Module 1

Approach to the patient with Neurologic disease:

Neurology is regarded by many as one of the most difficult and exacting medical specialties. Students and residents coming to the neurology ward or clinic for the first time are easily discouraged by what they see. Having had brief contact with neuroanatomy, neurophysiology, and neuropathology, they are already somewhat intimidated by the complexity of the nervous system. The ritual they then witness of putting the patient through a series of maneuvers designed to evoke certain mysterious signs, the names of which are difficult to pronounce, is hardly reassuring; in fact, the procedure often appears to conceal the very intellectual processes by which neurologic diagnosis is attained.

Moreover, the students have had little or no experience with the many special tests used in neurologic diagnosis— such as lumbar puncture, electroencephalography, CT, MRI, and other imaging procedures— nor do they know how to interpret the results of such tests. Neurology textbooks only confirm their fears as they read the detailed accounts of the many rare diseases of the nervous system. The authors believe that many of the difficulties in comprehending neurology can be overcome by adhering to the basic principles of clinical medicine. First and foremost, it is necessary to learn and acquire facility in the use of the clinical method. Without a full appreciation of this method, the student is virtually as helpless with a new clinical problem as a botanist or chemist who would undertake a research problem without understanding the steps in the scientific method. And even the experienced neurologist faced with a complex clinical problem resorts to this basic approach. The importance of the clinical method stands out more clearly in the study of neurologic disease than in certain other fields of medicine. In most cases, the clinical method consists of an orderly series of steps, as follows:

1. The symptoms and signs are secured by history and physical examination.
2. The symptoms and physical signs considered relevant to the problem at hand are interpreted in terms of physiology and anatomy—that is, one identifies the disorder(s) of function and the anatomic structure(s) that are implicated.
3. These analyses permit the physician to localize the disease process, i.e., to name the part or parts of the nervous system involved. This step is called anatomic, or topographic, diagnosis. Often one recognizes a characteristic clustering of symptoms and signs, constituting a syndrome of anatomic, physiologic, or temporal type. The formulation of symptoms and signs in syndromic terms is particularly helpful in ascertaining the locus and nature of the disease. This step is called syndromic diagnosis and is often conducted in parallel with anatomic diagnosis.
4. From the anatomic diagnosis and other medical data— particularly the mode and speed of onset, evolution, and course of the illness, the involvement of nonneurologic organ systems, the relevant past and family histories, and the laboratory findings— one deduces the pathologic diagnosis and, when the mechanism and causation of the disease can be determined, the etiologic diagnosis. This may include the rapidly increasing number of molecular and genetic etiologies if they have been worked out for a particular process.

5. Finally, the physician should assess the degree of disability and determine whether it is temporary or permanent (functional diagnosis); this is important in managing the patient's illness and judging the potential for restoration of function. It goes without saying that all of these steps are undertaken in the service of effective treatment, an ever-increasing prospect in neurology. As will be emphasized repeatedly in later sections, there is therefore always a premium in the diagnostic process on the discovery of treatable diseases. The foregoing approach to the diagnosis of neurologic disease is summarized in Fig. 1-1, a procedural diagram by which the clinical problem is solved in a series of sequential finite steps.

This systematic approach, allowing the confident localization and often precise diagnosis of disease, is one of the intellectual attractions of neurology. Of course, the solution to a clinical problem need not always be schematized in this way. The clinical method offers a much wider choice in the order and manner by which information is collected and interpreted. In fact, in some cases, adherence to a formal scheme is not necessary at all. In relation to the aforementioned syndromic diagnosis, the clinical picture of Parkinson disease, for example, is usually so characteristic that the nature of the illness is at once apparent. In other cases it is not necessary to carry the clinical analysis beyond the stage of the anatomic diagnosis, which in itself may virtually indicate the cause of a disease. For example, when cerebellar ataxia, a unilateral Horner syndrome, paralysis of a vocal cord, and analgesia of the face of acute onset are combined with loss of pain and temperature sensation in the opposite arm, trunk, and leg, the most likely cause is an occlusion of the vertebral artery, because all the involved structures can be localized to the lateral medulla, within the territory of this artery. Thus, the anatomic diagnosis determines and limits the etiologic possibilities. If the signs point to disease of the peripheral nerves, it is usually not necessary to consider the causes of disease of the spinal cord. Some signs themselves are almost specific— e.g., opsoclonus for paraneoplastic cerebellar degeneration and Argyll Robertson pupils for neurosyphilitic or diabetic oculomotor neuropathy. Irrespective of the intellectual process that one utilizes in solving a particular clinical problem, the fundamental steps in diagnosis always involve the accurate elicitation of symptoms and signs and their correct interpretation in terms of disordered function of the nervous system. Most often when there is uncertainty or disagreement as to diagnosis, it will be found later that the symptoms of disordered function were incorrectly interpreted in the first place. Thus, if a complaint of dizziness is identified as vertigo instead of light-headedness or if partial continuous epilepsy is mistaken for

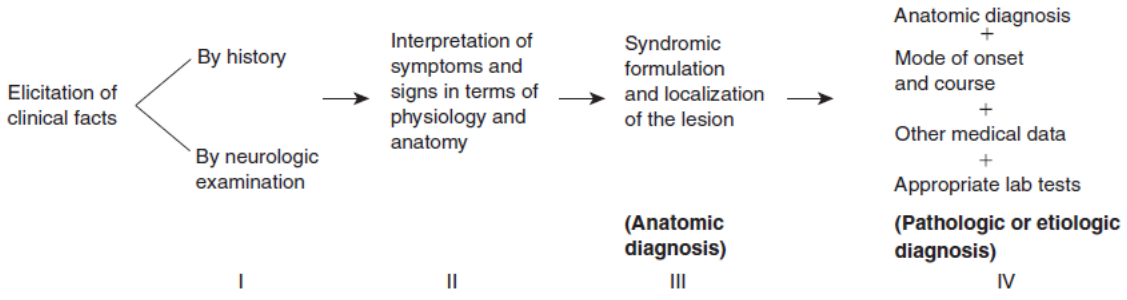


Figure 1-1. *Steps in the diagnosis of neurologic disease.*

an extrapyramidal movement disorder such as choreoathetosis, then the clinical method is derailed from the beginning. Repeated examinations may be necessary to establish the fundamental clinical findings beyond doubt and to ascertain the course of the illness. Hence the aphorism that a second examination is the most helpful diagnostic test in a difficult neurologic case. Different disease processes may cause identical symptoms, which is understandable in view of the fact that the same parts of the nervous system may be affected by any one of several processes. For example, a spastic paraplegia may result from spinal cord tumor, a genetic defect, or multiple sclerosis. Conversely, the same disease may present with different groups of symptoms and signs. However, despite the many possible combinations of symptoms and signs in a particular disease, a few combinations occur with greater frequency than others and can be recognized as highly characteristic of that disease. The experienced clinician acquires the habit of attempting to categorize every case in terms of a characteristic symptom complex, or syndrome.

One must always keep in mind that syndromes are not disease entities but rather abstractions set up by clinicians in order to facilitate the diagnosis of disease. For example, the symptom complex of right-left confusion and inability to write, calculate, and identify individual fingers constitutes the so-called Gerstmann syndrome, recognition of which determines the anatomic locus of the disease (region of the left angular gyrus) and at the same time narrows the range of possible etiologic factors. In the initial analysis of a neurologic disorder, anatomic diagnosis takes precedence over etiologic diagnosis. To seek the cause of a disease of the nervous system without first ascertaining the parts or structures that are affected would be analogous in internal medicine to attempting an etiologic diagnosis without knowing whether the disease involved the lungs, stomach, or kidneys. Discerning the cause of a clinical syndrome (etiologic diagnosis) requires knowledge of an entirely different order. Here one must be conversant with the clinical details, including the mode of onset, course, and natural history of a multiplicity of disease entities. Many of these facts are well known and not difficult to master; they form the substance of later chapters. When confronted with a constellation of clinical features that do not lend themselves to a simple or sequential analysis, one resorts to considering the broad classical division of diseases in medicine, as summarized in Table 1-1.

