alcohol addiction — sometimes referred to as alcoholism or alcohol dependence — together are one of the nation's major health problems.

Nearly 14 million people abuse alcohol or are alcoholic. *Fetal alcohol syndrome*, affecting about 0.5 to 3 of every 1,000 babies born in the United States, is the leading preventable cause of mental retardation. Cirrhosis, the main chronic health problem associated with alcohol addiction, and other chronic liver diseases are responsible for more than 25,000 deaths each year. The annual cost of alcohol abuse and addiction is estimated at \$185 billion.

Genetic and environmental factors contribute to alcoholism, but no single factor or combination of factors enables doctors to predict who will become an alcoholic.

Alcohol activates the endogenous opioid system so that susceptible individuals may feel an opioidlike euphoria from their own endorphins when they drink. Based on animal research showing that opiate receptors were involved in the dopamine-reward activation of alcohol, naltrexone, a medication developed for heroin addiction, was used to treat alcoholics. Clinical trials began in 1983, and in 1995, naltrexone was approved by the U.S. Food and Drug Administration (FDA) for the treatment of alcoholism.



**BRAIN DRUG REWARD SYSTEMS.** Scientists are not certain about all the structures involved in the human brain reward system. However, studies of rat and monkey brains, and brain imaging studies in humans, have provided many clues. These illustrations show what areas are most likely part of the reward systems in the human brain. A central group of structures is common to the actions of all drugs. These structures include a collection of dopamine-containing neurons found in the ventral tegmental area. These neurons are connected to the nucleus accumbens and other areas, such as the prefrontal cortex. Cocaine exerts its effects mainly through this system. Opiates act in this system and many other brain regions, including the amygdala, that normally use opioid peptides. Opioids are naturally occurring brain chemicals that induce the same actions as drugs, such as heroin and morphine. Alcohol activates the core reward system and additional structures throughout the brain because it acts where GABA and glutamate are used as neurotransmitters. GABA and glutamate are widely distributed in the brain, including in the cortex, hippocampus, amygdala, and nucleus accumbens.

*Ethanol*, the active ingredient in alcoholic beverages, reduces anxiety, tension, and inhibitions. In low doses, it may act as a stimulant, whereas at higher doses, it acts as a depressant. In both cases, it significantly alters mood and behavior. It can also cause heat loss and dehydration.

The drug, which is easily absorbed into the bloodstream and the brain, affects several neurotransmitter systems. For example, alcohol's interaction with the gamma-aminobutyric acid (GABA) receptor can calm anxiety, impair muscle control, and delay reaction time. At higher doses, alcohol also decreases the function of N-methyl-d-aspartate (NMDA) receptors that recognize the neurotransmitter glutamate. This interaction can cloud thinking and eventually lead to coma.

**Club drugs** Ecstasy, herbal ecstasy, Rohypnol ("roofies"), GHB (gamma hydroxy-butyrate), and ketamine are among the drugs used by some teens and young adults as part of raves and trances. These drugs are rumored to increase stamina and to produce intoxicating highs that are said to deepen the rave or trance experience. Recent research, however, is uncovering the serious damage that can occur in several parts of the brain from use of some of these drugs.

MDMA, called "Adam," "ecstasy," or "XTC" on the street, is a synthetic psychoactive drug with hallucinogenic and amphetamine-like properties. Users encounter problems similar to those found with the use of amphetamines and cocaine. Recent research also links chronic ecstasy use to long-term changes in those parts of the brain critical to thought, memory, and pleasure.

Rohypnol, GHB, and ketamine are predominantly central nervous system depressants. Because they are often colorless, tasteless, and odorless, they can be added easily to beverages and ingested unknowingly. These drugs have emerged as the so-called *date-rape drugs*. When mixed with alcohol, Rohypnol can incapacitate victims and prevent them from resisting sexual assault. Rohypnol may be lethal when mixed with alcohol and other depressants. Since about 1990 in the United States, GHB has been abused for its euphoric, sedative, and anabolic (body-building) effects. It, too, has been associated with sexual assault. Ketamine is another central nervous system depressant abused as a date-rape drug. Ketamine, or "Special K," is a fast-acting general anesthetic. It has sedative, hypnotic, analgesic, and hallucinogenic properties. It is marketed in the United States and a number of foreign countries as a general anesthetic — a drug that brings about a reversible loss of consciousness — in both human and veterinary medical practice.

Many users tend to experiment with a variety of club drugs in combination. This practice creates a larger problem, because combinations of any of these drugs, particularly with alcohol, can lead

to unexpected adverse reactions and even death after high doses. Physical exhaustion also can enhance some toxicities and problems.

**Marijuana** This drug distorts perception and alters the sense of time, space, and self. In certain situations, marijuana can produce intense anxiety.

In radioactive tracing studies, scientists found that *tetrahydrocannabinol* (THC), the active ingredient in marijuana, binds to specific receptors, many of which coordinate movement. This may explain why people who drive after they smoke marijuana are impaired. The hippocampus, a structure involved with memory storage and learning, also contains many receptors for THC. This may explain why heavy users or those intoxicated on marijuana have poor short-term memory and problems processing complex information. Scientists recently discovered that these receptors normally bind to natural internal chemicals termed endocannabinoids, one of which is called *anandamide*. A large effort is now addressing the development of medications that target the endogenous cannabinoid system, with the hope that these will prove beneficial in treating a number of different brain disorders, including addiction, anxiety, and depression.

**Nicotine** In 2003, more than 70 million people smoked, at least occasionally, making nicotine one of the most widely abused substances. Tobacco kills more than 430,000 U.S. citizens each year — more than alcohol, cocaine, heroin, homicide, suicide, car accidents, fire, and AIDS combined. Tobacco use is the leading preventable cause of death in the United States. Smoking is responsible for approximately 7 percent of total U.S. health-care costs, an estimated \$80 billion each year. The direct and indirect costs of smoking are estimated at more than \$138 billion per year.

Nicotine, the addicting substance in tobacco, acts through the well-known cholinergic nicotinic receptor. This drug can act as both a stimulant and a sedative. Nicotine stimulates the adrenal glands, and the resulting discharge of epinephrine causes a "kick": a sudden release of glucose paired with an increase in blood pressure, respiration, and heart rate. Nicotine also suppresses insulin output from the pancreas, which means that smokers are always slightly hyperglycemic. In addition, nicotine releases dopamine in the brain regions that control motivation, which is one reason that people continue to smoke.

Much better understanding of addiction, coupled with the identification of nicotine as an addictive drug, has been instrumental in the development of treatments. Nicotine gum, the transdermal patch, nasal spray, and inhalers are equally effective in treating the more than one million people addicted to nicotine. These techniques are used to relieve withdrawal symptoms and produce less severe physiological alterations than tobacco-based systems.

They generally provide users with lower overall nicotine levels than they receive with tobacco and totally eliminate exposure to smoke and its deadly contents. The first non-nicotine prescription drug, bupropion, an antidepressant, has been approved for use as a pharmacological treatment for nicotine addiction. An exciting advance is the use of varenicline for smoking cessation, which directly interacts with the cholinergic nicotinic receptor in a key component of the brain's reward circuitry and prevents nicotine from activating this circuit. The development of varenicline is a prime example of how basic science research can lead to the production of novel medications. Behavioral treatments also are important in helping an individual learn coping skills for both short- and long-term prevention of relapse.

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**Opiates** Humans have used opiate drugs, such as morphine, for thousands of years. Monkeys and rats readily self-administer heroin or morphine and, like humans, will become tolerant and physically dependent with unlimited access. Withdrawal symptoms range from mild, flulike discomfort to severe muscle pain, stomach cramps, diarrhea, and unpleasant mood.

Opiates increase the amount of dopamine released in the brain reward system and mimic the effects of endogenous opioids. Heroin injected into a vein reaches the brain in 15 to 20 seconds and binds to opiate receptors found in many brain regions, including the reward system. Activation of the receptors in the reward circuits causes a brief rush of intense euphoria, followed by a couple of hours of a relaxed, contented state.

Opiates create effects like those elicited by the naturally occurring opioid peptides. They relieve pain, depress breathing, cause nausea and vomiting, and stop diarrhea — important medical uses. In large doses, heroin can make breathing shallow or stop altogether — the cause of death in thousands of people who have died of heroin overdose.

A standard treatment for opiate addiction involves *methadone*, a long-acting oral opioid that helps keep craving, withdrawal, and relapse under control. Methadone helps opiate addicts rehabilitate themselves by preventing withdrawal symptoms that can motivate continued drug use. Naloxone and naltrexone are available medications that act as antagonists at opioid receptors; in other words, they can curb the allure of opiates by blocking the opiate receptors so that opiates produce no pleasurable effects when they are taken. The blockers alone are sometimes useful for addicts who are highly motivated to quit. In addition, scientists are developing a long-lasting version of naltrexone that needs to be taken only once a month.

