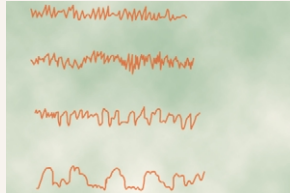


# States of Brain Activity—Sleep, Brain Waves, Epilepsy, Psychoses



All of us are aware of the many different states of brain activity, including sleep, wakefulness, extreme excitement, and even different levels of mood such as exhilaration, depression, and fear. All these states result from different activating or inhibiting forces generated usually within the brain itself. In Chapter 58, we began a partial discussion of this subject when we described different

systems that are capable of activating large portions of the brain. In this chapter, we present brief surveys of specific states of brain activity, beginning with sleep.

## Sleep

Sleep is defined as unconsciousness from which the person can be aroused by sensory or other stimuli. It is to be distinguished from *coma*, which is unconsciousness from which the person cannot be aroused. There are multiple stages of sleep, from very light sleep to very deep sleep; sleep researchers also divide sleep into two entirely different types of sleep that have different qualities, as follows.

**Two Types of Sleep.** During each night, a person goes through stages of two types of sleep that alternate with each other. They are called (1) *slow-wave sleep*, because in this type of sleep the brain waves are very strong and very low frequency, as we discuss later, and (2) *rapid eye movement sleep* (REM sleep), because in this type of sleep the eyes undergo rapid movements despite the fact that the person is still asleep.

Most sleep during each night is of the slow-wave variety; this is the deep, restful sleep that the person experiences during the first hour of sleep after having been awake for many hours. REM sleep, on the other hand, occurs in episodes that occupy about 25 per cent of the sleep time in young adults; each episode normally recurs about every 90 minutes. This type of sleep is not so restful, and it is usually associated with vivid dreaming.

## Slow-Wave Sleep

Most of us can understand the characteristics of deep slow-wave sleep by remembering the last time we were kept awake for more than 24 hours and then the deep sleep that occurred during the first hour after going to sleep. This sleep is exceedingly restful and is associated with decrease in both peripheral vascular tone and many other vegetative functions of the body. For instance, there are 10 to 30 per cent decreases in blood pressure, respiratory rate, and basal metabolic rate.

Although slow-wave sleep is frequently called “dreamless sleep,” dreams and sometimes even nightmares do occur during slow-wave sleep. The difference between the dreams that occur in slow-wave sleep and those that occur in REM sleep is that those of REM sleep are associated with more bodily muscle activity, and the dreams of slow-wave sleep usually are not remembered. That

is, during slow-wave sleep, consolidation of the dreams in memory does not occur.

### REM Sleep (Paradoxical Sleep, Desynchronized Sleep)

In a normal night of sleep, bouts of REM sleep lasting 5 to 30 minutes usually appear on the average every 90 minutes. When the person is extremely sleepy, each bout of REM sleep is short, and it may even be absent. Conversely, as the person becomes more rested through the night, the durations of the REM bouts increase.

There are several important characteristics of REM sleep:

1. It is usually associated with active dreaming and active bodily muscle movements.
2. The person is even more difficult to arouse by sensory stimuli than during deep slow-wave sleep, and yet people usually awaken spontaneously in the morning during an episode of REM sleep.
3. Muscle tone throughout the body is exceedingly depressed, indicating strong inhibition of the spinal muscle control areas.
4. Heart rate and respiratory rate usually become irregular, which is characteristic of the dream state.
5. Despite the extreme inhibition of the peripheral muscles, irregular muscle movements do occur. These are in addition to the rapid movements of the eyes.
6. The brain is highly active in REM sleep, and overall brain metabolism may be increased as much as 20 per cent. The electroencephalogram (EEG) shows a pattern of brain waves similar to those that occur during wakefulness. This type of sleep is also called *paradoxical sleep* because it is a paradox that a person can still be asleep despite marked activity in the brain.

In summary, REM sleep is a type of sleep in which the brain is quite active. However, the brain activity is not channeled in the proper direction for the person to be fully aware of his or her surroundings, and therefore the person is truly asleep.

### Basic Theories of Sleep

#### Sleep Is Believed to Be Caused by an Active Inhibitory Process.

An earlier theory of sleep was that the excitatory areas of the upper brain stem, the *reticular activating system*, simply fatigued during the waking day and became inactive as a result. This was called the *passive theory of sleep*. An important experiment changed this view to the current belief that *sleep is caused by an active inhibitory process*: it was discovered that transecting the brain stem at the level of the midpons creates a brain whose cortex never goes to sleep. In other words, there seems to be some center located below the mid-pontile level of the brain stem that is required to cause sleep by inhibiting other parts of the brain.