Table 1-1
The major categories of neurologic disease

Infectious
Genetic-congenital
Traumatic
Degenerative
Toxic
Metabolic
Inherited
Acquired
Neoplastic
Inflammatory-immune

Taking the history:

In neurology more than any other specialty, the physician is dependent upon the cooperation of the patient for a reliable history, especially for a description of symptoms that are unaccompanied by observable signs of disease. And if the symptoms are in the sensory sphere, only the patient can tell what he* sees, hears, or feels. The first step in the clinical encounter is to enlist the patient's trust and cooperation and make him realize the importance of the examination procedure. The practice of making notes at the bedside or in the office is particularly recommended. Immediate recording of the history assures maximal reliability. Of course, no matter how reliable the history appears to be, verification of the patient's account by a knowledgeable and objective informant is always desirable. The following points about taking the neurologic history deserve further comment:

1. Special care must be taken to avoid suggesting to the patient the symptoms that one seeks. In the clinical interview, the conduct of the examiner has a great influence on the patient. Repetition of this truism may seem tedious, but it is evident that conflicting histories can often be traced to leading questions that either suggested symptoms to the patient or led to a distortion of the patient's story. Errors and inconsistencies in the recorded history are as often the fault of the physician as of the patient. As a corollary, the patient should be discouraged from framing his symptom(s) in terms of a diagnosis that he may have heard;rather, he should be urged to give as accurate a description of the symptom as possible— being asked, for example, to choose a single word that best describes his pain and to describe precisely what he means by a particular term, such as dizziness, imbalance, or vertigo. The patient who is given to highly circumstantial and rambling accounts can be kept on the subject of his illness by discreet questions that draw out essential points.

2. The setting in which the illness occurred, its mode of onset and evolution, and its course are of paramount importance. One must attempt to learn precisely how each symptom began and progressed. Often the nature of the disease process can be decided from these data alone. If such information cannot be supplied by the patient or his family, it may be necessary to judge the course of the illness by what the patient was able to do at different times (e.g., how far he could walk, when he could no longer negotiate stairs or carry on his usual work) or by changes in the clinical findings between successive examinations, provided that the physician had recorded the findings accurately and has quantitated them in some way. 3. Since neurologic diseases often impair mental function, it is necessary, in every patient who might have cerebral disease, for the physician to decide, by an initial assessment of the mental status and the circumstances under which symptoms occurred, whether or not the patient is competent to give a history of the illness. If the patient's powers of attention, memory, and coherence of thinking are inadequate, the history must be obtained from a spouse, relative, friend, or employer. Also, illnesses that are characterized by seizures or other forms of episodic confusion abolish or impair the patient's memory of events occurring during these episodes. In general, students (and some physicians as well) tend to be careless in estimating the mental capacities of their patients. Attempts are sometimes made to take histories from patients who are feebleminded or so confused that they have no idea why they are in a doctor's office or a hospital, or from patients who for other reasons could not possibly have been aware of the details of their illnesses.

THE NEUROLOGIC EXAMINATION:

The neurologic examination begins with observations of the patient while the history is being obtained. The manner in which the patient tells the story of his illness may betray confusion or incoherence in thinking, impairment of memory or judgment, or difficulty in comprehending or expressing ideas. Observation of such matters is an integral part of the examination and provides information as to the adequacy of cerebral function. The physician should learn to obtain this type of information without embarrassment to the patient. A common error is to pass lightly over inconsistencies in history and inaccuracies about dates and symptoms, only to discover later that these flaws in memory were the essential features of the illness. Asking the patient to give his own interpretation of the possible meaning of symptoms may sometimes expose unnatural concern, anxiety, suspiciousness, or even delusional thinking. One then generally proceeds from an examination of the cranial nerves, neck, and trunk to the testing of motor, reflex, and sensory functions of the upper and lower limbs. This is followed by an assessment of the function of sphincters and the autonomic nervous system and suppleness of the neck and spine (meningeal irritation). Gait and station (standing position) should be observed before or after the rest of the examination. In addition, it is often instructive to observe the patient in the course of his natural activities, such as walking or dressing;this may disclose subtle abnormalities of gait and movement that might not be evident in formal testing.

Testing of HigherCortical Functions:

These functions are tested in detail if the patient's history or behavior during the general examination has provided a reason to suspect some defect. Questions should then be directed toward determining the patient's orientation in time and place and insight into his current medical problem. Attention, speed of response, ability to give relevant answers to simple questions, and the capacity for sustained and coherent mental effort all lend themselves to straightforward observation. Useful bedside tests of attention, concentration, memory, and clarity of thinking include the repetition of a series of digits in forward and reverse order, serial subtraction of 3s or 7s from 100, recall of three items of information or a short story after an interval of 3 min, and naming the last six presidents or prime ministers. The patient's account of his recent illness, medical consultations, dates of hospitalization, and his dayto-day recollection of medical procedures, meals, and other incidents are excellent tests of memory;the narration of the illness and the patient's choice of words (vocabulary) provide information about his intelligence and coherence of thinking. Many other tests can be devised for the same purpose. Often the examiner can obtain a better idea of the clarity of the patient's sensorium and soundness of intellect by using these few tests and noting the manner in which he deals with them than by relying on the score of a formal intelligence test. If there is any suggestion of a speech or language disorder, the nature of the patient's spontaneous speech should be noted. In addition, his ability to read, write, and spell, execute spoken commands, repeat words and phrases spoken by the examiner, name objects and parts of objects, and solve simple arithmetical problems should be assessed. The ability to carry out commanded tasks (praxis) has great salience in the evaluation of several aspects of cortical function. Bisecting a line, drawing a clock or the floor plan of one's home or a map of one's country,

and copying figures are useful tests of visuospatial perception and are indicated in cases of suspected cerebral disease.

Testing of Cranial Nerves:

The function of the cranial nerves must be investigated more fully in patients who have neurologic symptoms than in those who do not. If one suspects a lesion in the anterior fossa, the sense of smell should be tested in each nostril;then it should be determined whether odors can be discriminated. Visual fields should be outlined by confrontation testing, in some cases by testing each eye separately;if any abnormality is suspected, it should be checked on a perimeter and scotomas sought on the tangent screen or, more accurately, by computed perimetry. Pupil size and reactivity to light and accommodation during convergence, the position of the eyelids, and the range of ocular movements should next be observed. Sensation over the face is tested with a pin and wisp of cotton; also, the presence or absence of the corneal reflexes may be determined. Facial movements should be observed as the patient speaks and smiles, for a slight weakness may be more evident in these circumstances than on movements to command. The auditory meati and tympanic membranes should be inspected with an otoscope. A 256 double-vibration tuning fork held next to the ear and on the mastoid discloses hearing loss and distinguishes middle-ear (conductive) from neural deafness. Audiograms and other special tests of auditory and vestibular function are needed if there is any suspicion of disease of the eighth nerve or the cochlear and labyrinthine end organs. The vocal cords must be inspected with special instruments in cases of suspected medullary or vagus nerve disease, especially when there is hoarseness. Voluntary pharyngeal elevation and elicited reflexes are meaningful if there is a difference on the two sides;bilateral absence of the gag reflex is seldom significant. Inspection of the tongue, both protruded and at rest, is helpful;atrophy and fasciculations may be seen and weakness detected. Slight deviation of the protruded tongue as a solitary finding can usually be disregarded. The pronunciation of words should be noted. The jaw jerk and the snout, buccal, and sucking reflexes should be sought, particularly if there is a question of dysphagia, dysarthria, or dysphonia.