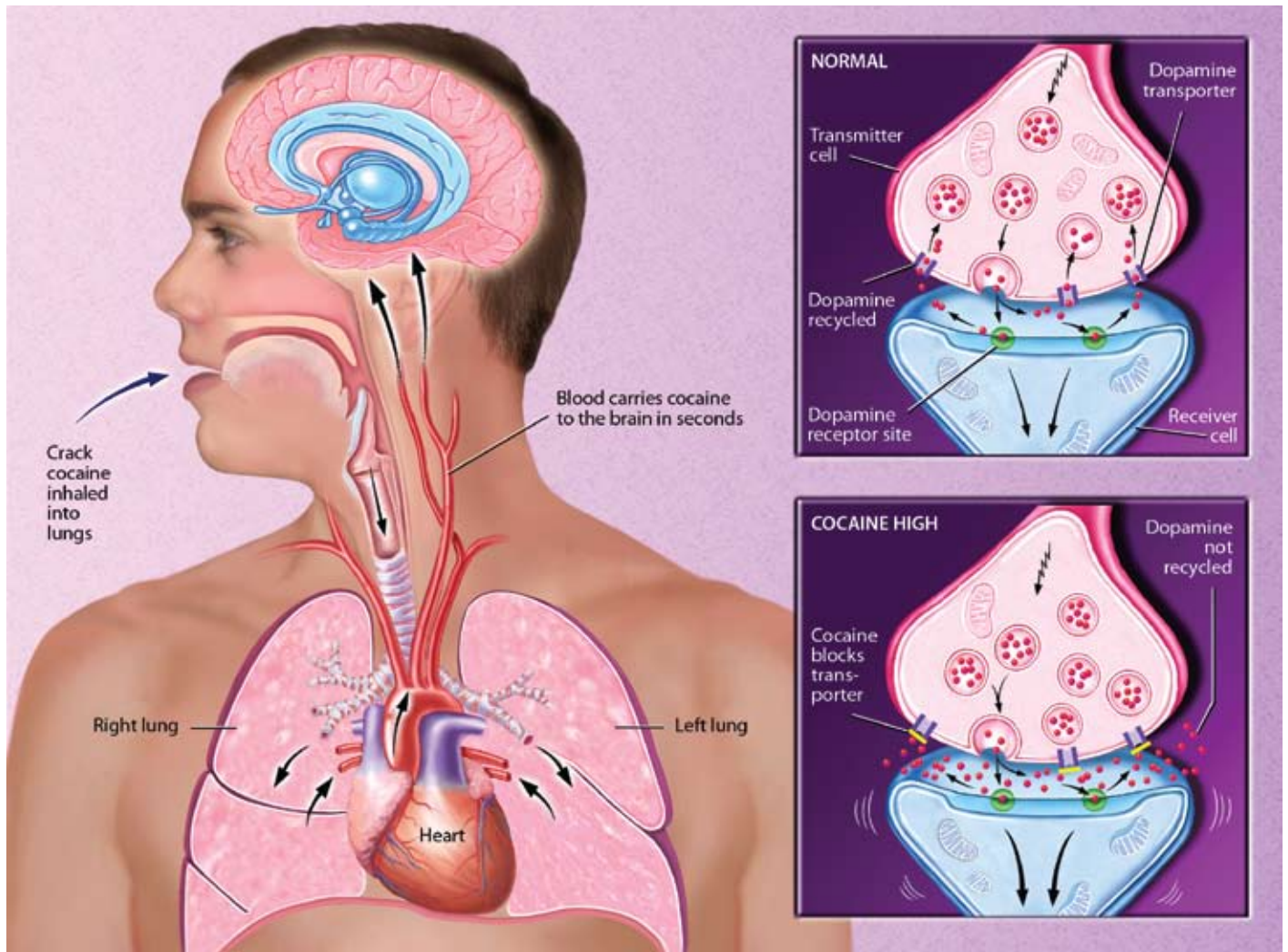
Another medication to treat heroin addiction, buprenorphine, causes a weaker effect on the receptors than methadone and creates only a limited high, which deters an addict from abusing the medication itself. Buprenorphine has been prescribed for over 500,000 patients in the United States.

**Psychostimulants** This class of drugs includes cocaine and amphetamines. In 2003, there were an estimated 2.3 million chronic cocaine users and 5.9 million occasional cocaine users in the United States. A popular, chemically altered form of cocaine, crack, is smoked. It enters the brain in seconds, producing a rush of euphoria and feelings of power and self-confidence. A smokable form of methamphetamine, “crystal meth,” also has become popular. The key biochemical factor that underlies the reinforcing effects of psychostimulant drugs is their ability to greatly elevate the brain chemical dopamine in specific brain regions, such as the *nucleus accumbens*, and repeated use of these drugs progressively increases their ability to activate brain dopamine systems. This is thought to result in a progressively increasing motivation to take the drugs, eventually leading to addiction.

Cocaine users often go on binges, consuming a large amount of the drug in just a few days. A *crash* occurs after this period of intense drug-taking and includes symptoms of emotional and physical exhaustion and depression. These symptoms may result from an actual crash in dopamine and serotonin function as well as an increased response of the brain systems that react to stress. Vaccines to produce antibodies to cocaine in the bloodstream are in clinical trials.

## Alzheimer's disease

One of the most frightening and devastating of all neurological disorders is the dementia that occurs in the elderly. The most common cause of this illness is Alzheimer's disease (AD). Rare before age 60 but increasingly prevalent in each decade thereafter, AD affects more than 40 percent of those age 85 and over and nearly



**HOW CRACK COCAINE AFFECTS THE BRAIN.** Crack cocaine takes the same route as nicotine by entering the bloodstream through the lungs. Within seconds, it is carried by the blood to the brain. The basis for increased pleasure occurs at the gap where the impulses that represent neural messages are passed from one neuron to another. This gap is called a synapse. Dopamine-containing neurons normally relay their signals by releasing dopamine into many synapses. Dopamine crosses the synapse and fits into receptors on the surface of the receiving cell. This triggers an electrical signal that is relayed through the receiver. Then, to end the signal, dopamine molecules break away from the receptors and are pumped back into the nerve terminals that released them. Cocaine molecules block the pump or “transporter,” causing more dopamine to accumulate in the synapse. Pleasure circuits are stimulated again and again, producing euphoria.

20 percent of those ages 75 to 84. As many as 5 million Americans have AD. The disease is predicted to affect approximately 14 million individuals in the United States by the year 2040.

The earliest symptoms of AD include forgetfulness; disorientation to time or place; and difficulty with concentration, calculation, language, and judgment. As the disease progresses, some patients have severe behavioral disturbances and may even become psychotic. In the final stages, the affected individual is incapable of self-care and becomes bed-bound. Patients usually die from pneumonia or some other complication of immobility. AD, which in

2005 was reported to have killed 72,000 Americans, is the seventh leading cause of death in the United States.

In the earliest stages, the clinical diagnosis of possible or probable AD can be made with greater than 80 percent accuracy. As the course of the disease progresses, the accuracy of diagnosis at Alzheimer’s research centers exceeds 90 percent. The diagnosis depends on medical history, physical and neurological examinations, psychological testing, laboratory tests, and brain imaging studies. New brain imaging strategies promise to enable doctors to visualize AD neuropathology during life. At present, however, final

confirmation of the diagnosis requires examination of brain tissue, usually obtained at autopsy.

The causes and mechanisms of the brain abnormalities underlying AD are not yet fully understood, but great progress has been made through genetics, biochemistry, cell biology, and experimental treatments. Reductions occur in levels of markers for many neurotransmitters, including acetylcholine, somatostatin, monoamines, and glutamate, that allow cells to communicate with one another. Damage to these neural systems, which are critical for attention, memory, learning, and higher cognitive abilities, is believed to cause the clinical symptoms.

Microscopic examination of AD brain tissue shows abnormal accumulations of a small fibrillar peptide, termed *beta amyloid*, in the spaces around synapses (*neuritic plaques*) and abnormal accumulations of a modified form of the protein tau in the cell bodies of neurons (*neurofibrillary tangles*). In all forms of AD, plaques and tangles mostly develop in brain regions important for memory and intellectual functions. New brain imaging strategies show amyloid plaques and tau tangles labeled by a mildly radioactive chemical marker in living people.

Early-onset AD is a rare, dominantly inherited form of the disease. Recently, scientists have identified AD-associated mutations. The gene encoding the *amyloid precursor protein* (APP) is on chromosome 21. In other families with early-onset AD, mutations have been identified in the presenilin 1 and 2 genes. Genes that cause dominant Alzheimer's appear to do so by causing beta amyloid plaques to accumulate. *Apolipoprotein E* (apoE), which influences susceptibility in late life, exists in three forms. The variant known as *APOE epsilon 4* is clearly associated with enhanced risk.

Currently approved treatments do not modify the course of the disease and offer only temporary mitigation of some symptoms of AD, such as agitation, anxiety, unpredictable behavior, sleep disturbances, and depression. Five drugs have been approved by the FDA to treat AD. Four prevent the breakdown of acetylcholine, a brain chemical important for memory and thinking. The fifth regulates glutamate, a brain chemical that may cause brain cell death when produced in large amounts. These agents improve memory deficits temporarily and provide some symptomatic relief but do not prevent progression of the disease. Several other approaches, such as antioxidants, are being tested.

An exciting area of research is the introduction of AD-causing genes in mice. These mice, carrying mutant genes linked to inherited AD, develop behavioral abnormalities and some of the microscopic changes in tissue structure that occur in humans. It is hoped that these mouse models will prove useful for studying the mechanisms of AD and testing novel therapies, although appropri-

ate caution must be taken. Experimental therapies in models of other neurodegenerative diseases — amyotrophic lateral sclerosis, for example — have been effective in mice but not in humans with the disease.