#### Neuronal Centers, Neurohumoral Substances, and Mechanisms That Can Cause Sleep—A Possible Specific Role for Serotonin

Stimulation of several specific areas of the brain can produce sleep with characteristics near those of natural sleep. Some of these areas are the following:

1. The most conspicuous stimulation area for causing almost natural sleep is the *raphe nuclei in the lower half of the pons and in the medulla*. These nuclei are a thin sheet of special neurons located in the midline. Nerve fibers from these nuclei spread locally in the brain stem reticular formation and also upward into the thalamus, hypothalamus, most areas of the limbic system, and even the neocortex of the cerebrum. In addition, fibers extend downward into the spinal cord, terminating in the posterior horns where they can inhibit incoming sensory signals, including pain, as discussed in Chapter 48. It is also known that many nerve endings of fibers from these raphe neurons secrete *serotonin*. When a drug that blocks the formation of serotonin is administered to an animal, the animal often cannot sleep for the next several days. Therefore, it has been assumed that serotonin is a transmitter substance associated with production of sleep.
2. Stimulation of some areas in the *nucleus of the tractus solitarius* can also cause sleep. This nucleus is the termination in the medulla and pons for visceral sensory signals entering by way of the vagus and glossopharyngeal nerves.
3. Stimulation of several regions in the diencephalon can also promote sleep, including (1) the rostral part of the hypothalamus, mainly in the suprachiasmatic area, and (2) an occasional area in the diffuse nuclei of the thalamus.

#### Lesions in Sleep-Promoting Centers Can Cause Intense Wakefulness.

Discrete lesions in the *raphe nuclei* lead to a high state of wakefulness. This is also true of bilateral lesions in the *medial rostral suprachiasmatic area in the anterior hypothalamus*. In both instances, the excitatory reticular nuclei of the mesencephalon and upper pons seem to become released from inhibition, thus causing the intense wakefulness. Indeed, sometimes lesions of the anterior hypothalamus can cause such intense wakefulness that the animal actually dies of exhaustion.

#### Other Possible Transmitter Substances Related to Sleep.

Experiments have shown that the cerebrospinal fluid as well as the blood or urine of animals that have been kept awake for several days contains a substance or substances that will cause sleep when injected into the brain ventricular system of another animal. One likely substance has been identified as *muramyl peptide*, a low-molecular-weight substance that accumulates in the cerebrospinal fluid and urine in animals kept awake for several days. When only micrograms of this

sleep-producing substance are injected into the third ventricle, almost natural sleep occurs within a few minutes, and the animal may stay asleep for several hours. Another substance that has similar effects in causing sleep is a nonapeptide isolated from the blood of sleeping animals. And still a third sleep factor, not yet identified molecularly, has been isolated from the neuronal tissues of the brain stem of animals kept awake for days. It is possible that prolonged wakefulness causes progressive accumulation of a sleep factor or factors in the brain stem or in the cerebrospinal fluid that lead to sleep.

**Possible Cause of REM Sleep.** Why slow-wave sleep is broken periodically by REM sleep is not understood. However, drugs that mimic the action of acetylcholine increase the occurrence of REM sleep. Therefore, it has been postulated that the large acetylcholine-secreting neurons in the upper brain stem reticular formation might, through their extensive efferent fibers, activate many portions of the brain. This theoretically could cause the excess activity that occurs in certain brain regions in REM sleep, even though the signals are not channeled appropriately in the brain to cause normal conscious awareness that is characteristic of wakefulness.

### Cycle Between Sleep and Wakefulness

The preceding discussions have merely identified neuronal areas, transmitters, and mechanisms that are related to sleep. They have not explained the cyclical, reciprocal operation of the sleep-wakefulness cycle. There is as yet no explanation. Therefore, we can let our imaginations run wild and suggest the following possible mechanism for causing the sleep-wakefulness cycle.

When the sleep centers are *not* activated, the mesencephalic and upper pontile reticular activating nuclei are released from inhibition, which allows the reticular activating nuclei to become spontaneously active. This in turn excites both the cerebral cortex and the peripheral nervous system, both of which send numerous *positive feedback* signals back to the same reticular activating nuclei to activate them still further. Therefore, once wakefulness begins, it has a natural tendency to sustain itself because of all this positive feedback activity.

Then, after the brain remains activated for many hours, even the neurons themselves in the activating system presumably become fatigued. Consequently, the positive feedback cycle between the mesencephalic reticular nuclei and the cerebral cortex fades, and the sleep-promoting effects of the sleep centers take over, leading to rapid transition from wakefulness back to sleep.

This overall theory could explain the rapid transitions from sleep to wakefulness and from wakefulness to sleep. It could also explain arousal, the insomnia that occurs when a person's mind becomes preoccupied with a thought, and the wakefulness that is produced by bodily physical activity.

## Physiologic Effects of Sleep

Sleep causes two major types of physiologic effects: first, effects on the nervous system itself, and second, effects on other functional systems of the body. The nervous system effects seem to be by far the more important because any person who has a transected spinal cord in the neck (and therefore has no sleep-wakefulness cycle below the transection) shows no harmful effects in the body beneath the level of transection that can be attributed directly to a sleep-wakefulness cycle.

Lack of sleep certainly does, however, affect the functions of the central nervous system. Prolonged wakefulness is often associated with progressive malfunction of the thought processes and sometimes even causes abnormal behavioral activities.

We are all familiar with the increased sluggishness of thought that occurs toward the end of a prolonged wakeful period, but in addition, a person can become irritable or even psychotic after forced wakefulness. Therefore, we can assume that sleep in multiple ways restores both normal levels of brain activity and normal "balance" among the different functions of the central nervous system. This might be likened to the "rezeroing" of electronic analog computers after prolonged use, because computers of this type gradually lose their "baseline" of operation; it is reasonable to assume that the same effect occurs in the central nervous system because overuse of some brain areas during wakefulness could easily throw these areas out of balance with the remainder of the nervous system.