Tests of Motor Function:

In the assessment of motor function, it should be kept in mind that observations of the speed and strength of movements and of muscle bulk, tone, and coordination are usually more informative than the state of tendon reflexes. It is essential to have the limbs fully exposed and to inspect them for atrophy and fasciculations. The next step is to watch the patient maintain the arms outstretched in the prone and supine positions;perform simple tasks, such as alternately touching his nose and the examiner's finger;make rapid alternating movements that necessitate sudden acceleration and deceleration and changes in direction, such as tapping one hand on the other while alternating pronation and supination of the forearm; rapidly touch the thumb to each fingertip;and accomplish simple tasks such as buttoning clothes, opening a safety pin, or handling common tools. Estimates of the strength of leg muscles with the patient in bed are often unreliable;there may seem to be little or no weakness even though the patient cannot arise from a chair or from a kneeling position without help. Running the heel down the front of the shin, alternately touching the examiner's finger with the toe and the opposite knee with the heel, and rhythmically tapping the heel on the shin are the only tests of coordination that need be carried out in bed. The maintenance of both arms against gravity is

a useful test;the weak one, tiring first, soon begins to sag, or, in the case of a corticospinal lesion, to resume the more natural pronated position ("pronator drift"). The strength of the legs can be similarly tested, either with the patient supine and the legs flexed at hips and knees or with the patient prone and the knees bent. Also, abnormalities of movement and posture and tremors may be exposed.

Tests of Reflex Function:

Testing of the biceps, triceps, supinator (radial-periosteal), patellar, Achilles, and cutaneous abdominal and plantar reflexes permits an adequate sampling of reflex activity of the spinal cord. Elicitation of tendon reflexes requires that the involved muscles be relaxed; underactive or barely elicitable reflexes can be facilitated by voluntary contraction of other muscles (Jendrassik maneuver). The plantar response poses special difficulty because several different reflex responses can be evoked by stimulating the sole of the foot along its outer border from heel to toes. These are (1) the quick, high-level avoidance response;(2) the slower, spinal flexor nocifensive (protective) reflex (flexion of knee and hip and dorsiflexion of toes and foot, "triple flexion")— dorsiflexion of the large toe as part of this reflex is the well-known Babinski sign; (3) plantar grasp reflex;and (4) support reactions. Avoidance and withdrawal responses interfere with the interpretation of the Babinski sign and can sometimes be overcome by utilizing the several alternative stimuli that are known to elicit the Babinski response (squeezing the calf or Achilles tendon, flicking the fourth toe, downward scraping of the shin, lifting the straight leg, and others). An absence of the superficial cutaneous reflexes of the abdominal, cremasteric, and other muscles are useful ancillary tests for detecting corticospinal lesions.

Testing of Sensory Function:

This is undoubtedly the most difficult part of the neurologic examination. Usually sensory testing is reserved for the end of the examination and, if the findings are to be reliable, should not be prolonged for more than a few minutes. Each test should be explained briefly;too much discussion of these tests with a meticulous, introspective patient may encourage the reporting of useless minor variations of stimulus intensity. It is not necessary to examine all areas of the skin surface. A quick survey of the face, neck, arms, trunk, and legs with a pin takes only a few seconds. Usually one is seeking differences between the two sides of the body (it is better to ask whether stimuli on opposite sides of the body feel the same than to ask if they feel different), a level below which sensation is lost, or a zone of relative or absolute analgesia (loss of pain sensibility) or anesthesia (loss of touch sensibility). Regions of sensory deficit can then be tested more carefully and mapped out. Moving the stimulus from an area of diminished sensation into a normal area enhances the perception of a difference. The vibration sense may be tested by comparing the thresholds at which the patient and examiner lose perception at comparable bony prominences. We usually record the number of seconds for which the examiner appreciates vibration at the malleolus or toe after the patient reports that the fork has stopped buzzing. The finding of a zone of heightened sensation ("hyperesthesia") calls attention to a disturbance of superficial sensation. Variations in sensory findings from one examination to another reflect differences in technique of examination as well as inconsistencies in the responses of the patient.

Testing of Gait and Stance

The examination is completed by observing the patient stand and walk. An abnormality of stance and gait may be the most prominent or only neurologic abnormality, as in certain cases of cerebellar or frontal lobe disorder;and an impairment of posture and highly automatic adaptive movements in walking may provide the most definite diagnostic clues in the early stages of Parkinson disease and progressive supranuclear palsy. Having the patient walk tandem or on the sides of the soles may bring out a lack of balance and dystonic postures in the hands and trunk. Hopping or standing on one foot may also betray a lack of balance or weakness, and standing with feet together and eyes closed will bring out a disequilibrium that is due to deep sensory loss.

SHORTCOMINGS OF THE CLINICAL METHOD:

If one adheres faithfully to the clinical method outlined here, neurologic diagnosis is greatly simplified. In most cases one can reach an anatomic diagnosis. The cause of the disease may prove more elusive and usually entails the intelligent and selective employment of a number of the laboratory procedures described in the next chapter. However, even after the most assiduous application of the clinical method and laboratory procedures, there are numerous patients whose diseases elude diagnosis. In such circumstances we have often been aided by the following rules of thumb:

1. Focus the clinical analysis on the principal symptom and signs and avoid being distracted by minor signs and uncertain clinical data. As mentioned earlier, when the main sign has been misinterpreted—say a tremor has been taken for ataxia or fatigue for weakness—the clinical method is derailed from the start.
2. Avoid early closure of diagnosis. Often this is the result of premature fixation on some item in the history or examination, closing the mind to alternative diagnostic considerations. The first diagnostic formulation should be regarded as only a testable hypothesis, subject to modification when new items of information are secured. Should the disease be in a stage of transition, time will allow the full picture to emerge and the diagnosis to be clarified.
3. When several of the main features of a disease in its classic form are lacking, an alternative diagnosis should always be entertained. In general, however, one is more likely to encounter rare manifestations of common diseases than the typical manifestations of rare diseases (a paraphrasing of Bayes theorem). 4. It is preferable to base diagnosis on one's experience with the dominant symptoms and signs and not on statistical analyses of the frequency of clinical phenomena. For the most part the methods of probability-based decision analysis have proved to be disappointing in relation to neurologic disease because of the impossibility of weighing the importance of each clinical datum.
5. Whenever reasonable and safe, obtain tissue for examination, for this adds the certainty of histopathology to the clinical study.

As pointed out by Chimowitz, students tend to err in failing to recognize a disease they have not seen, and experienced clinicians may fail to recognize a rare variant of a common disease. There is no doubt that some clinicians are more adept than others at solving difficult clinical problems. Their talent is not intuitive, as sometimes is presumed, but is attributable to having paid close attention to the details of their experience with many diseases and having catalogued them for future reference. The

unusual case is recorded in memory and can be resurrected when another one like it is encountered. Long experience also teaches one to not immediately accept the obvious explanation.

LUMBAR PUNCTURE AND EXAMINATION OF CEREBROSPINAL FLUID

The information yielded by examination of the cerebrospinal fluid (CSF) is crucial in the diagnosis of certain neurologic diseases, particularly infectious and inflammatory conditions, subarachnoid hemorrhage, and diseases that alter intracranial pressure.

Indications for Lumbar Puncture

1. To obtain pressure measurements and procure a sample of the CSF for cellular, cytologic, chemical, and bacteriologic examination.
2. To aid in therapy by the administration of spinal anesthetics and occasionally antibiotics or antitumor agents, or by reduction of CSF pressure.
3. To inject a radiopaque substance, as in myelography, or a radioactive agent, as in radionuclide cisternography.