Researchers have begun to modulate the actions of genes that play critical roles in the production of amyloid in animal models. These genes encode the amyloid-producing enzymes beta and gamma secretases, which cleave amyloid peptide from the precursor. The amyloid peptide is then released from the neuron into the extracellular space, where it can accumulate and form AD plaques. Amyloid-destroying enzymes, known as alpha secretases, break up the amyloid peptide, preventing amyloid accumulation. Anti-amyloid therapies for AD aim either to remove existing amyloid or decrease production of new amyloid.

Within the past three to five years, greater appreciation has developed for the surprisingly important roles that diet and lifestyle play in determining risk for AD. Cognitive activity, physical activity, and heart-healthy diets lower the risk for AD, while obesity, high blood pressure, high cholesterol, metabolic syndrome, and diabetes raise the risk. Some evidence indicates that successful management of these cardiovascular risks can delay the onset or slow the progression of dementia.

## Amyotrophic lateral sclerosis

This progressive disorder strikes more than 5,000 Americans annually, with an average survival time of just three to five years from symptom onset. It is the most common disorder within a group of diseases affecting motor neurons and costs Americans some \$300 million annually.

Commonly known as Lou Gehrig's disease, amyotrophic lateral sclerosis (ALS) affects neurons that control voluntary muscle movements such as walking. For reasons that are not completely understood, motor neurons in the brain and spinal cord begin to disintegrate. Because signals from the brain are not carried by these damaged nerves to the body, the muscles begin to weaken and deteriorate from the lack of stimulation and resulting disuse.

The first signs of progressive paralysis are usually seen in the hands and feet. They include weakness in the legs, difficulty walking, and clumsiness of the hands when washing and dressing. Eventually, almost all muscles under voluntary control, including those of the respiratory system, are affected. Despite the paralysis, however, the mind and the senses remain intact. Death is usually caused by respiratory failure or pneumonia.

No specific test identifies ALS, but muscle biopsies, blood studies, electrical tests of muscle activity, computed tomography (CT) and magnetic resonance imaging (MRI) scans, and X-rays

of the spinal cord help identify the disease and rule out other disorders. Still, diagnosis is often difficult because the causes of ALS remain unknown. Potential causes or contributors to the disease include glutamate toxicity, oxidative stress, environmental factors, and an autoimmune response in which the body's defenses turn against body tissue.

In more than 90 percent of cases, ALS is sporadic, arising in individuals with no known family history of the disorder. In the other 5 to 10 percent of cases, ALS is *familial* — transmitted to family members because of a gene defect.

Scientists have now identified several genes that are responsible for some forms of ALS. The most common and well studied of these are mutations in the gene that codes for *superoxide dismutase*. Scientists believe that whatever they learn from studying this gene and others will have relevance for understanding the more common sporadic form of motor neuron disease.

Once ALS is diagnosed, physical therapy and rehabilitation methods can help strengthen unused muscles. Various drugs can ease specific problems, such as twitching and muscle weakness, but there is no cure. An anti-glutamate drug moderately slows the disease. Additional drugs are now under study. Protecting or regenerating motor neurons using nerve growth factors, other more potent drugs, and stem cells may someday provide additional hope for patients.

## Anxiety disorders

The most widespread mental illnesses, anxiety disorders annually affect an estimated 12.6 percent of the adult population, or 24.8 million Americans. They include obsessive-compulsive disorder (OCD); panic disorder; phobias, such as fear of heights, agoraphobia (fear of open spaces), and social anxiety disorder; generalized anxiety disorder; and post-traumatic stress disorder (PTSD). Some can keep people completely housebound. Anxiety disorders often occur together with depression, and individuals doubly afflicted are at a high risk of suicide.

In OCD, people become trapped, often for many years, in repetitive thoughts and behaviors, which they recognize as groundless but cannot stop. Such behavior includes repeatedly washing hands or checking that doors are locked or stoves turned off. The illness is estimated to affect 5 to 6 million Americans annually. Environmental factors and genetics probably play a role in the development of the disorder. Positron emission tomography (PET) scans reveal abnormalities in both cortical and deep areas of the brain, implicating central nervous system changes in OCD patients.

Scientists have recently discovered that certain breeds of large dogs that develop *acral lick syndrome*, severely sore paws from

compulsive licking, respond to the serotonergic antidepressant clomipramine, which was the first effective treatment developed for OCD in people. This and other serotonergic antidepressants and the selective serotonin reuptake inhibitors (SSRIs), such as sertraline and paroxetine, are effective in treating OCD. A specialized type of behavioral intervention, *exposure and response prevention*, also is effective in many patients.

Panic disorder, with a lifetime prevalence rate of 1.7 to 3.5 percent in the United States, usually starts “out of the blue.” Patients experience an overwhelming sense of impending doom, accompanied by sweating, weakness, dizziness, and shortness of breath. With repeated attacks, patients may develop anxiety in anticipation of another attack and avoid public settings where attacks might occur. If these patients are untreated, they may develop *agoraphobia* and become virtually housebound. Antidepressants, including SSRIs, are effective, as is cognitive behavioral therapy.

Phobia is an intense, irrational fear of a particular object or situation. Individuals can develop phobias of almost anything, including dogs, dating, blood, snakes, spiders, or driving over bridges. Exposure to the feared object or situation can trigger an extreme fear reaction that may include a pounding heart, shortness of breath, and sweating. Cognitive behavioral therapy is an effective treatment.

Extreme stressors such as trauma in combat, being a victim of assault or sexual abuse, or experiencing or witnessing a crime can lead to a form of stress that can last a lifetime. Termed PTSD, the lifetime prevalence rate in the United States for this disorder is 6.8 percent (9.7 percent in women and 1.8 percent in men). It is characterized by intense fear, helplessness or horror, intrusive recollections of the traumatic event, avoidance and numbing, and hyperarousal. In addition, PTSD is associated with dysregulation of the hypothalamic-pituitary-adrenal axis, disordered sleep, and major depressive disorder. Military personnel are at elevated risk for exposure to trauma and not surprisingly have higher prevalence rates when compared to the general population.

Scientists have learned that very high levels of norepinephrine are released in the brain during stress and that patients with PTSD have heightened levels of this chemical long after the traumatic event has passed. High levels of norepinephrine strengthen the primitive emotional reactions of the amygdala, the fear center of the brain, while weakening the rational functions of the prefrontal cortex, which quiets the amygdala. Very high levels of norepinephrine release can strengthen the consolidation of emotional memories and strengthen fear responses through the stimulation of alpha-1 and beta receptors in the amygdala. In contrast, stimulation of alpha-1 receptors in the prefrontal cortex takes this higher brain region “offline.” The prefrontal cortex normally allows us to suppress troubling memories and thoughts, and inhibits

the amygdala to let us know that we are safe (the extinction of the fear response). Imaging studies show that patients with PTSD have weaker prefrontal function and stronger amygdala activation, consistent with their symptoms.

New successful medications for PTSD have arisen from this basic research. The alpha-1 blocker, prazosin, a drug used to lower blood pressure for more than 20 years, is now used to treat nightmares experienced with PTSD; those treated with prazosin include people with very long-standing illness, such as Holocaust survivors. Beta-blockers such as propranolol also are being tested in individuals exposed to trauma, but these agents must be administered close in time after the trauma, before PTSD has been established, which brings up complex ethical issues.

The discovery of brain receptors for the benzodiazepine antianxiety drugs has sparked research to identify the brain's own antianxiety chemical messengers. The benzodiazepine receptors are a component of the GABA receptor and enhance the responsiveness to endogenous GABA, the major inhibitory neurotransmitter in the brain. Indeed, recent studies have revealed alterations in certain GABA receptors in the central nervous system of patients with PTSD. This finding may lead to ways to regulate this brain system and correct its possible defects in anxiety disorders.

PTSD also is treated with antidepressant and atypical antipsychotic medications and with psychotherapies such as cognitive behavioral therapy or eye movement desensitization and reprocessing therapy.

## Attention deficit hyperactivity disorder

Attention deficit hyperactivity disorder (ADHD) was first described more than 100 years ago. Characterized by excessively inattentive, hyperactive, or impulsive behaviors, ADHD affects an estimated 2 million children in the United States, or 3 to 5 percent of children. Studies show that 30 percent to 70 percent of these children will continue to experience ADHD symptoms as adults.

By definition, symptoms of ADHD appear before age 7, last for six months or longer, and impair normal functioning in at least two types of settings — at school, among friends, at home, or at work, in the case of adults. Currently, no objective diagnostic test for ADHD exists. Diagnosis requires a comprehensive evaluation, including a clinical interview, parent and teacher ratings, and, sometimes, learning disorder or psychological testing. Multiple evaluation techniques are required because healthy children occasionally show similar behavior, and other conditions, disorders, or environmental triggers — such as stress — may be associated with the same behaviors.

Twin and family studies show that ADHD has a strong genetic influence, and genes encoding components of dopamine and norepinephrine transmission have been implicated. Studies increasingly are finding correlations between ADHD and differences in

brain volume or function. Smaller volume and reduced activity are often observed in prefrontal cortical-striatal-cerebellar circuits, particularly in the right hemisphere. Recent studies show a delay in cortical development in some children with ADHD, speculated to represent the subgroup who “grow out” of the disorder.

Recent imaging studies are consistent with reduced catecholamine transmission in at least some patients with this disorder.

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As prefrontal circuits require an optimal level of catecholamine stimulation, reduced catecholamine transmission could lead to weakened prefrontal cortical regulation of attention and behavior and symptoms of ADHD.