We might postulate that *the principal value of sleep is to restore natural balances among the neuronal centers*. The specific physiologic functions of sleep remain a mystery, and they are the subject of much research.

## Brain Waves

Electrical recordings from the surface of the brain or even from the outer surface of the head demonstrate that there is continuous electrical activity in the brain. Both the intensity and the patterns of this electrical activity are determined by the level of excitation of different parts of the brain resulting from *sleep*, *wakefulness*, or brain diseases such as *epilepsy* or even *psychoses*. The undulations in the recorded electrical potentials, shown in Figure 59-1, are called *brain waves*, and the entire record is called an EEG (electroencephalogram).

The intensities of brain waves recorded from the surface of the scalp range from 0 to 200 microvolts, and their frequencies range from once every few seconds to 50 or more per second. The character of the waves is dependent on the degree of activity in respective parts of the cerebral cortex, and the waves change markedly between the states of wakefulness and sleep and coma.

Much of the time, the brain waves are irregular, and no specific pattern can be discerned in the EEG. At other times, distinct patterns do appear, some of which are characteristic of specific abnormalities of the brain such as epilepsy, which is discussed later.

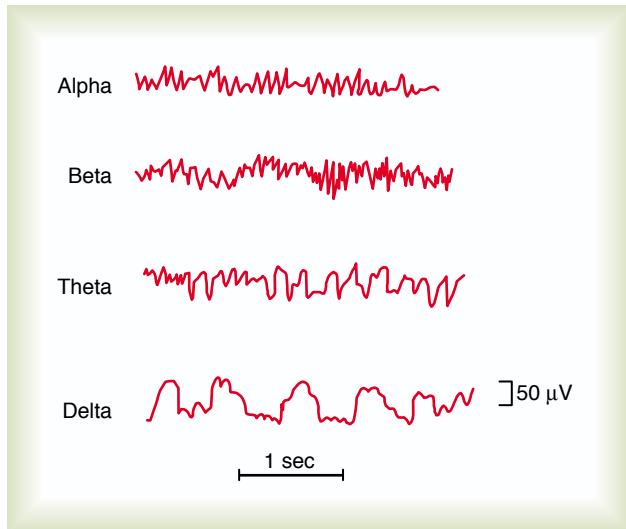


Figure 59-1

Different types of brain waves in the normal electroencephalogram.

In normal healthy people, most waves in the EEG can be classified as *alpha*, *beta*, *theta*, and *delta* waves, which are shown in Figure 59-1.

*Alpha waves* are rhythmical waves that occur at frequencies between 8 and 13 cycles per second and are found in the EEGs of almost all normal adult people when they are awake and in a quiet, resting state of cerebration. These waves occur most intensely in the occipital region but can also be recorded from the parietal and frontal regions of the scalp. Their voltage usually is about 50 microvolts. During deep sleep, the alpha waves disappear.

When the awake person's attention is directed to some specific type of mental activity, the alpha waves are replaced by asynchronous, higher-frequency but lower-voltage *beta waves*. Figure 59-2 shows the effect on the alpha waves of simply opening the eyes in bright light and then closing the eyes. Note that the visual sensations cause immediate cessation of the alpha waves and that these are replaced by low-voltage, asynchronous beta waves.

*Beta waves* occur at frequencies greater than 14 cycles per second and as high as 80 cycles per second. They are recorded mainly from the parietal and frontal regions during specific activation of these parts of the brain.

*Theta waves* have frequencies between 4 and 7 cycles per second. They occur normally in the parietal and temporal regions in children, but they also occur during emotional stress in some adults, particularly during disappointment and frustration. Theta waves also occur in many brain disorders, often in degenerative brain states.

*Delta waves* include all the waves of the EEG with frequencies less than 3.5 cycles per second, and they often have voltages two to four times greater than most other types of brain waves. They occur in very deep sleep, in infancy, and in serious organic brain disease. They also occur in the cortex of animals that have had subcortical transections separating the cerebral cortex from the thalamus. Therefore, delta waves can occur strictly in the cortex independent of activities in lower regions of the brain.

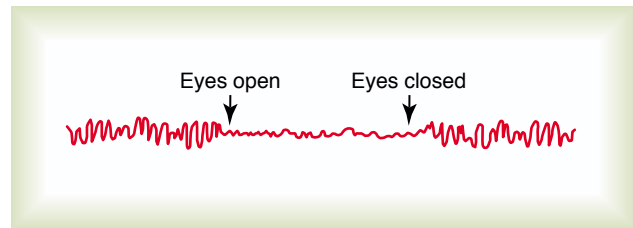


Figure 59-2

Replacement of the *alpha* rhythm by an asynchronous, low-voltage *beta* rhythm when the eyes are opened.