Lumbar puncture (LP) carries a certain risk if the CSF pressure is very high (evidenced by headache and papilledema), for it increases the possibility of a fatal cerebellar or transtentorial herniation. The risk is considerable when papilledema is due to an intracranial mass, but it is much lower in patients with subarachnoid hemorrhage or pseudotumor cerebri, conditions in which repeated LPs have actually been employed as a therapeutic measure. In patients with purulent meningitis, there is also a small risk of herniation, but this is far outweighed by the need for a definitive diagnosis and the institution of appropriate treatment at the earliest moment. With this last exception, therefore, LP should be preceded by computed tomography (CT) or MRI whenever an elevation of intracranial pressure is suspected. If radiologic procedures do disclose a mass lesion that is causing displacement of brain tissue toward the tentorial opening or into the foramen magnum (the presence of a mass alone is of less concern) and if it is considered absolutely essential to have the information yielded by CSF examination, the LP maybe performed—with certain precautions. A fine-bore (no. 22 or 24) needle should be used, and if the pressure proves to be very high— over 400 mmH2O— one should obtain the necessary sample of fluid and then, according to the suspected disease and patient's condition, administer mannitol (or urea) and observe a fall in pressure on the manometer. Dexamethasone or an equivalent corticosteroid may also be given, in an initial intravenous dose of 10 mg, followed by doses of 4 to 6 mg every 6 h in order to produce a sustained reduction in intracranial pressure. Cisternal puncture and lateral cervical subarachnoid puncture, although safe in the hands of an expert, are too hazardous to entrust to those without experience. LP is preferred except in obvious instances of spinal block requiring a sample of cisternal fluid or myelography above the lesion.

Technique of Lumbar Puncture

Experience teaches the importance of meticulous technique. LP should be done under sterile conditions. Local anesthetic is injected in and beneath the skin, which should render the procedure

almost painless. Warming of the analgesic by rolling the vial between the palms seems to diminish the burning sensation that accompanies cutaneous infiltration.

The patient is positioned on his side, preferably on the left side for right-handed physicians, with hips and knees flexed, the axis of the hips vertical, and the head as close to the knees as comfort permits (the tighter the fetal position, the easier the entry into the subarachnoid space). The patient's hips should be vertical, the back aligned near the edge of the bed, and a pillow placed under the ear. The puncture is easiest to perform at the L3-L4 interspace, which corresponds to the axial plane of the iliac crests, or at the space above or below. In infants and young children, in whom the spinal cord may extend to the level of the L3-L4 interspace, lower spaces should be used.

Experienced anesthesiologists, from their work with spinal anesthesia, have suggested that the smallest possible needle be used and that the bevel be oriented in the longitudinal plane of the dural fibers (see below regarding atraumatic needles). It is usually possible to appreciate a a palpable "give" as the needle transgresses the dura, followed by a subtle "pop" on puncturing the arachnoid membrane. At this point, the trocar should be removed slowly from the needle in order to avoid sucking a nerve rootlet into the lumen and causing radicular pain;sciatic pain during the procedure indicates that the needle is placed too far laterally. If the flow of CSF slows, the patient's head can be elevated slowly. The capillary action of the contact of CSF with the edge of a collecting tube can be utilized to speed the flow.

Occasionally, one resorts to gentle aspiration with a small-bore syringe to overcome the resistance of proteinaceous and viscous CSF. Failure to enter the lumbar subarachnoid space after two or three trials can usually be overcome by performing the puncture with the patient in the sitting position and then helping him to lie on one side for pressure measurements and fluid removal. The "dry tap" is more often due to an improperly placed needle than to obliteration of the subarachnoid space by a compressive lesion of the cauda equina or chronic adhesive arachnoiditis. There are few serious complications of LP (beyond the slight risk of inducing brain herniation in the circumstances described above).

The most common is headache, which has been estimated to occur in one-third of patients, but in severe form in far fewer. The pain is presumably the result of a reduction of CSF pressure and tugging on cerebral and dural vessels as the patient assumes the erect posture. Despite its common implementation, recumbency or oral fluid administration after LP has not been shown to prevent headache. In the study by Strupp and colleagues, the use of an atraumatic needle alone almost halved the incidence of headache. (Curiously, headaches are twice as frequent after diagnostic LP as they are after spinal anesthesia.) Patients with generally frequent headaches before LP reportedly have higher rates of headache afterwards. When it is severe, the headache may be associated with vomiting and some neck stiffness. Quite rarely there is unilateral or bilateral sixth nerve or other cranial nerve palsies, even at times without headache.

RADIOGRAPHIC EXAMINATION OF SKULL AND SPINE

For a long time, plain films of the cranium constituted a "routine" part of the study of the neurologic patient, but it is evident that the yield of useful information from this procedure is relatively small.
Even in patients with head injury, where radiography of the skull would seem to be an optimal method of examination, a fracture is found in only 1 of 16 cases, at a cost of thousands of dollars per

fracture and a small risk from radiation exposure. Nevertheless plain skull films are useful in demonstrating fractures, changes in contour of the skull, bony erosions and hyperostoses, infection in paranasal sinuses and mastoids, and changes in the basal foramina. Plain films of the spine are able to demonstrate destructive lesions of vertebrae, both neoplastic and infectious, fracture-dislocations, and Paget disease. Sequential refinements of radiologic technique have greatly increased the yield of valuable information in special cases, but without question the most important recent advances in neuroradiology, and indeed in neurology, have come about with the development of CT and MRI. They represent a quantum leap in our ability to visualize pathology in the living person.

Computed Tomography

In this procedure, conventional x-radiation is attenuated as it passes successively through the skull, CSF, cerebral gray and white matter, and blood vessels. The intensity of the exiting radiation relative to the incident radiation is measured, the data are integrated, and images are reconstructed by computer. This major achievement in mathematical methodology, attributed to Hounsfield and others, permitted the astonishing technologic advance from plain radiographs of the skull to reconstructed images of the cranium and its contents in any plane. More than thirty thousand 2- to 4-mm x-ray beams are directed successively at several horizontal levels of the cranium. The differing densities of bone, CSF, blood, and gray and white matter are distinguishable in the resulting picture. One can see hemorrhage, softened and edematous brain, abscess, and tumor tissue and also the precise size and position of the ventricles and midline structures. The radiation exposure is not significantly greater than that from plain skull films. The latest generation of CT scanners affords pictures of brain, spine, and orbit of great clarity. As illustrated in Fig. 2-1, in transverse section of the brain, one actually sees displayed the caudate and lenticular nuclei and the internal capsules and thalami.

The position and width of all the main sulci can be measured, and the optic nerves and medial and lateral rectus muscles stand out clearly in the posterior parts of the orbit. The brainstem, cerebellum, and spinal cord are easily visible in the scan at appropriate levels. The scans are also useful in imaging parts of the body that surround peripheral nerves and plexuses, thereby demonstrating tumors, inflammatory lesions, and hematomas that involve these nerves. In imaging of the head, CT has a number of advantages over MRI, the most important being safety when metal is present in the body and the clarity of imaging of blood from the moment of bleeding. Other advantages are its lower cost, easy availability, shorter examination time, and superior visualization of calcium, fat, and bone, particularly of the skull base and vertebrae. Also, if constant monitoring and use of life-support equipment is required during the imaging procedure, it is accomplished more readily in the CT than the MRI machine. Recent advances in CT technology (spiral, or helical CT) have greatly increased the speed of the scanning procedure and have made possible the visualization, with great clarity, of the cerebral vasculature (CT angiography;see furtheron).