ADHD is commonly treated with medications such as stimulants (e.g., methylphenidate) and newer, nonstimulant drugs. These agents all act by enhancing catecholamine transmission in the prefrontal cortex. Despite the widespread use of stimulants, concerns about their risks linger. Thus, parents and clinicians have to balance the benefits of a child with better attention and behavioral regulation on one hand, and the uncertainty about the risks of exposing children to psychotropic drugs on the other.

## Autism

An autism spectrum disorder (ASD) is diagnosed in 1 of every 150 babies born in the United States (approximately 1.7 million Americans), an incidence far greater than in the 1970s owing mainly to changes in diagnostic criteria, grouping of multiple disorders into one spectrum, and enhanced clinician referral based on greater awareness. ASD is characterized by communication difficulties; absent, delayed, or abnormal language; impaired social skills; and narrow, obsessive interests or repetitive behaviors. Common associated symptoms include mental retardation, seizures, and behavioral abnormalities.

Currently, ASD is diagnosed in 3- to 5-year-olds based on behavioral symptoms. New research indicates that very sensitive measures of social engagement and interaction can detect differences in the first year of life, a time when many affected children exhibit accelerated growth of the brain. This abnormal growth is a potential marker for early evaluation that may also indicate that development has gone awry.

Studies of brain neurophysiology, tissue, and imaging indicate that ASD is a disorder that disrupts basic developmental processes that occur both before and after birth, potentially including neural cell proliferation, migration, survival, axon and dendrite extension, and synapse formation. Specific brain regions involved in language, cognition, and social communication, or the connections among them, may be formed abnormally. Research also indicates that genetic factors are major contributors to ASD (10 to 20 percent of cases have identified genetic causes), with potential involvement of environmental factors.

Although no cure exists, many affected children respond well to highly structured environments and specialized education and language programs, with earlier interventions leading to better outcomes. Associated symptoms respond to medications.

Knowledge of specific functional deficits in social and cognitive circuits is leading to distinct clinical training to improve brain activity and behavioral outcomes, whereas genetic findings may allow new targeted therapies at the molecular level. One day, genetic tests may complement behavioral indicators to allow earlier diagnosis and intervention as well as the means to overcome and possibly prevent ASD symptoms.

## Bipolar disorder

Patients with bipolar disorder, previously known as manic-depressive illness, usually experience episodes of deep depression and manic highs, with a return to relatively normal functioning in between. They also have an increased risk of suicide. Bipolar disorder annually affects 1.2 percent of Americans age 18 or older, or 2.2 million individuals. Approximately equal numbers of men and women suffer from this disorder.

Bipolar disorder tends to be chronic, and episodes can become more frequent without treatment. As bipolar disorder runs in families, efforts are underway to identify the responsible gene or genes.

Bipolar patients can benefit from a broad array of treatments. One of these is lithium. During the 1940s, researchers showed that lithium injections into guinea pigs made them placid, which implied mood-stabilizing effects. When given to manic patients, lithium calmed them and enabled them to return to work and live relatively normal lives. Regarded as both safe and effective, lithium is often used to prevent recurrent episodes.

Other useful medications include certain anticonvulsants, such as valproate or carbamazepine, which can have mood-stabilizing effects and may be especially useful for difficult-to-treat bipolar episodes. Newer anticonvulsant medications are being studied to determine how well they work in stabilizing mood cycles.

## Brain tumors

Although brain tumors are not always *malignant* — a condition that spreads and becomes potentially lethal — these growths always are serious because they can interfere with normal brain activity.

Primary brain tumors arise within the brain, whereas metastatic (also called secondary) brain tumors spread from other parts of the body through the bloodstream. The incidence of primary brain tumors is about 15 per population of 100,000. About 44,000 new cases occur in the United States annually.

Symptoms vary according to location and size, but seizures and headache are among the most common. To expand, *gliomas*, typically malignant brain tumors, release the neurotransmitter glutamate at toxic concentrations. This kills off neurons in their vicinity, making room for the tumor's expansion. The released glutamate explains seizures originating from tissue surrounding the tumor. An expanding tumor can increase pressure within the skull, causing headache, vomiting, visual disturbances, and impaired mental functioning. Brain tumors are diagnosed with MRI and CT scanning.

Treatment options for primary brain tumors are limited. Surgery is generally the first step if the tumor is accessible and vital structures will not be disturbed. Radiation is used to stop a tumor's growth or cause it to shrink. Chemotherapy destroys tumor cells that may remain after surgery and radiation but is not very effective for gliomas. Steroid drugs relieve brain swelling, and antiepileptic drugs control seizures.

New therapies for brain tumors are developed in organized studies called clinical trials. Many of these trials focus on targeted therapy — treatment aimed at biologic characteristics of tumors. Targeted therapies include vaccines created from the patient's own tumor combined with substances that boost the immune system or kill tumor cells; *monoclonal* antibodies, which home in on receptors on the surface of the tumor cells; *anti-angiogenic* therapy, in which the tumor's blood supply is restricted; *immunotherapy*, which uses the body's own immune system against the tumor; *gene therapy*, in which bioengineered genes are delivered to the cancer cells to kill them; and several approaches for a targeted delivery of antibodies, toxins, or growth-inhibiting molecules that attach specifically to the tumor cells and interfere with their growth. A scorpion-derived toxin called chlorotoxin that interferes with tumor spread has shown promise in clinical studies where it extended life expectancy significantly.

Researchers are exploring the role of stem cells in the origin of brain tumors. *Epidemiologists*, or scientists studying disease in human populations, also are looking into tumor genetics and patients' lifestyle, environment, occupation, and medical history for clues as to the causes of these tumors. International efforts are underway to increase awareness of brain tumors, encourage research collaboration, and explore new and innovative therapies.

## Down syndrome

Down syndrome, the most frequently occurring chromosomal condition, appears in 1 of every 732 babies. It typically occurs when an extra copy of chromosome 21 — or part of its long arm — is present in the egg or, less commonly, in the sperm, at the time of conception. It is not known why this error occurs, and the error has not been linked to any environmental or behavioral factors, either before or during pregnancy, but the risk is markedly increased with the age of the mother. At age 35, the risk is about 1 in 365 births; at age 40, it is 1 in 110. Because of higher fertility rates in younger women, 80 percent of children with Down syndrome are born to women under 35 years of age. Prenatal screening tests, such as the Triple and Quadruple Screens, can accurately detect Down syndrome in about 70 percent of fetuses. Definitive prenatal diagnoses can be obtained with either chorionic villus sampling or amniocentesis.

Down syndrome is associated with approximately 50 physical and developmental characteristics. An individual with Down syndrome is likely to possess, to various degrees, some of these characteristics: mild to moderate intellectual disabilities; low muscle tone; an upward slant to the eyes; a flat facial profile; an enlarged tongue; and an increased risk of congenital heart defects, respiratory problems, and digestive tract obstruction. Nearly all people with Down syndrome show some neuropathological changes like those seen in Alzheimer's disease by age 40, and most show cognitive decline by age 60.

Babies with Down syndrome develop much as typical children do but at a somewhat slower rate. They learn to sit, walk, talk, and toilet train, just like their peers. Early intervention programs can begin shortly after birth and can help foster an infant's development.

Thanks to medical advances and a greater understanding of the potential of those with this condition, people with Down syndrome have been able to have longer and fuller lives. They are being educated in their neighborhood schools, participating in community activities, and finding rewarding employment and relationships.

Although there is no cure for or means of preventing Down syndrome, scientists are moving closer to understanding the role that the genes on chromosome 21 play in a person's development.

Once this mystery is understood, they hope to decode the biochemical processes that occur in Down syndrome and learn to treat or cure this disorder.

## Dyslexia

An estimated 15 to 20 percent of the population, as many as 60 million Americans, has some form of learning disability involving difficulties in the acquisition and use of listening, speaking, reading, writing, reasoning, or mathematical abilities. These challenges often occur in people with normal or even high intelligence.

*Dyslexia*, or specific reading disability, is the most common and most carefully studied of the learning disabilities. It affects 80 percent of all those identified as learning-disabled. Dyslexia is characterized by an unexpected difficulty in reading in children and adults who otherwise possess the intelligence, motivation, and schooling considered necessary for accurate and fluent reading. Studies indicate that although there can be improvement, dyslexia is a persistent, chronic condition.

There is now a strong consensus that the central difficulty in most forms of dyslexia reflects a deficit within the language system

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— and more specifically, in a component of the language system called phonology. This results in difficulty transforming the letters on the page to the sounds of language.

As children approach adolescence, one manifestation of dyslexia may be a very slow reading rate. Children may learn to read words accurately, but their reading will not be fluent or automatic,

reflecting the lingering effects of a phonologic deficit. Because they can read words accurately — albeit very slowly — dyslexic adolescents and young adults may mistakenly be assumed to have “outgrown” their dyslexia. The ability to read aloud accurately, rapidly, and with good expression, as well as facility with spelling, may be most useful clinically in distinguishing students who are average from those who are poor readers. In some languages that are more consistent in the relationship between letters and sounds, for instance Finnish and Italian, slow reading may be the only manifestation of dyslexia at any age.