## Origin of Brain Waves

The discharge of a single neuron or single nerve fiber in the brain can never be recorded from the surface of the head. Instead, many thousands or even millions of neurons or fibers *must fire synchronously*; only then will the potentials from the individual neurons or fibers summate enough to be recorded all the way through the skull. Thus, the intensity of the brain waves from the scalp is determined mainly by the numbers of neurons and fibers that fire *in synchrony* with one another, not by the total level of electrical activity in the brain. In fact, strong *nonsynchronous* nerve signals often nullify one another in the recorded brain waves because of opposing polarities. This is demonstrated in Figure 59-2, which shows, when the eyes were closed, synchronous discharge of many neurons in the cerebral cortex at a frequency of about 12 per second, thus causing *alpha waves*. Then, when the eyes were opened, the activity of the brain increased greatly, but synchronization of the signals became so little that the brain waves mainly nullified one another, and the resultant effect was very low voltage waves of generally high but irregular frequency, the *beta waves*.

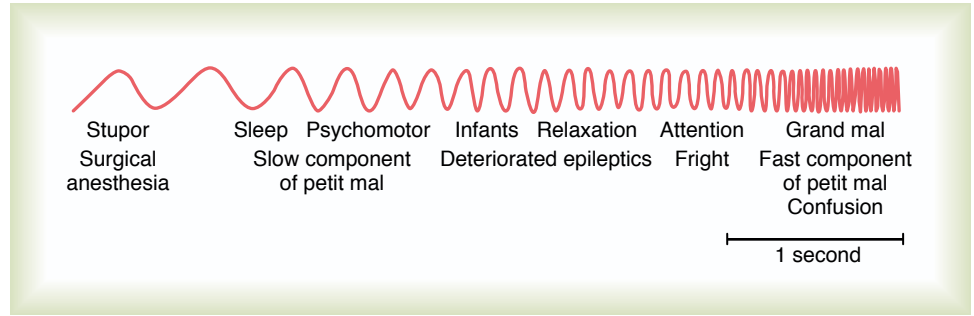
**Origin of Alpha Waves.** Alpha waves will *not* occur in the cerebral cortex without cortical connections with the thalamus. Conversely, stimulation in the nonspecific layer of *reticular nuclei* that surround the thalamus or in “diffuse” nuclei deep inside the thalamus often sets up electrical waves in the thalamocortical system at a frequency between 8 and 13 per second, which is the natural frequency of the alpha waves. Therefore, it is believed that the alpha waves result from spontaneous feedback oscillation in this diffuse thalamocortical system, possibly including the reticular activating system in the brain stem as well. This oscillation presumably causes both the periodicity of the alpha waves and the synchronous activation of literally millions of cortical neurons during each wave.

**Origin of Delta Waves.** Transection of the fiber tracts from the thalamus to the cerebral cortex, which blocks thalamic activation of the cortex and thereby eliminates the alpha waves, nevertheless does not block delta waves in the cortex. This indicates that some synchronizing mechanism can occur in the cortical neuronal system by itself—mainly independent of lower structures in the brain—to cause the delta waves.

Delta waves also occur during deep slow-wave sleep; this suggests that the cortex then is mainly released

**Figure 59–3**

Effect of varying degrees of cerebral activity on the basic rhythm of the electroencephalogram. (Redrawn from Gibbs FA, Gibbs EL: *Atlas of Electroencephalography*, 2nd ed, Vol I: Methodology and Controls. © 1974. Reprinted by permission of Prentice-Hall, Inc., Upper Saddle River, NJ.)



from the activating influences of the thalamus and other lower centers.

### Effect of Varying Levels of Cerebral Activity on the Frequency of the EEG

There is a general correlation between level of cerebral activity and average frequency of the EEG rhythm, the average frequency increasing progressively with higher degrees of activity. This is demonstrated in Figure 59–3, which shows the existence of delta waves in stupor, surgical anesthesia, and deep sleep; theta waves in psychomotor states and in infants; alpha waves during relaxed states; and beta waves during periods of intense mental activity. *During periods of mental activity, the waves usually become asynchronous rather than synchronous, so that the voltage falls considerably, despite markedly increased cortical activity, as shown in Figure 59–2.*

### Changes in the EEG at Different Stages of Wakefulness and Sleep

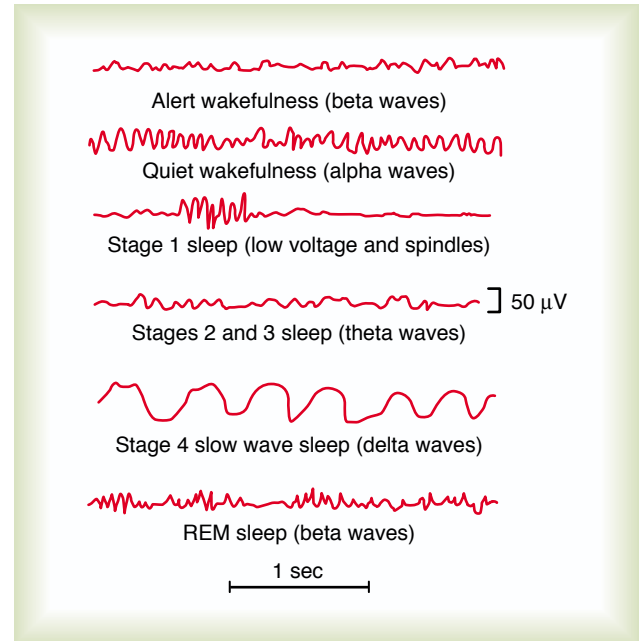
Figure 59–4 shows EEG patterns from a typical person in different stages of wakefulness and sleep. Alert wakefulness is characterized by high-frequency *beta waves*, whereas quiet wakefulness is usually associated with *alpha waves*, as demonstrated by the first two EEGs of the figure.