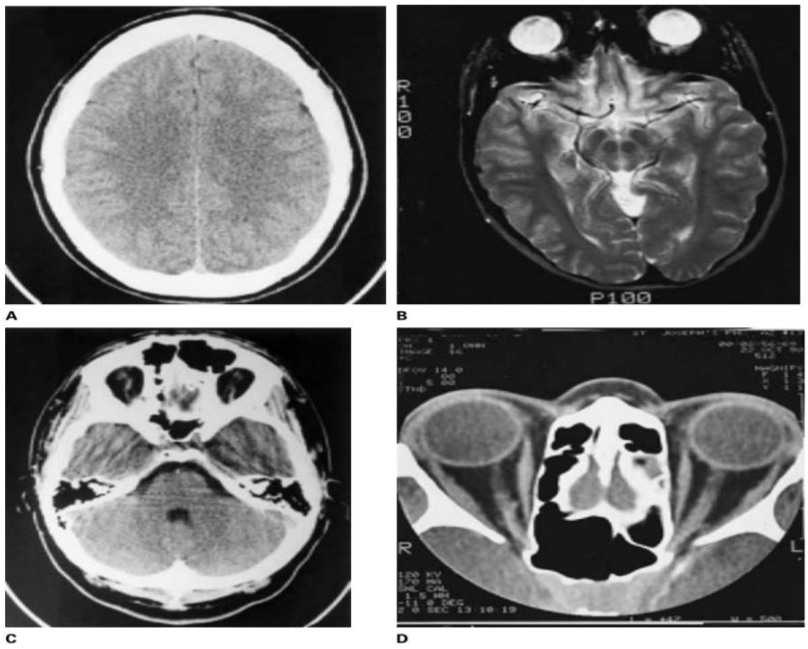


Figure 2-1. Normal axial CT scans of the brain, orbits, and lumbar spine from a young healthy man. *A.* Image through the cerebral hemispheres at the level of the corona radiata. The dense bone of the calvarium is white. Gray matter appears denser than white matter. The triangular shape of the sagittal sinus in axial section is seen posteriorly. *B.* Image at the level of the lenticular nuclei. The caudate and lenticular nuclei are more dense than the internal capsule. CSF within the frontal and occipital horns of the lateral ventricle as well as surrounding the pineal body appears dark. *C.* Image at the level of the posterior fossa. Again, the CSF within the fourth ventricle
and prepontine cisterns appears dark. The basilar artery is seen as a small, round, dense focus anterior to the pons. Typical artifact generated by temporal bones creates streaking across the inferior temporal lobes. The mastoid and sphenoid sinuses are black due to their aeration. *D.* Thin-section axial image through the midorbits. The sclera appears as a dense band surrounding the globe. Medial and lateral rectus muscles have a fusiform shape. Orbital fat appears dark due to its low attenuation value. Air contained within the sphenoid sinus and ethmoid air cells appears black.

By injecting 5 to 25 mL of a water-soluble radiopaque dye through a LP needle and then tipping the patient on a tilt table, the entire spinal subarachnoid space can be visualized. The procedure is almost as harmless as the LP except for cases of complete spinal block, in which high concentrations of dye near the block can cause pain and regional myoclonus. Ruptured lumbar and cervical discs, cervical spondylotic bars and bony spurs encroaching on the spinal cord or roots, and spinal cord tumors can be diagnosed accurately. Iophendylate (Pantopaque), a formerly used fat-soluble dye, is still approved by the FDA but is now employed only in special circumstances(e.g., visualizing the upper level of a spinal canal lesion that completely obstructs the flow of dye from below). If iophendylate is left in the subarachnoid space, particularly in the presence of blood or inflammatory exudate, it may incite a severe arachnoiditisof the spinal cord and brain. The CT body scan also provides excellent images of the spinal canal and intervertebral foramina in three planes, making the combination of water-soluble dye and CT scanning a useful means of visualizing spinal and posterior fossa lesions (Fig. 2-1*E* and *F*). Contrast myelography is particularly useful in visualizing small areas within the spinal canal, such as the lateral recesses and spinal nerve root sleeves. MRI provides even sharper visualization of the
spinal canal and its contents as well as the vertebrae and intervertebral discs;it has therefore largely replaced contrast myelography because it does not require LP.

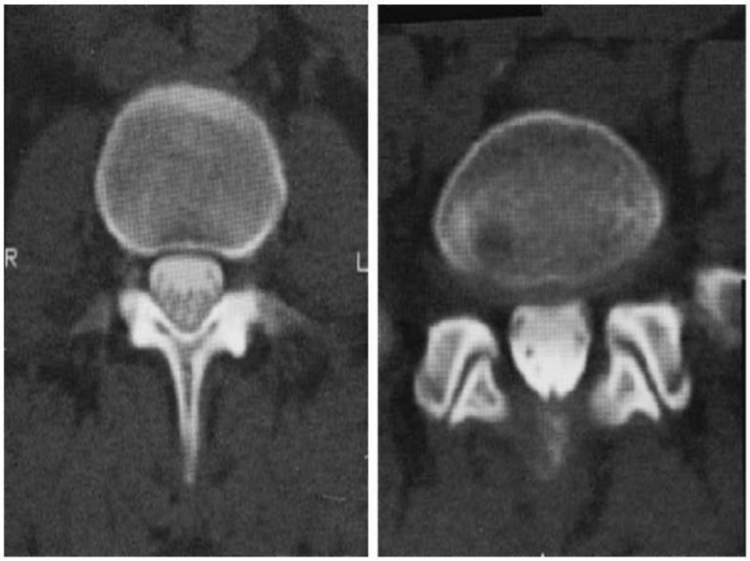


Figure 2-1 (Continued). *E.* and *F.* Axial images of the lumbar spine following myelography. Contrast contained within the thecal sac appears white. The filling defects are caused by nerve roots at the L3-4 and L5-S1 levels. Bony structures appear dense, and the facet joints are well seen. There is no evidence of disc herniation or canal stenosis. (Illustrations courtesy of Dr. Burton Drayer and Dr. Andrew Mancall.)

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI), formerly referred to as nuclear magnetic resonance, also provides "slice" images of the brain in any plane, but it has the great advantages over CT of using nonionizing energy and providing better resolution of different structures within the brain and other organs. For the visualization of most neurologic diseases, MRI is the procedure of choice. An MRI examination is accomplished by placing the patient within a powerful magnetic field, causing certain endogenous isotopes (atoms) of the tissues and CSF to align themselves in the longitudinal orientation of the magnetic field. Application of a brief (few milliseconds) radiofrequency (RF) pulse into the field changes the axis of alignment of the atoms from the longitudinal to the transverse plane. When the RF pulse is turned off, the atoms return to their original alignment. The RF energy that was absorbed and then emitted results in a magnetic signal that is detected by electromagnetic receiver coils. To create contrasting tissue images from these signals, the RF pulse must be repeated many times (a pulse sequence), the signals being measured after the application of each pulse. The scanner stores the signals as a matrix of data, which is subjected to computer analysis and from which an image is constructed. Nuclear magnetic resonance can be detected from several endogenous isotopes, but current technology uses signals derived from hydrogen atoms (1H), because hydrogen is the most abundant element in tissue and yields the strongest magnetic signal. The image is essentially a map of the hydrogen content of tissue, therefore reflecting largely the water concentration, but influenced also by the physical and chemical environment of the hydrogen atoms. Different tissues have different rates of proton relaxation, yielding different signal intensities and hence tissue contrast.