A range of investigations indicates that there are differences in brain regions between dyslexic and nonimpaired readers involving three important left hemisphere neural systems, two posteriorly (parieto-temporal, occipito-temporal) and one anteriorly around the left inferior frontal region (Broca’s area). Converging evidence using functional brain imaging indicates that dyslexic readers demonstrate a functional disruption in an extensive system in the posterior portion of the brain. The disruption occurs within the neural systems linking visual representations of letters to the phonologic structures they represent, and the resulting brain images are referred to as the neural signature of dyslexia.

It is clear that dyslexia runs in families, and research has advanced understanding of its genetic basis. Following the gradual identification over the past 20 years of sites on the human genome that are associated with an increased risk for developing dyslexia, in the past four years, six candidate dyslexia susceptibility genes have been reported, and multiple studies have confirmed some of these candidates. These *risk alleles*, the term given to gene variants that increase the risk of developing a condition or illness, have been shown to play important roles in the development of the brain during fetal life, and some of them may eventually be confirmed to play a role in dyslexia.

Interventions to help children with dyslexia focus on teaching the child that words can be segmented into smaller units of sound and that these sounds are linked with specific letter patterns. In addition, children with dyslexia require practice in reading stories, both to allow them to apply their newly acquired decoding skills to reading words in context and to experience reading for meaning and enjoyment.

## Huntington’s disease

Affecting some 30,000 Americans and placing 200,000 more at risk, Huntington’s disease (HD) is now considered one of the most common hereditary brain disorders. The disease, which killed folk singer Woody Guthrie in 1967, progresses slowly over a 10- to 20-year period and eventually robs the affected individual of the

ability to walk, talk, think, and reason. HD usually appears between the ages of 30 and 50. It affects both the basal ganglia, which control coordination, and the brain cortex, which serves as the center for thought, perception, and memory.

The most recognizable symptoms include involuntary jerking movements of the limbs, torso, and facial muscles. These are often accompanied by mood swings, depression, irritability, slurred speech, and clumsiness. As the disease progresses, common symptoms include difficulty swallowing, unsteady gait, loss of balance, impaired reasoning, and memory problems. Eventually, the individual becomes totally dependent on others for care, with death often due to pneumonia, heart failure, or another complication.

Diagnosis consists of a detailed clinical examination and family history. Brain scans may be helpful. The identification in 1993 of the gene that causes HD has simplified genetic testing, which can be used to help confirm a diagnosis. HD researchers and

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*Affecting some 30,000 Americans and placing 200,000 more at risk, Huntington’s disease is now considered one of the most common hereditary brain disorders.*

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genetic counselors, however, have established specific protocols for predictive testing to ensure that the psychological and social consequences of a positive or negative result are understood. Predictive testing is available only for adults, though children under 18 may be tested to confirm a diagnosis of juvenile-onset HD. Prenatal testing may be performed. The ethical issues of testing must be considered, and the individual must be adequately informed, because there is no effective treatment or cure.

The HD mutation is an expanded triplet repeat in the HD gene — a kind of molecular stutter in the DNA. This abnormal gene codes for an abnormal version of the protein called Huntingtin. The Huntingtin protein, whose normal function is still unknown, is widely distributed in the brain and appears to be associated with proteins involved in transcription, protein turnover, and energy production. The cause of HD probably involves the gain

of a new and toxic function. Cell and animal models can replicate many features of the disease and are now being used to test new theories and therapies. Although currently no effective treatments for slowing disease progression exist, clinical and observational trials are being conducted. Any of these may yield an effective treatment that would slow the progression or delay onset of the disease while researchers continue working toward a cure.

## Major depression

This condition, with its harrowing feelings of sadness, hopelessness, pessimism, loss of interest in life, and reduced emotional well-being, is one of the most common and debilitating mental disorders. Depression is as disabling as heart disease or arthritis. Depressed individuals are 18 times more likely to attempt suicide than people with no mental illness.

Annually, major depression affects 5 percent of the population, or 9.8 million Americans, aged 18 years and older. Fortunately, 80 percent of patients respond to drugs, psychotherapy, or a combination of the two. Some severely depressed patients can be helped with electroconvulsive therapy.

Depression arises from many causes: biological (including genetic), psychological, environmental, or a combination of these. Stroke, hormonal disorders, antihypertensives, and birth control pills also can play a part.

Physical symptoms — disturbances of sleep, sex drive, energy level, appetite, and digestion — are common. Some of these symptoms may reflect the fact that the disorder affects the delicate hormonal feedback system linking the hypothalamus, the pituitary gland, and the adrenal glands. For example, many depressed patients secrete excess cortisol, a stress hormone, and do not respond appropriately to a hormone that should counter cortisol secretion. When tested in sleep laboratories, depressed patients' electroencephalograms often exhibit abnormalities in their sleep patterns.

The modern era of drug treatment for depression began in the late 1950s. Most antidepressants affect norepinephrine or serotonin in the brain, apparently by correcting the abnormal signals that control mood, thoughts, and other sensations. The *tricyclic antidepressants* primarily block the reuptake and inactivation of serotonin and norepinephrine to varying degrees. Another class of antidepressant medications is the *monoamine oxidase inhibitors* (MAOIs). These agents inhibit monoamine oxidase, an enzyme that breaks down serotonin and norepinephrine, allowing these chemicals to remain active.

The popular medication fluoxetine is the first of a class of drugs called *selective serotonin reuptake inhibitors*, or SSRIs. SSRIs block the reuptake and inactivation of serotonin and keep it active in certain brain circuits. Hence, they are functionally similar to the

tricyclic antidepressants but act selectively on the serotonin system and have much less toxicity. Several newer antidepressants, such as bupropion, are also very effective but may affect the synaptic levels of dopamine.

## Multiple sclerosis

The most common central nervous system disease of young adults after epilepsy, multiple sclerosis (MS) is a lifelong ailment of unknown origin that affects more than 400,000 Americans. MS is diagnosed mainly in individuals between the ages of 20 and 50, with 2 of 3 cases occurring in women. The disease results in earning losses of about \$10.6 billion annually for U.S. families with MS.

Although a cause has yet to be found, MS is thought to be an autoimmune disease in which the body's natural defenses act against the myelin and nerve fibers in the central nervous system as though they were foreign tissue. Some nerve fibers are actually cut in association with the loss of myelin. In MS, when brain tissue is destroyed, it is either repaired or replaced by scars of hardened sclerotic patches of tissue. Areas of disease activity are called lesions or *plaques* and appear in multiple places within the central nervous system. These effects are comparable to the loss of insulating material around an electrical wire, or cutting of the wire itself, which interferes with the transmission of signals.

Siblings of people with MS are 10 to 15 times more likely than the general population to be diagnosed with the disorder, whereas the risk for disease concordance for identical twins is about 30 percent. In addition, the disease is as much as five times more prevalent in temperate zones, such as the northern United States and northern Europe, than it is in the tropics. Caucasians are more susceptible than other races. Women are at a higher risk than men. Thus, both genetic and environmental factors are probably involved in the cause. Previous studies had suggested that MS susceptibility peaked before age 15; more recent, larger studies suggest that there is no exact age cutoff.

The most common symptoms of MS are numbness, fatigue, blurred vision, and clumsiness. These can occur singly or in combination, vary in intensity, and last from several weeks to months or may remain permanent symptoms. In some patients, symptoms include slurred speech, weakness, loss of coordination, pain, uncontrollable tremors, loss of bladder control, memory and other cognitive problems, depression, and paralysis (rarely). Muscle spasticity can affect balance and coordination, causing stiffness and involuntary jerking movement — and, if untreated, can create *contractures*, or the “freezing” of a joint that prevents movement.

MS cannot be cured at present, but several medications help control forms of MS where attacks or relapses occur. A wide range

of medications and therapies are available to control symptoms such as spasticity, pain, fatigue, and mood swings, as well as bladder, bowel, or sexual dysfunctions. Steroids, which have been used to treat MS for more than three decades, may effectively shorten attacks and speed recovery from MS-related acute attacks. Many promising new agents to control MS or to alleviate its symptoms are in clinical trials. Treatments given early in the disease are the most effective.

## Neurological AIDS

In 2007, about 2.5 million people worldwide became infected with *human immunodeficiency virus* (HIV); 33 million are now living with HIV. Advanced HIV infection is known as *acquired immunodeficiency syndrome*, or AIDS. The epidemic is still the most intense in sub-Saharan Africa but is gaining speed in Asia and Eastern Europe. The impact of AIDS in the United States has been muted because of life-prolonging drugs, but in developing countries only 2 million of the 6 million people who need therapy are receiving such treatment. Women now represent half of all cases worldwide.

Although the principal target of HIV is the immune system, the nervous system may be profoundly affected. Some 20 to 40 percent of untreated patients with full-blown AIDS also develop clinically significant dementia that includes movement impairment, with a smaller percentage still suffering from an overt dementia. Those affected have mental problems ranging from mild difficulty with concentration or coordination to progressive, fatal dementia.

Despite advances in treating other aspects of the disease, AIDS dementia remains incompletely understood. Most current hypotheses center on an *indirect* effect of HIV infection related to secreted viral products or cell-coded signal molecules called *cytokines*. Convincing evidence also exists that some proteins of the virus itself are neurotoxic and may play a role in the ongoing damage that occurs during infection. The viral Tat, released by infected cells, has been among the proteins suspected of neurotoxicity. In any case, HIV infection appears to be the prime mover in this disorder because antiviral treatment may prevent or reverse this condition in many patients.