Slow-wave sleep is divided into four stages. In the first stage, a stage of very light sleep, the voltage of the EEG waves becomes very low; this is broken by “*sleep spindles*,” that is, short spindle-shaped bursts of alpha waves that occur periodically. In stages 2, 3, and 4 of slow-wave sleep, the frequency of the EEG becomes progressively slower until it reaches a frequency of only 1 to 3 waves per second in stage 4; these are *delta waves*.

Finally, the bottom record in Figure 59–4 shows the EEG during REM sleep. It is often difficult to tell the difference between this brain wave pattern and that of an awake, active person. The waves are irregular and high-frequency, which are normally suggestive of desynchronized nervous activity as found in the awake state. Therefore, REM sleep is frequently called *desynchronized sleep* because there is lack of synchrony in the firing of the neurons, despite significant brain activity.

## Epilepsy

Epilepsy (also called “seizures”) is characterized by *uncontrolled* excessive activity of either part or all of the

**Figure 59–4**

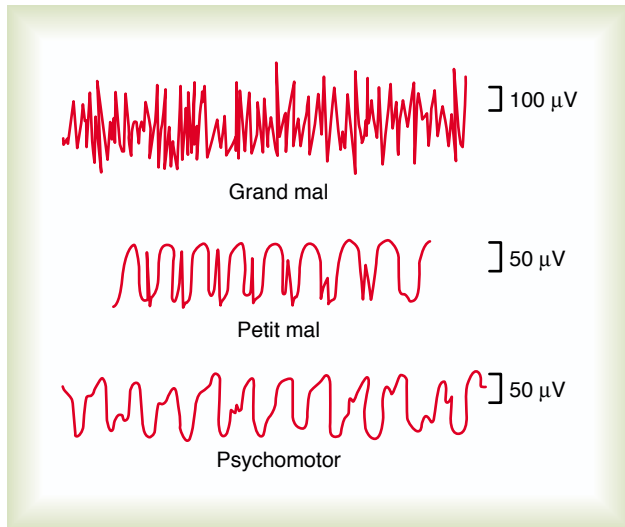
Progressive change in the characteristics of the brain waves during different stages of wakefulness and sleep.

central nervous system. A person who is predisposed to epilepsy has attacks when the basal level of excitability of the nervous system (or of the part that is susceptible to the epileptic state) rises above a certain critical threshold. As long as the degree of excitability is held below this threshold, no attack occurs.

Epilepsy can be classified into three major types: *grand mal epilepsy*, *petit mal epilepsy*, and *focal epilepsy*.

### Grand Mal Epilepsy

Grand mal epilepsy is characterized by extreme neuronal discharges in all areas of the brain—in the cerebral cortex, in the deeper parts of the cerebrum, and even in the brain stem. Also, discharges transmitted all the way into the spinal cord sometimes cause generalized *tonic seizures* of the entire body, followed toward the end of the attack by alternating tonic and spasmodic muscle contractions called *tonic-clonic seizures*. Often the person bites or “swallows” his or her tongue and may have difficulty breathing, sometimes to the extent that cyanosis occurs. Also, signals transmitted from the

**Figure 59-5**

Electroencephalograms in different types of epilepsy.

brain to the viscera frequently cause urination and defecation.

The usual grand mal seizure lasts from a few seconds to 3 to 4 minutes. It is also characterized by *postseizure depression* of the entire nervous system; the person remains in stupor for 1 to many minutes after the seizure attack is over, and then often remains severely fatigued and asleep for hours thereafter.

The top recording of Figure 59-5 shows a typical EEG from almost any region of the cortex during the tonic phase of a grand mal attack. This demonstrates that high-voltage, high-frequency discharges occur over the entire cortex. Furthermore, the same type of discharge occurs on both sides of the brain at the same time, demonstrating that the abnormal neuronal circuitry responsible for the attack strongly involves the basal regions of the brain that drive the two halves of the cerebrum simultaneously.

In laboratory animals and even in human beings, grand mal attacks can be initiated by administering a neuronal stimulant such as the drug pentylenetetrazol, or they can be caused by insulin hypoglycemia, or by passage of alternating electrical current directly through the brain. Electrical recordings from the thalamus as well as from the reticular formation of the brain stem during the grand mal attack show typical high-voltage activity in both of these areas similar to that recorded from the cerebral cortex. Presumably, therefore, a grand mal attack involves not only abnormal activation of the thalamus and cerebral cortex but also abnormal activation in the subthalamic brain stem portions of the brain activating system itself.

**What Initiates a Grand Mal Attack?** Most people who have grand mal attacks have hereditary predisposition to epilepsy, a predisposition that occurs in about 1 of every 50 to 100 persons. In such people, factors that can increase the excitability of the abnormal “epileptogenic” circuitry enough to precipitate attacks include (1) strong emotional stimuli, (2) alkalosis caused by overbreathing, (3) drugs, (4) fever, and (5) loud noises or flashing lights.