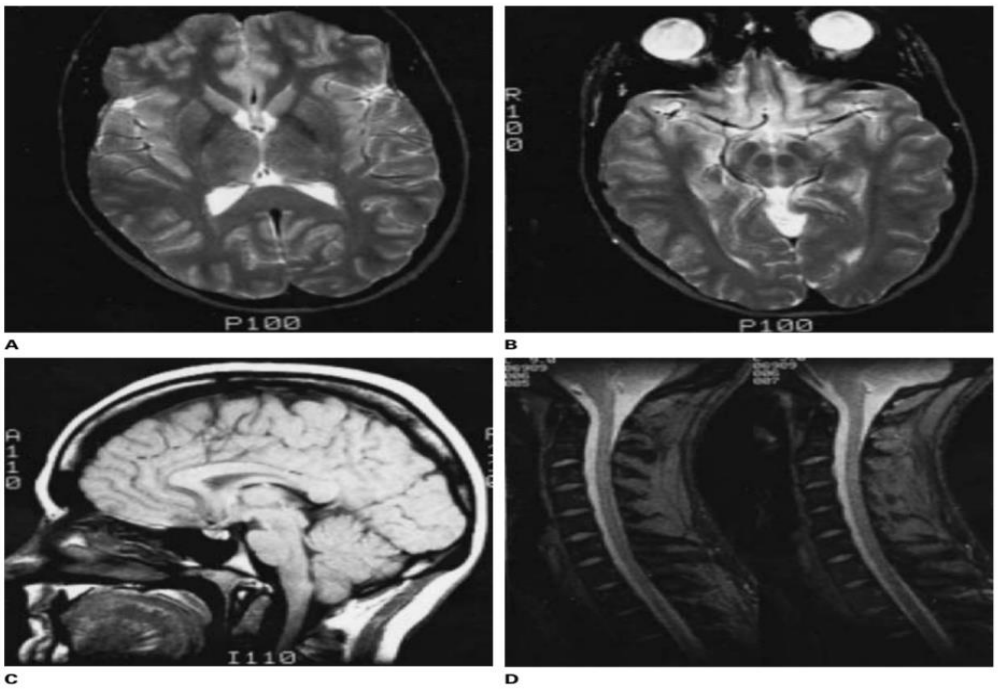
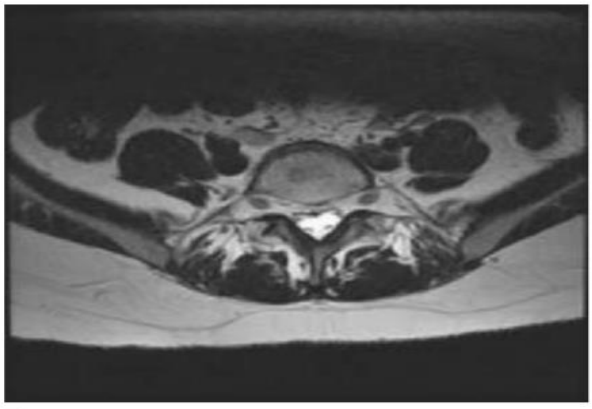


Figure 2-2. Normal MRI of the brain and the cervical and lumbar spine. *A.* T2-weighted (SE 2500/90) axial image at the level of the lenticular nuclei. Note that gray matter appears brighter than white matter. The CSF within the lateral ventricles is very bright. The caudate nuclei, putamen, and thalamus appear brighter than the internal capsule, while the globus pallidus is darker. *B.* T2-weighted (SE 2500/90) axial image at the level of the midbrain. The red nucleus and substantia nigra are dark due to normal iron accumulation. The CSF within the lateral ventricles and subarachnoid spaces appears bright, as does the vitreous. Signal is absent ("flow void") from the rapidly flowing anterior, middle, and posterior cerebral arteries. *C.* T1-weighted (SE 700/17) midline sagittal image of the brain. Note that white matter appears brighter than gray matter and the corpus callosum is well defined. Subcutaneous fat and calvarial marrow appear very bright. The pons, medulla, and cervicomedullary junction are well delineated, and the region of the pituitary gland is normally demonstrated. *D.* Gradient echo sagittal image of the cervical spine. Note the bright signal intensity of the CSF, which provides a "myelographic" effect. Intervertebral discs also demonstrate high signal intensity. The spinal cord and brain demonstrate intermediate signal intensity, and the craniocervical junction is clearly defined.

Angiography:

This technique has evolved over the last 50 years to the point where it is relatively safe and an extremely valuable method for the diagnosis of aneurysms, vascular malformations, narrowed or occluded arteries and veins, arterial dissections, and angiitis. Since the advent of CT and MRI, the use of angiography has practically been limited to the diagnosis of these vascular disorders, and refinements in the former two techniques [MR angiography (MRA) and spiral and helical CT scanning, described further on] promise to eliminate even these applications of conventional x-ray angiography. However, new endovascular procedures for the ablation of aneurysms, arteriovenous malformations, and vascular tumors still require the incorporation of conventional angiography. Following local anesthesia, a needle is placed in the femoral or brachial artery ;a cannula is then threaded through the needle and along the aorta and the arterial branches to be visualized. In this way, a contrast medium can be injected to visualize the arch of the aorta, the origins of the carotid and vertebral

systems, and the extensions of these systems through the neck and into the cranial cavity. Highly experienced arteriographers can visualize the cerebral and spinal cord arteries down to about 0.1 mm in lumen diameter (under optimal conditions) and small veins of comparable size.



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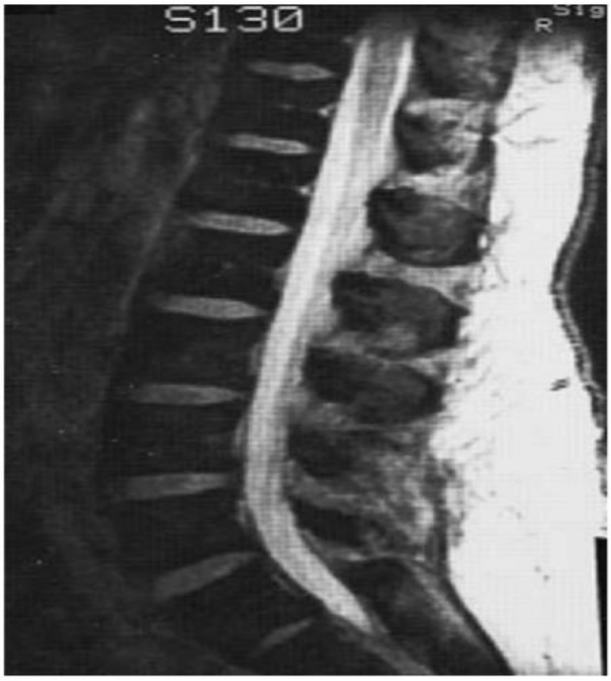

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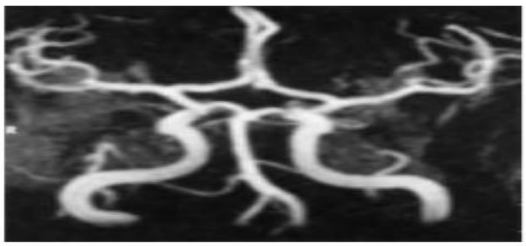
Figure 2-2 (Continued). *E*. T1-weighted (SE 600/20) axial image of the lumbar spine at the L3-4 level. Note that bone marrow appears brighter than disc material. The neural foramina are filled with fat, which demonstrates high signal intensity, and a small amount of fat is present within the spinal canal posterior to the thecal sac. The CSF within the thecal sac is dark, and nerve roots of intermediate signal intensity are demonstrated posteriorly. The facet joints are well seen. *F*. Gradient-echo sagittal image of the lumbar spine. Again, note the bright signal intensity of the CSF, creating a "myelographic" effect. The conus medullaris is well demonstrated, and individual nerve roots can be seen streaming inferiorly.