Experts believe that serious neurologic symptoms are uncommon early in HIV infection. Later, however, patients develop difficulty with concentration and memory and experience general slowing of their mental processes. At the same time, patients may develop leg weakness and a loss of balance. Imaging techniques, such as CT and MRI, show that the brains in these patients have undergone some shrinkage. The examination of brain cells under a microscope suggests that abnormalities are present principally in

subcortical areas. Neurons in the cortex also may be altered or lost.

Recent studies indicate that highly active combination antiretroviral treatment — *cocktails* of three or more drugs active against HIV — is effective in reducing the incidence of AIDS dementia. Such treatment also can effectively reverse but not eliminate the cognitive abnormalities attributed to brain HIV infection.

Peripheral neuropathy, nerve death in extremities that causes severe pain, is also a major neurological problem commonly seen in HIV patients. It is believed that the virus triggers a distal sensory neuropathy through neurotoxic mechanisms. This has often been unmasked or exacerbated by certain antiretroviral drugs that have mitochondrial toxicity and tend to make the neuropathies more frequent and serious. More than half of advanced patients have neuropathy, making it a major area for preventive and symptomatic therapeutic trials.

Despite remarkable advances toward new therapies, some patients develop these neurological problems and fail to respond to treatment, thus requiring additional approaches to prevention and treatment of the symptoms. In addition, because of immunodeficiency in HIV patients, otherwise rare opportunistic infections and malignancies are relatively common.

## Neurological trauma

Some 1.4 million people suffer traumatic head injuries each year in the United States, of whom roughly 50,000 die. Those who survive face a lifetime of disability, and economic costs approach \$60 billion annually.

No magic bullet has yet been found, but doctors have discovered several methods to stave off severe neurological damage caused by head and spinal cord injuries and to improve neurological function following trauma. These treatments include better imaging techniques, methods to understand and improve the brain's ability to regenerate and repair itself, and improved rehabilitation techniques.

Greater access to and use of CT and MRI offer physicians the opportunity to diagnose the extent of trauma and to avoid secondary injury related to *edema*, or swelling, and a reduction in blood flow to the brain (*ischemia*).

In general, patients who arrive in the emergency room and are diagnosed with a severe head injury are monitored for pressure on the brain from bleeding or swelling. Treatments for increases in intracranial pressure include the removal of cerebrospinal fluid, moderate hyperventilation to decrease blood volume, and the administration of drugs to reduce cellular metabolism or to remove water from the injured tissue. No drug for improving outcomes of traumatic brain injury has yet been approved. A recent pilot

clinical trial for patients with moderate to severe closed head injury found that the hormone progesterone cut the number of deaths in severely injured patients by 50 percent, and those in the moderately injured group had improved functional recovery 30 days after injury. Treatments for the injury-induced reduction of cerebral blood flow include the administration of drugs that increase mean arterial blood pressure. In combination with the reduction in intracranial pressure, this results in an increase in blood flow, allowing more blood to reach vital areas.

In addition to helping the physician avoid cerebral edema and reductions in cerebral blood flow following traumatic brain injury, imaging can reveal mass lesions produced by the initial injury. These mass lesions can consist of bleeding on the surface or within the brain as well as the formation of contusions (bruises). Once blood leaks from vessels and comes into direct contact with brain tissue, it can add focal pressure, thereby reducing cerebral blood flow, or can by itself be toxic to brain cells. As a consequence, it may be removed surgically. Contusions can be troubling because they can increase pressure as well as contribute to the development of post-traumatic epilepsy. As a last resort to reduce increased intracranial pressure, part of the skull may be removed to allow the brain to swell, a procedure known as a *craniotomy*.

An estimated 250,000 individuals are living with spinal cord injury in the United States. Some 11,000 new injuries are reported annually and are caused mostly by motor vehicle accidents, sports injuries, violence, and falls. Economic costs approach \$10 billion a year.

Researchers have found that people who suffer spinal cord injuries may become less severely impaired if they receive high intravenous doses of a commonly used steroid drug, *methylprednisolone*, within eight hours of the injury. Building on these clues and insight into precisely how and why spinal cord cells die after injury, researchers hope to develop new therapies to reduce the extent of spinal cord damage after trauma.

Scientists have known that, after a spinal cord injury, animals can regain the ability to bear their weight and walk at various speeds on a treadmill belt. More recently, scientists have recognized that the level of this recovery depends to a large degree on whether these tasks are practiced — that is, trained for — after injury. People with spinal cord injury also respond to training interventions.

Scientists have discovered that new nerve cells can be born in the adult brain, but these new cells do not seem capable of helping the injured brain regenerate. Studies are underway to determine how to “jump-start” the pathway that stimulates *neurogenesis*, the birth of new nerve cells. Researchers are trying to decipher how certain environmental cues can be used or overcome to attract these new cells — or transplanted stem

or progenitor cells — to areas of brain injury to facilitate regeneration and repair.

These and other recent discoveries are pointing the way toward new therapies to promote nerve regeneration after brain and spinal cord injury. Although these new therapies have not yet reached the clinic, several approaches are on the path to clinical trials.

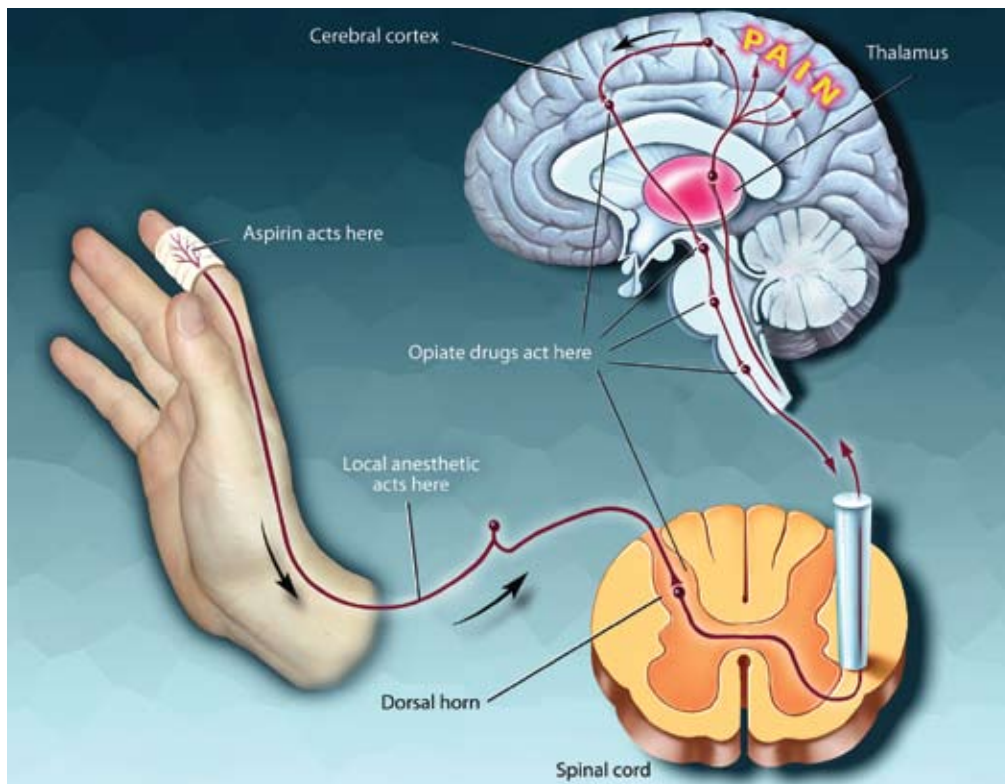
## Pain

If there is a universal experience, pain is it. Each year, more than 97 million Americans suffer chronic, debilitating headaches or a bout with a bad back or the pain of arthritis — all at a total cost of some \$100 billion. But it need not be that way. New discoveries about how chemicals in the body transmit and regulate pain messages have paved the way for new treatments for both chronic and acute pain.

*Local anesthesia*, or loss of sensation in a limited area of a person's body, is used to prevent pain during diagnostic procedures, labor, and surgical operations. Local anesthetics temporarily interrupt the action of all nerve fibers, including pain-carrying ones, by interfering with the actions of sodium channels. Historically, the most familiar of these agents was Novocain, which was used by dentists. Lidocaine is more popular today.

*Analgesia* refers to the loss of pain sensation. The four main types of analgesics are *nonopioids* (aspirin and related nonsteroidal anti-inflammatory drugs, or NSAIDs, such as ibuprofen and naproxen), *opioids* (morphine, codeine), antiepileptic agents (gabapentin, pregabalin), and antidepressants (amitriptyline). NSAIDs are useful for treating mild or moderate pain, such as headache, sprains, or toothache. Because NSAIDs are anti-inflammatory, they also are useful in treating injuries or conditions such as arthritis. NSAIDs inhibit the cyclo-oxygenase (COX) enzymes that make the inflammatory and pain-producing chemical prostaglandin. Acetaminophen has analgesic properties but does not reduce inflammation. Often moderate pain is treated by combining a mild opioid, such as codeine, with aspirin or an NSAID. Opioids are the most potent painkillers and are used for severe pain. Opioids, however, have a high abuse potential and can affect breathing.

The antiepileptic and antidepressant drugs are useful primarily for *neuropathic pain*, pain due to injury to the nervous system, which includes the pain of diabetic neuropathy, post-herpetic neuralgia, phantom limb pain, and post-stroke pain. The best results have been reported with antidepressants that regulate both serotonin and norepinephrine. Interestingly, SSRIs are not effective for neuropathic pain. Topical lidocaine may be effective for the treatment of some neuropathic pain conditions where light touch of the skin can produce severe pain.