Even in people who are not genetically predisposed, certain types of traumatic lesions in almost any part of the brain can cause excess excitability of local brain areas, as we discuss shortly; these, too, sometimes transmit signals into the activating systems of the brain to elicit grand mal seizures.

**What Stops the Grand Mal Attack?** The cause of the extreme neuronal overactivity during a grand mal attack is presumed to be massive simultaneous activation of many reverberating neuronal pathways throughout the brain. Presumably, the major factor that stops the attack after a few minutes is *neuronal fatigue*. A second factor is probably *active inhibition* by inhibitory neurons that have been activated by the attack.

### Petit Mal Epilepsy

Petit mal epilepsy almost certainly involves the thalamocortical brain activating system. It is usually characterized by 3 to 30 seconds of unconsciousness (or diminished consciousness) during which time the person has twitch-like contractions of muscles usually in the head region, especially blinking of the eyes; this is followed by return of consciousness and resumption of previous activities. This total sequence is called the *absence syndrome* or absence epilepsy. The patient may have one such attack in many months or, in rare instances, may have a rapid series of attacks, one after the other. The usual course is for the petit mal attacks to appear first during late childhood and then to disappear by the age of 30. On occasion, a petit mal epileptic attack will initiate a grand mal attack.

The brain wave pattern in petit mal epilepsy is demonstrated by the middle recording of Figure 59-5, which is typified by a *spike and dome pattern*. The spike and dome can be recorded over most or all of the cerebral cortex, showing that the seizure involves much or most of the thalamocortical activating system of the brain. In fact, animal studies suggest that it results from oscillation of (1) inhibitory thalamic reticular neurons (which are *inhibitory* gamma-aminobutyric acid [GABA]-producing neurons) and (2) *excitatory* thalamocortical and corticothalamic neurons.

### Focal Epilepsy

Focal epilepsy can involve almost any local part of the brain, either localized regions of the cerebral cortex or deeper structures of both the cerebrum and brain stem. Most often, focal epilepsy results from some localized organic lesion or functional abnormality, such as (1) scar tissue in the brain that pulls on the adjacent neuronal tissue, (2) a tumor that compresses an area of the brain, (3) a destroyed area of brain tissue, or (4) congenitally deranged local circuitry.

Lesions such as these can promote extremely rapid discharges in the local neurons; when the discharge rate rises above several hundred per second, synchronous waves begin to spread over adjacent cortical regions. These waves presumably result from *localized reverberating circuits* that gradually recruit adjacent areas of the cortex into the epileptic discharge zone. The process spreads to adjacent areas at a rate as slow as a few millimeters a minute to as fast as several centimeters per second. When such a wave of excitation spreads over the motor cortex, it causes progressive “march” of muscle

contractions throughout the opposite side of the body, beginning most characteristically in the mouth region and marching progressively downward to the legs but at other times marching in the opposite direction. This is called *jacksonian epilepsy*.

A focal epileptic attack may remain confined to a single area of the brain, but in many instances, the strong signals from the convulsing cortex excite the mesencephalic portion of the brain activating system so greatly that a grand mal epileptic attack ensues as well.

Another type of focal epilepsy is the so-called *psychomotor seizure*, which may cause (1) a short period of amnesia; (2) an attack of abnormal rage; (3) sudden anxiety, discomfort, or fear; and/or (4) a moment of incoherent speech or mumbling of some trite phrase. Sometimes the person cannot remember his or her activities during the attack, but at other times, he or she is conscious of everything that he or she is doing but unable to control it. Attacks of this type frequently involve part of the limbic portion of the brain, such as the hippocampus, the amygdala, the septum, and/or portions of the temporal cortex.

The lowest tracing of Figure 59-5 demonstrates a typical EEG during a psychomotor seizure, showing a low-frequency rectangular wave with a frequency between 2 and 4 per second and with occasional superimposed 14-per-second waves.

#### **Surgical Excision of Epileptic Foci Can Often Prevent Seizures.**

The EEG can be used to localize abnormal spiking waves originating in areas of organic brain disease that predispose to focal epileptic attacks. Once such a focal point is found, surgical excision of the focus frequently prevents future attacks.

### **Psychotic Behavior and Dementia—Roles of Specific Neurotransmitter Systems**

Clinical studies of patients with different psychoses or different types of dementia have suggested that many of these conditions result from diminished function of neurons that secrete a specific neurotransmitter. Use of appropriate drugs to counteract loss of the respective neurotransmitter has been successful in treating some patients.

In Chapter 56, we discussed the cause of Parkinson's disease. This disease results from loss of neurons in the substantia nigra whose nerve endings secrete *dopamine* in the caudate nucleus and putamen. Also in Chapter 56, we pointed out that in Huntington's disease, loss of GABA-secreting neurons and acetylcholine-secreting neurons is associated with *specific abnormal motor patterns plus dementia* occurring in the same patient.

#### **Depression and Manic-Depressive Psychoses—Decreased Activity of the Norepinephrine and Serotonin Neurotransmitter Systems**

Much evidence has accumulated suggesting that *mental depression psychosis*, which occurs in about 8 million people in the United States, might be caused by *diminished formation in the brain of norepinephrine or serotonin, or both*. (New evidence has implicated still other

neurotransmitters.) Depressed patients experience symptoms of grief, unhappiness, despair, and misery. In addition, they often lose their appetite and sex drive and have severe insomnia. Often associated with these is a state of psychomotor agitation despite the depression.