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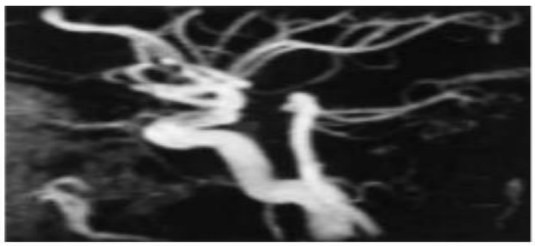

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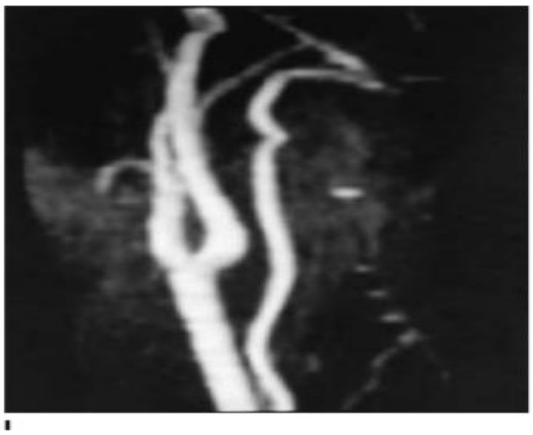

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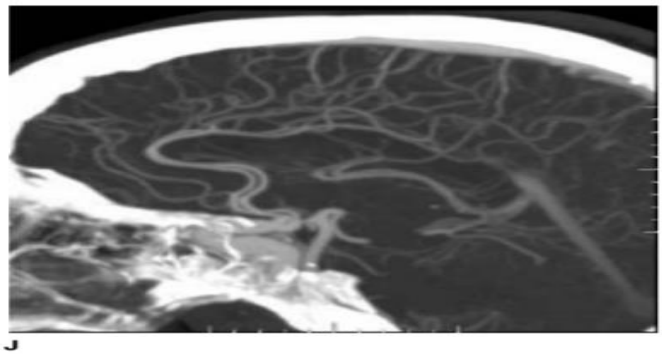

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Magnetic Resonance and Computed Tomographic (Spiral, Helical) Angiography

These are noninvasive techniques for visualizing the main intracranial arteries that can reliably detect intracranial vascular lesions and extracranial carotid artery stenosis. They approach but have not yet reached the radiographic resolution of invasive angiography for distal vessels and for the fine detail of occlusive lesions, but they are very useful in gauging the patency of the large cervical and basal vessels (Fig. 2-2*G* to *I*). Visualization of the cerebral veins is also possible. Unlike MR angiography, the CT technique requires the injection of intravenous dye but has the great advantage of showing blood vessels and their anomalies in relation to adjacent brain and bone (Fig. 2-2*J*). The use of these and other methods for the investigation of carotid artery disease (ultrasound Doppler flow and imaging techniques) is discussed further below and in Chap.34, on cerebral vascular disease.

Positron Emission Tomography

This technique, commonly known as PET, measures the regionalcerebral concentration of systemically administered radioactive tracers. Positron-emitting isotopes (usually 11C, 18F, 13N, and 15O) are produced in a cyclotron or linear accelerator and incorporated into biologically active compounds in the body. The concentration of the tracers in various parts of the brain is determined noninvasively, by detectors outside the body, and tomographic images are constructed by techniques similar to those used in CT and MRI. Local patterns of cerebral blood flow, oxygen uptake, and glucose utilization can be measured by PET scanning, and the procedure has proved to be of value in grading primary brain tumors, distinguishing tumor tissue from radiation necrosis, localizing epileptic foci, and differentiating types of dementing diseases. The ability of the technique to quantitate neurotransmitters and their receptors promises to be of importance in the study of Parkinson disease and other degenerative diseases. This technology is found in relatively few medical centers and requires costly facilities and support staff;it is therefore not utilized for routine diagnosis.

Single-Photon Emission Computed Tomography (SPECT)

This technique, which has evolved from PET, utilizes isotopes that do not require a cyclotron for their production. Here also radioligands (usually containing iodine) are incorporated into biologically active compounds, which, on decay, emit only a single photon. This procedure allows the study of regional cerebral blood flow under conditions of cerebral ischemia or during intense tissue metabolism. The restricted anatomic resolution provided by SPECT has limited its clinical usefulness, but its wider availability makes it appealing for clinical use. This has proved particularly true in helping to distinguish between Alzheimer dementia and a number of focal cerebral (lobar) atrophies and in the localization of epileptic foci in patients who are candidates for cortical resection. Once injected, the isotope localizes rapidly in the brain, with regional absorption proportional to blood flow, and is then stable for an hour or more. It is thus possible to inject the isotope at the time of the seizure onset, while the patient is undergoing video and electroencephalographic monitoring, and to scan the patient later. As with PET, the clinical potential of this technique has yet to be fully realized.

Ultrasound Scanning

In recent years this technique has been refined to the point where it has become a principal methodology for clinical study of the fetal and neonatal brain and an important ancillary test for the cerebral vessels and the heart in adults. The instrument for this application consists of a transducer

capable of converting electrical energy to ultrasound waves of a frequency ranging from 5 to 20 kHz. These are transmitted through the intact skull into the brain. The different tissues have a variable acoustic impedance and send echoes back to the transducer, which displays them as waves of variable height or as points of light of varying intensity. In this way, one can obtain images of choroid plexuses, ventricles, and central nuclear masses. Usually several coronal and parasagittal views are obtained by placing the transducer over open fontanelles or the thin calvarium of an infant. Intracerebral and subdural hemorrhages, mass lesions, and congenital defects can readily be visualized.

Similar instruments are used to insonate the basal vessels of the circle of Willis ("transcranial Doppler"), the cervical carotid and vertebral arteries, and the temporal arteries for the study of cerebrovascular disease. Their greatest use is in detecting and estimating the degree of stenosis of the origin of the internal carotid artery. In addition to providing a sound image of the vascular structures, the Doppler frequency shift caused by flowing red blood cells creates a display of velocities at each site in a vessel. The two techniques combined have been called "carotid duplex"; they allow an accurate localization of the locus of maximal stenosis as reflected by the highest rates of flow and turbulence. The display scale for the Doppler shift is color-coded in order to make the insonated image and flow map easy to view and interpret. The transcranial Doppler utilizes a 2-MHz pulsed signal that is able to transgress the calvarial bone in adults and then receives a frequency-shifted signal from the blood flowing in the lumen of the basal vessels. This allows the detection of vascular stenoses and the greatly increased blood flow velocity caused by vasospasm from subarachnoid hemorrhage.

Clinical Significance of Minor EEG Abnormalities

The gross EEG abnormalities discussed above are by themselves clearly abnormal, and any formulation of the patient's clinical state should attempt to account for them. These abnormalities include seizure discharges, generalized and extreme slowing, definite slowing with a clear-cut asymmetry or focal slowing or suppression of amplitude, and absence of normal rhythms. Lesser degrees of these abnormalities form a continuum between the undoubtedly abnormal and the completely normal and are of correspondingly minor significance. Findings such as 14- and 6-per-second positive spikes or small sharp waves during sleep, scattered 5- or 6-per-second slowing, minor voltage asymmetries, and persistence of "breakdown" for a few minutes after hyperventilation are interpreted as borderline abnormalities. The latter abnormalities may be meaningful, but only if correlated with particular clinical phenomena. Whereas borderline deviations in an otherwise entirely normal person have no clinical significance, the same minimal EEG findings associated with particular clinical signs and symptoms become important. The significance of a normal or "negative" EEG in certain patients suspected of having a cerebral lesion has been discussed above. In summary, the results of the EEG, like those of the EMG and electrocardiogram, are meaningful only in relation to the illnesses under consideration and the clinical state of the patient at the time the recordings were made.