**HOW PAINKILLERS WORK.** At the site of injury, the body produces prostaglandins that increase pain sensitivity. Aspirin, which acts primarily in the periphery, prevents the production of prostaglandins. Acetaminophen is believed to block pain impulses in the brain itself. Local anesthetics intercept pain signals traveling up the nerve. Opiate drugs, which act primarily in the central nervous system, block the transfer of pain signals from the spinal cord to the brain.

Studies of the body's own pain-control system not only demonstrated the existence of naturally occurring opioids (the endorphins) but also identified the receptors through which opioids exert their effects. The finding that opiate receptors are concentrated in the spinal cord led to the use of injections of morphine and other opioids into the cerebrospinal fluid (in which the spinal cord is bathed) without causing paralysis, numbness, or other severe side effects. This technique came about through experiments with animals that first showed that injecting opioids into the spinal cord could produce profound pain control. It is now commonly used in humans to treat pain after surgery and in some patients to treat chronic pain using an implanted pump.

New targets are on the horizon. Molecular biology and genetic approaches have identified many molecules (ion channels and receptors) that are predominantly, if not exclusively, expressed by the *nociceptor*, the peripheral nerve fiber that initially responds to the injury stimulus. Because adverse side effects of drugs arise from the widespread location of the molecules targeted by analgesics (e.g., constipation results from morphine's action on opioid recep-

tors in the gut), new analgesics that target only the nociceptor may have a better side-effect profile. Among the many nociceptor targets are specialized receptor channels (one of which is activated by capsaicin, the pungent ingredient in hot peppers, and another by mustard oil) and a variety of acid-sensing sodium and calcium ion channels.

Blocking the activity of many of these molecules has proven effective in animal studies, suggesting that the development of drugs that target these molecules in humans may have great value for the treatment of acute and persistent pain.

However, it should be emphasized that pain experience is the product of brain function.

The pain is in the brain, not in the nociceptors that respond to the injury. In addition to the sensory-discriminative aspects, pain involves emotional factors

and the meaning of previous painful experiences, which need to be addressed concurrently in order to treat pain. The fact that placebos and hypnosis can significantly reduce pain clearly illustrates the importance of these psychological factors. New targets for the treatment of pain also include approaches that identify molecules in the brain associated with the elaboration of persistent pain.

## Parkinson's disease

This neurologic disorder afflicts 1 million individuals in the United States, most of whom are older than 50. Parkinson's disease is characterized by symptoms of slowness of movement, muscular rigidity, tremor, and postural instability.

The discovery in the late 1950s that the level of dopamine was decreased in the brains of Parkinson's patients was followed in the 1960s by the successful treatment of this disorder by administration of the drug levodopa, which is converted to dopamine in the brain. The successful treatment of Parkinson's by replacement therapy is one of the greatest success stories in neurology.

Levodopa is now combined with another drug, carbidopa, that reduces the peripheral breakdown of levodopa, thus allowing greater levels to reach the brain and reducing side effects. Also playing an important role are newer drugs, such as inhibitors of dopamine breakdown and dopamine agonists.

Genetic studies have demonstrated several heritable gene abnormalities in certain families, but most cases of Parkinson's occur sporadically. It is believed, however, that hereditary factors may render some individuals more vulnerable to environmental factors, such as pesticides. The discovery in the late 1970s that a chemical substance, MPTP, can cause parkinsonism in drug addicts stimulated intensive research on the causes of the disorder. MPTP was accidentally synthesized by illicit drug designers seeking to produce a heroinlike compound. MPTP was found to be converted in the brain to a substance that destroys dopamine neurons. Parkinson's continues to be studied intensively in both rodent and primate MPTP models.

In the past several decades, scientists have shown in primate models of Parkinson's that specific regions in the basal ganglia, a group of cellular structures deep in the brain, are abnormally overactive. Most important, they found that surgical deactivation or destruction of these overactive nuclei — the pallidum and subthalamic nucleus — can greatly reduce symptoms of Parkinson's disease.

The past decade has witnessed a resurgence in this surgical procedure, pallidotomy, and more recently chronic deep-brain stimulation. These techniques are highly successful for treating patients who have experienced significant worsening of symptoms and are troubled by the development of drug-related involuntary movements. The past decade has also seen further attempts to treat such patients with surgical implantation of cells, such as fetal cells, capable of producing dopamine. Replacement therapy with stem cells also is being explored. More recently, gene transfer of trophic factors has been studied in animal models and is being tested in clinical trials. Lastly, four clinical trials are currently underway testing the hypothesis that gene therapy can provide symptomatic (in some cases) or neuroprotective (in others) benefit to patients with Parkinson's.

## Schizophrenia

Marked by disturbances in thinking, emotional reactions, and social behavior, schizophrenia usually results in chronic illness and personality change. Delusions, hallucinations, and thought disorder are common.

Affecting about 1 percent of the population, or 2 million Americans each year, schizophrenia is disabling and costly.

On a given day, these patients occupy up to 100,000 hospital beds. Annual costs total about \$32.5 billion.

Schizophrenia is thought to reflect changes in the brain, possibly caused by disruption of neurodevelopment through genetic predisposition, which may be exacerbated by environmental factors such as maternal infections or direct brain trauma. Brain scans and postmortem studies show abnormalities in some people with

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*Schizophrenia is thought to reflect changes in the brain, possibly caused by disruption of neurodevelopment through genetic predisposition, which may be exacerbated by environmental factors such as maternal infections or direct brain trauma.*

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schizophrenia, such as enlarged ventricles (fluid-filled spaces) and reduced size of certain brain regions. Functional neuroimaging scans such as PET and functional magnetic resonance imaging (fMRI) taken while individuals perform cognitive tasks, particularly those involving memory and attention, show abnormal functioning in specific brain areas of people with this illness. Brain systems using the chemicals dopamine, glutamate, and GABA appear to be particularly involved in the pathogenesis of the disorder. Recently, several genes involved in controlling nerve cell communication have been identified that appear to increase the risk of developing schizophrenia.

The disorder usually is diagnosed between the ages of 15 and 25. Few patients recover fully following treatment, and most continue to have moderate or severe symptoms that may be exacerbated by life stressors. About 15 percent of patients return to a productive life after a single episode, 60 percent will have intermittent episodes throughout their lives, and an additional 25 percent will not recover their ability to live as independent adults. Deficits in cognition are frequent, lifelong manifestations in most patients, even those who show good recovery from more acute positive symptoms. The negative symptoms may be the most debilitating in terms of leading a productive life and generally are resistant to drug treatment.

The first antipsychotic drug, *chlorpromazine*, serendipitously was discovered to reduce symptoms of schizophrenia in the 1950s. Clinical trials demonstrated that chlorpromazine was more effective than placebo or a sedative. Subsequently, more than 20 effective antipsychotic drugs were developed. Antipsychotics act by blocking certain dopamine receptors. This action accounts for the high prevalence of parkinsonian side effects associated with the use of the first generation of antipsychotics and the risk of developing an irreversible movement disorder, tardive dyskinesia.

The second generation of antipsychotic medications, developed to be more effective in treating the positive symptoms of schizophrenia, can lead to debilitating side effects such as very large weight gain, blood disorders, and muscle pain and dysfunction. Safer drugs are being sought.

## Seizures and epilepsy

Seizures are due to sudden, disorderly discharges of interconnected neurons in the brain that temporarily alter one or more brain functions. Epilepsy is a chronic neurological disorder characterized by the occurrence of unprovoked seizures. In developed countries, epilepsy affects approximately 50 of every 100,000 people. It affects three to four times that number in developing countries.

Many different types of epilepsy have been recognized. Epilepsy can start at any age and can be idiopathic (having an uncertain cause) or symptomatic (having a known or presumed cause). Most idiopathic epilepsies probably are due to the inheritance of one or more mutant genes, often a mutant ion channel gene. Symptomatic epilepsies result from a wide variety of brain diseases or injuries, including birth trauma, head injury, neurodegenerative disease, brain infection, brain tumor, or stroke.

Epilepsies are of two types, generalized and partial. *Generalized seizures* typically result in loss of consciousness and can cause a range of behavioral changes, including convulsions or sudden changes in muscle tone. They arise when there is simultaneous excessive electrical activity over a wide area of the brain, often involving the thalamus and cerebral cortex. In *partial epilepsies*, seizures typically occur with maintained consciousness or with altered awareness and behavioral changes. Partial seizures can produce localized visual, auditory, and skin sensory disturbances; repetitive uncontrolled movements; or confused, automatic behaviors. Such seizures arise from excessive electrical activity in one area of the brain, such as a restricted cortical or hippocampal area.

Many antiepileptic drugs are available. Their principal targets are either ion channels or neurotransmitter receptors. Generalized epilepsies often are readily controlled by antiepileptic drugs, with up to 80 percent of patients seizure-free with treatment. Unfortu-

nately, partial epilepsies are generally more difficult to treat. Often, they can be controlled with a single antiepileptic that prevents seizures or lessens their frequency, but sometimes a combination of these drugs is necessary. Identification of the mutated genes underlying epilepsy may provide new targets for the next generation of antiseizure drugs.

Surgery is an excellent option for patients with specific types of partial seizures who do not respond to antiepileptic drugs. Surgery requires the precise location and removal of the brain area from which the partial seizures originate. After surgery, most properly selected patients experience improvement or complete remission of seizures for at least several years.