Moderate numbers of *norepinephrine-secreting neurons* are located in the brain stem, especially in the *locus ceruleus*. These neurons send fibers upward to most parts of the brain limbic system, thalamus, and cerebral cortex. Also, many *serotonin-producing neurons* located in the *midline raphe nuclei* of the lower pons and medulla send fibers to many areas of the limbic system and to some other areas of the brain.

A principal reason for believing that depression might be caused by diminished activity of norepinephrine- and serotonin-secreting neurons is that drugs that block secretion of norepinephrine and serotonin, such as reserpine, frequently cause depression. Conversely, about 70 per cent of depressive patients can be treated effectively with drugs that increase the excitatory effects of norepinephrine and serotonin at the nerve endings—for instance, (1) *monoamine oxidase inhibitors*, which block destruction of norepinephrine and serotonin once they are formed; and (2) *tricyclic antidepressants*, such as *imipramine* and *amitriptyline*, which block reuptake of norepinephrine and serotonin by nerve endings so that these transmitters remain active for longer periods after secretion.

Mental depression can be treated by electroconvulsive therapy—commonly called “shock therapy.” In this therapy, electrical current is passed through the brain to cause a generalized seizure similar to that of an epileptic attack. This has been shown to enhance norepinephrine activity.

Some patients with mental depression alternate between depression and mania, which is called either *bipolar disorder* or *manic-depressive psychosis*, and a few people exhibit only mania without the depressive episodes. Drugs that diminish the formation or action of norepinephrine and serotonin, such as lithium compounds, can be effective in treating the manic phase of the condition.

It is presumed that the norepinephrine and serotonin systems normally provide drive to the limbic areas of the brain to increase a person's sense of well-being, to create happiness, contentment, good appetite, appropriate sex drive, and psychomotor balance—although too much of a good thing can cause mania. In support of this concept is the fact that pleasure and reward centers of the hypothalamus and surrounding areas receive large numbers of nerve endings from the norepinephrine and serotonin systems.

#### **Schizophrenia—Possible Exaggerated Function of Part of the Dopamine System**

Schizophrenia comes in many varieties. One of the most common types is seen in the person who hears voices and has delusions of grandeur, intense fear, or other types of feelings that are unreal. Many schizophrenics (1) are highly paranoid, with a sense of persecution from outside sources; (2) may develop incoherent speech, dissociation of ideas, and abnormal sequences of thought; and (3) are often withdrawn, sometimes with abnormal posture and even rigidity.

There are reasons to believe that schizophrenia results from one or more of three possibilities: (1) multiple areas in the cerebral cortex *prefrontal lobes* in which neural signals have become blocked or where processing of the signals becomes dysfunctional because many synapses normally excited by the neurotransmitter *glutamate* lose their responsiveness to this transmitter; (2) excessive excitement of a group of neurons that secrete *dopamine* in the behavioral centers of the brain, including in the frontal lobes; and/or (3) abnormal function of a crucial part of the brain's *limbic behavioral control system centered around the hippocampus*.

The reason for believing that the prefrontal lobes are involved in schizophrenia is that a schizophrenic-like pattern of mental activity can be induced in monkeys by making multiple minute lesions in widespread areas of the prefrontal lobes.

Dopamine has been implicated as a possible cause of schizophrenia because many patients with Parkinson's disease develop schizophrenic-like symptoms when they are treated with the drug called L-dopa. This drug releases dopamine in the brain, which is advantageous for treating Parkinson's disease, but at the same time it depresses various portions of the prefrontal lobes and other related areas.

It has been suggested that in schizophrenia excess dopamine is secreted by a group of dopamine-secreting neurons whose cell bodies lie in the ventral tegmentum of the mesencephalon, medial and superior to the substantia nigra. These neurons give rise to the so-called *mesolimbic dopaminergic system* that projects nerve fibers and dopamine secretion into the medial and anterior portions of the limbic system, especially into the hippocampus, amygdala, anterior caudate nucleus, and portions of the prefrontal lobes. All of these are powerful behavioral control centers.

An even more compelling reason for believing that schizophrenia might be caused by excess production of dopamine is that many drugs that are effective in treating schizophrenia—such as chlorpromazine, haloperidol, and thiothixene—all either decrease secretion of dopamine at dopaminergic nerve endings or decrease the effect of dopamine on subsequent neurons.

Finally, possible involvement of the hippocampus in schizophrenia was discovered recently when it was learned that *in schizophrenia, the hippocampus is often reduced in size*, especially in the dominant hemisphere.

### Alzheimer's Disease—Amyloid Plaques and Depressed Memory

Alzheimer's disease is defined as premature aging of the brain, usually beginning in mid-adult life and progressing rapidly to extreme loss of mental powers—similar to that seen in very, very old age. The clinical features of Alzheimer's disease include (1) an amnesic type of memory impairment, (2) deterioration of language, and (3) visuospatial deficits. Motor and sensory abnormalities, gait disturbances, and seizures are uncommon until the late phases of the disease. One consistent finding in Alzheimer's disease is loss of neurons in that part of the limbic pathway that drives the memory process. Loss of this memory function is devastating.