A new form of epilepsy treatment, electrical stimulation therapy, was introduced as another option for hard-to-control partial seizures. An implantable pacemakerlike device delivers small bursts of electrical energy to the brain via the vagus nerve on the side of the neck. While not curative, vagal nerve stimulation has been shown to reduce the frequency of partial seizures in many patients.

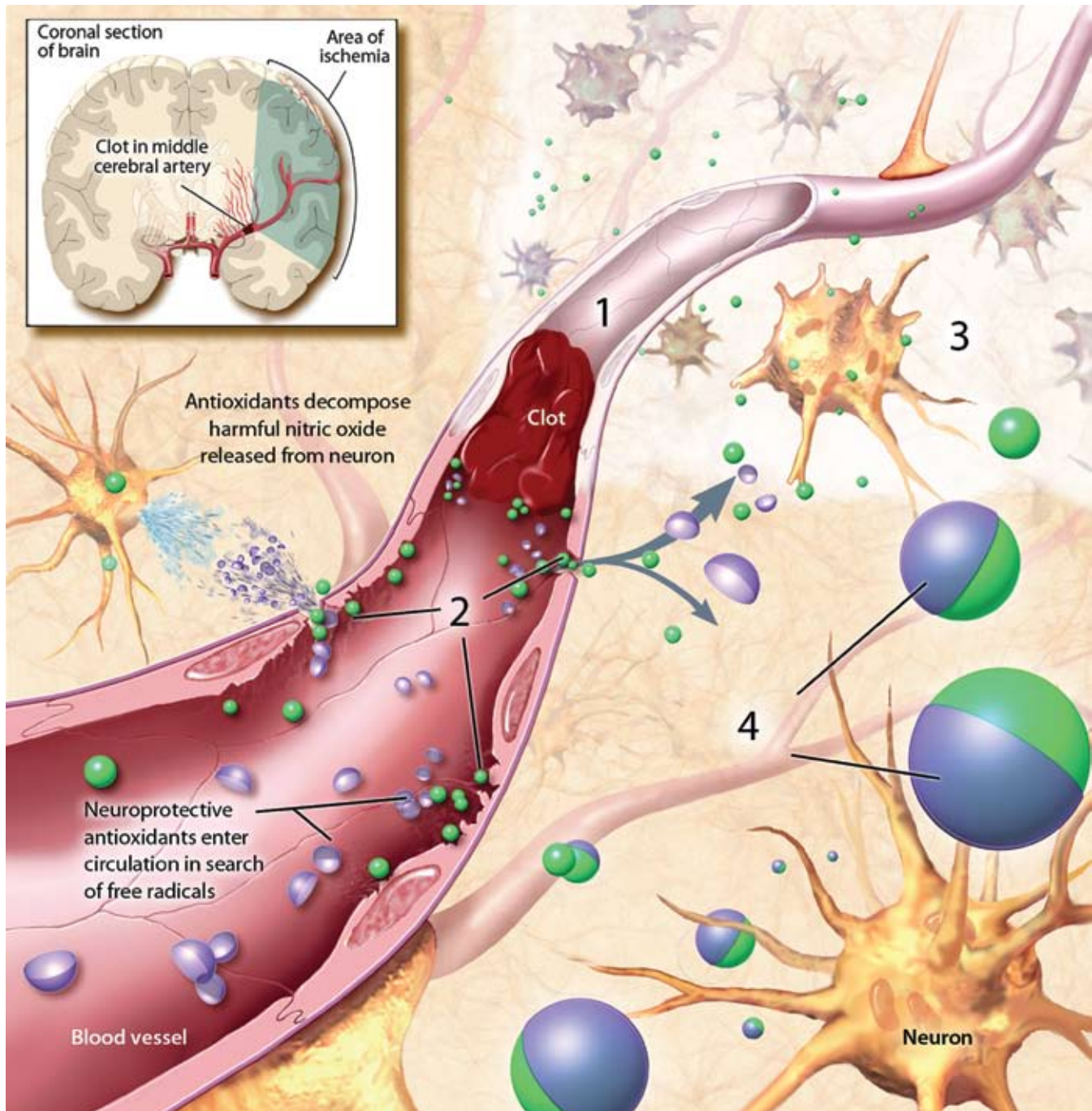
## Stroke

A stroke occurs when a blood vessel bringing oxygen and nutrients to the brain bursts or is clogged by a blood clot or some other particle. This deprives the brain of blood, causing the death of neurons within minutes. Depending on its location, a stroke can cause many permanent disorders, such as paralysis on one side of the body and loss of speech.

Until recently, if you or a loved one had a stroke, your doctor would tell your family there was no treatment. In all likelihood, the patient would live out the remaining months or years with severe neurological impairment.

This dismal scenario is now brightening. For one, use of the clot-dissolving bioengineered drug, tissue plasminogen activator (tPA), is now a standard treatment in many hospitals. This approach rapidly opens blocked vessels to restore circulation before oxygen loss causes permanent damage. Given within three hours of a stroke, it often can help in limiting the ensuing brain damage. Also, attitudes about the nation's third leading cause of death are changing rapidly. Much of this has come from new and better understanding of the mechanisms that lead to the death of neurons following stroke and from devising ways to protect these neurons.

Stroke affects roughly 700,000 Americans a year — 150,000 of whom die; total annual costs are estimated at \$51.2 billion. Stroke often occurs in individuals over 65 years of age, yet a third are younger. Stroke tends to occur more in males and African Americans and in those with risk factors such as diabetes, high blood pressure, heart disease, obesity, high cholesterol, and a family history of stroke.



**STROKE.** A stroke occurs when a blood vessel bringing oxygen and nutrients to the brain bursts or is clogged by a blood clot (1). This lack of blood leads to a cascade of neurochemical abnormalities that can cause cell death within minutes. Free radicals are released, causing damage to endothelial cells (2) and the mitochondria (3) of neurons. Normally the body readily disarms free radicals (4), but in stroke, endothelial cell damage allows many more than can be controlled to move into brain tissue. Depending on its location, a stroke can have different symptoms such as paralysis on one side of the body or a loss of speech.

Controlling risk factors with diet, exercise, and certain drugs can help prevent stroke. Other specific treatments involving surgery or arterial stents can clear clogs in the arteries of the neck region; these and treatments targeting heart disease can help prevent a cutoff of blood supply. Anticoagulant drugs can reduce the likelihood of clots forming, traveling to the brain, and causing a stroke. Other experimental therapies under investigation may lead to even bigger payoffs for patients in the future. Some strategies target mechanisms inside the neuron. In this way, the vicious cycle of local damage followed by a widening fringe of biochemical-induced neuronal death can be slowed. A number of classes of drugs have been shown to be effective in animal studies.

Emerging clinical evidence suggests that, following a stroke affecting movement in one arm, encouraging use of the weakened arm by temporarily restricting use of the unaffected arm can aid functional recovery. Another promising possibility for improving recovery after stroke is through the use of neural stem cells. Some animal studies have shown that an injection of stem cells aids recovery even if administered several days after the injury. Administration of growth factors may further enhance the benefits of stem cell transplantation.

## Tourette syndrome

One of the most common and least understood neurobiological disorders, Tourette syndrome (TS) is an inherited disorder that affects about 1 in 200 Americans. Males are affected three to four times as often as females.

Symptoms usually appear between the ages of 4 and 8, but in rare cases may emerge in the late teenage years. The symptoms include motor and vocal *tics* — repetitive, involuntary movements or utterances that are rapid and sudden and persist for more than one year. The types of *tics* may change frequently and increase or decrease in severity over time. In roughly one-half of individuals, this disorder lasts a lifetime, but the remaining patients may experience a remission or decrease in symptoms as they get older.

A high percentage of people with TS also have associated conditions such as problems with learning, difficulties with attention, and obsessive thoughts and compulsive rituals. Often these manifestations are more troublesome to individuals than the tics themselves, so physicians must consider them when choosing a treatment regimen.

TS is inherited and seems to result from abnormal activity in a brain system called the basal ganglia. Research suggests that genes associated with TS, perhaps together with in utero or early environmental conditions, cause abnormalities in basal ganglia

development or excesses in certain chemicals, including the neuro-transmitter dopamine.

The majority of people with TS are not significantly disabled by symptoms, and therefore do not require medication. However, antipsychotics and SSRIs, as well as drugs to control tics, nausea, high blood pressure, seizures, or anxiety, are available to help control symptoms when they interfere with functioning. Stimulant medications, such as methylphenidate and dextroamphetamine,

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that are prescribed for attention deficit hyperactivity disorder (ADHD) have been reported to improve attention and decrease tics in TS. For obsessive-compulsive symptoms that interfere significantly with daily functioning, SSRIs, antidepressants, and related medications may be prescribed.

Medication dosages that achieve maximum control of symptoms vary for each patient and must be gauged carefully by a doctor. The medicine is administered in small doses with gradual increases to the point where there is maximum alleviation of symptoms with minimal side effects. Some of the undesirable reactions to medications are weight gain, muscular rigidity, fatigue, motor restlessness, and social withdrawal, most of which can be reduced with specific medications. Some side effects such as depression and cognitive impairment can be alleviated with dosage reduction or a change of medication.

Other types of therapy also may be helpful. Psychotherapy and counseling can assist people with TS and help their families cope, and some behavior therapies can be very effective in reducing the severity of both tics and compulsions.