Alzheimer's disease is a progressive and fatal neurodegenerative disorder that results in impairment of the person's ability to perform activities of daily living as well as a variety of neuropsychiatric symptoms and

behavioral disturbances in the later stages of the disease. Patients with Alzheimer's disease usually require continuous care within a few years after the disease begins.

Alzheimer's disease is the most common form of dementia in the elderly and about 5 million people in the United States are estimated to be afflicted by this disorder. The percentage of persons with Alzheimer's disease approximately doubles with every five years of age, with about 1 percent of 60-year-olds and about 30 percent of 85-year-olds having the disease.

**Alzheimer's Disease Is Associated with Accumulation of Brain Beta-Amyloid Peptide.** Pathologically, one finds increased amounts of beta-amyloid peptide in the brains of patients with Alzheimer's disease. The peptide accumulates in amyloid plaques, which range in diameter from 10 micrometers to several hundred micrometers and are found in widespread areas of the brain, including in the cerebral cortex, hippocampus, basal ganglia, thalamus, and even the cerebellum. Thus, Alzheimer's disease appears to be a metabolic degenerative disease.

A key role for excess accumulation of beta-amyloid peptide in the pathogenesis of Alzheimer's disease is suggested by the following observations: (1) all currently known mutations associated with Alzheimer's disease increase the production of beta-amyloid peptide; (2) patients with trisomy 21 (Down syndrome) have three copies of the gene for amyloid precursor protein and develop neurological characteristics of Alzheimer's disease by midlife; (3) patients who have abnormality of a gene that controls apolipoprotein E, a blood protein that transports cholesterol to the tissues, have accelerated deposition of amyloid and greatly increased risk for Alzheimer's disease; (4) transgenic mice that overproduce the human amyloid precursor protein have learning and memory deficits in association with the accumulation of amyloid plaques; and (5) generation of anti-amyloid antibodies in humans with Alzheimer's disease appears to attenuate the disease process.

**Vascular Disorders May Contribute to Progression of Alzheimer's Disease.** There is also accumulating evidence that cerebrovascular disease caused by *hypertension* and *atherosclerosis* may play a role in Alzheimer's disease. Cerebrovascular disease is the second most common cause of acquired cognitive impairment and dementia and likely contributes to cognitive decline in Alzheimer's disease. In fact, many of the common risk factors for cerebrovascular disease, such as hypertension, diabetes, and hyperlipidemia, are also recognized to greatly increase the risk for developing Alzheimer's disease.

### References

- Aldrich MS: Sleep Medicine: Normal Sleep and Its Disorders. New York: Oxford University Press, 1999.
- Beardsley T: Waking up. Sci Am Jul 18, 1996.
- Bryant PA, Trinder J, Curtis N: Sick and tired: does sleep have a vital role in the immune system? Nat Rev Immunol 4:457, 2004.
- Cassidy I, Topol E: Convergence of atherosclerosis and Alzheimer's disease: inflammation, cholesterol, and misfolded proteins. Lancet 363:1139, 2004.

- Cummings JL: Alzheimer's disease. *N Engl J Med* 351:56, 2004.
- de la Torre JC: Is Alzheimer's disease a neurodegenerative or a vascular disorder? Data, dogma, and dialectics. *Lancet Neurol* 3:184, 2004.
- George AL Jr: Molecular basis of inherited epilepsy. *Arch Neurol* 61:473, 2004.
- Gerashchenko D, Shiromani PJ: Different neuronal phenotypes in the lateral hypothalamus and their role in sleep and wakefulness. *Mol Neurobiol* 29:41, 2004.
- Golde TE: Alzheimer disease therapy: can the amyloid cascade be halted? *J Clin Invest* 111:11, 2003.
- Gourfinkel-An I, Baulac S, Nabbout R, et al: Monogenic idiopathic epilepsies. *Lancet Neurol* 3:209, 2004.
- Greene R, Siegel J: Sleep: a functional enigma. *Neuromolecular Med* 5:59, 2004.
- Heller HC, Ruby NF: Sleep and circadian rhythms in mammalian torpor. *Annu Rev Physiol* 66:275, 2004.
- Iadecola C: Neurovascular regulation in the normal brain and in Alzheimer's disease. *Nat Rev Neurosci* 5:347-360, 2004.
- LaRoche SM, Helmers SL: The new antiepileptic drugs: scientific review. *JAMA* 291:605, 2004.
- McCormick DA, Contreras D: On the cellular and network bases of epileptic seizures. *Annu Rev Physiol* 63:815, 2001.
- Noebels JL: The biology of epilepsy genes. *Annu Rev Neurosci* 26:599, 2003.
- Selkoe DJ: Alzheimer disease: mechanistic understanding predicts novel therapies. *Ann Intern Med* 140:627, 2004.
- Selkoe DJ: Alzheimer's disease: genes, proteins, and therapy. *Physiol Rev* 81:741, 2001.
- Steinlein OK: Genetic mechanisms that underlie epilepsy. *Nat Rev Neurosci* 5:400-408, 2004.