Evoked Potentials

The stimulation of sense organs or peripheral nerves evokes an electrical response in the corresponding cortical receptive areas and in a number of subcortical relay stations. However, one cannot place a recording electrode near the nuclear relay stations, nor can one detect tiny potentials of only a few microvolts among the much larger background activity in the EEG or EMG. The use of averaging methods, introduced by Dawson in 1954, and the subsequent development of computer techniques have provided the means of overcoming these problems. Initially, emphasis was on the study of late waves (over 75 ms after the stimulus) because they are of high amplitude and easy to record. However, there is more clinical utility in recording the much smaller, so-called short-latency waveforms, which are received at each nuclear relay within the main sensory systems. These waveforms are maximized by the computer to a point where their latency and voltage can easily be measured. One of the most remarkable properties of evoked potentials is their resistance to anesthesia, sedative drugs, and—in comparison with EEG activity—even damage of the cerebral hemispheres. This permits their use for monitoring the integrity of cerebral pathways in situations that render the EEG useless. The details of these techniques are reviewed in Chiappa's monograph. The interpretation of evoked potentials (visual, auditory, and somatosensory) is based on the prolongation of the latencies of the waveforms after the stimulus, the interwave latencies, and asymmetries in timing. Norms have been established, but it is still advisable to confirm these in each laboratory. Typically 2.5 or 3 standard deviations above the mean latency for any measurement is taken as the definition of abnormality.

Visual Evoked Potentials

For many years it had been known that a light stimulus flashing on the retina often initiates a discernible waveform over the occipital lobes. In the EEG, such responses to fast rates of stimulation are referred to as the occipital driving response (Fig. 2-3B and C). In 1969, Regan and Heron observed that a visual evoked response could be produced by the sudden change of a viewed checkerboard pattern. The responses produced by rapidly repeating the pattern reversal, were easier to detect and measure than flash responses and more consistent in waveform from one individual to another. It became apparent that this type of stimulus, applied first to one eye and then to the other, could demonstrate conduction delays in the visual pathways of patients who had formerly suffered a disease of the optic nerve—even when there were no residual signs of reduced visual acuity, visual field abnormalities, alterations of the optic nerve head, or changes in pupillary reflexes. This procedure, called pattern-shift visual evoked responses (PSVER, or VER) or pattern-reversal visual evoked potentials, has been widely adopted as one of the most delicate tests of lesions in the visual system. Figure 2-4 illustrates the normal PSVER and two types of delayed responses. Usually, abnormalities in the amplitude and duration of PSVER accompany the abnormally prolonged latencies, but they are difficult to quantify. The expected latency for the positive polarity PSVER is near 100 ms (thus the term "P 100");an absolute latency over approximately 118 ms or a difference in latencies of greater than 9 ms between the two eyes signifies involvement of one optic nerve (Table 2-4). Bilateral prolongation of latencies, demonstrated by separate stimulation of each eye, can be due to lesions in both optic nerves, the optic chiasm, or the visual pathways posterior to the chiasm.

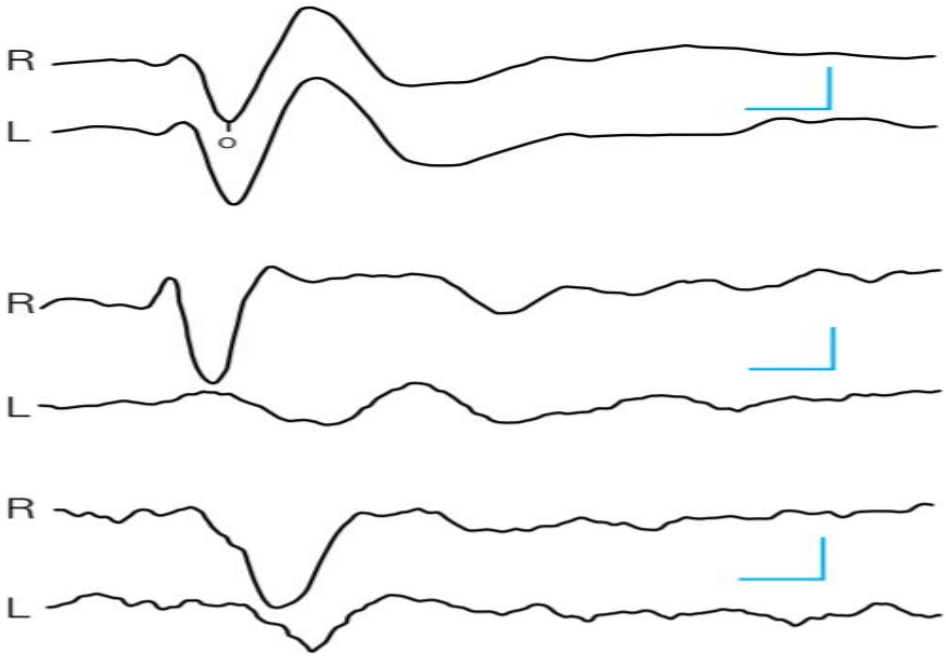

Figure 2-4. Pattern-shift visual evoked responses (PSVERs). Latency measured to first major positive peak (termed "P100" because of its latency from the stimulus of approximate 100 msec). Upper two tracings: These, from the right and left eyes, are normal. Middle tracings: PSVER from the right eye is normal but the latency of the response from the left eye is prolonged and its duration is increased. Lower tracings: PSVER from both eyes show abnormally prolonged latencies, somewhat greater on the left than on the right. Calibration: 50 ms, 2.5 *m*V. (Adapted by permission from Shahrokhi et al.)

As indicated above, PSVER is especially valuable in proving the existence of active or residual disease of an optic nerve. Examinations of large numbers of patients who were known to have had retrobulbar (optic) neuritis has shown that only a small proportion will have normal latencies. Furthermore, similar abnormalities of PSVER are found in about one-third of multiple sclerosis patients who have no history or clinical evidence of optic nerve involvement. This acquires significance in that the finding of abnormal PSVER in a patient with a clinically apparent lesion elsewhere in the CNS may usually be taken as evidence of multiple sclerosis. A compressive lesion of an optic nerve will have the same effect as a demyelinative one. Many other diseases of the optic nerves—including toxic and nutritional amblyopias, ischemic optic neuropathy, and the Leber type of hereditary optic neuropathy— show abnormalities of the PSVER. Glaucoma and other diseases involving structures anterior to the retinal ganglion cells may also produce increased latencies. Impaired visual acuity has little effect on the latency but does correlate well with the amplitude of the PSVER (a property that is exploited in computerized testing for visual acuity). By presenting the pattern-shift stimulus to one hemifield, it is sometimes possible to isolate a lesion to an optic tract or radiation, or one occipital lobe, but with less precision than that provided by the usual monocular test.

Brainstem Auditory Evoked Potentials

The effects of auditory stimuli can be studied in the same way as visual ones by a procedure called brainstem auditory evoked responses or potentials (BAERs or BAEPs). Between 1000 and 2000 clicks, delivered first to one ear and then to the other, are recorded through scalp electrodes and maximized by computer. A series of seven waves appears at the scalp within 10 ms after each stimulus. On the basis of depth recordings and the study of lesions produced in cats as well as pathologic studies of the brainstem in humans, it has been determined that each of the first five waves is generated by the brainstem structures indicated in Fig. 2-5. The generators of waves VI and VII are uncertain. Clinical interpretations of BAERs are based mainly on latency measurements of waves I, III, and V. The most important are the interwave latencies between I and III and III and V (see Table 2-4). The presence of wave I and its absolute latency are of particular value in testing the integrity of the auditory nerve. A lesion that affects one of the relay stations or its immediate connections manifests itself by a delay in its appearance and an absence or reduction in amplitude of subsequent waves. These effects are more pronounced on the side of the stimulated ear than contralaterally.

This is difficult to understand, since a majority of the cochlear-superior olivary-lateral lemniscal-medial geniculate fibers cross to the opposite side. It is also surprising that a severe lesion of one relay station would allow impulses, even though delayed, to continue their ascent and be recordable in the cerebral cortex. As indicated above, BAEPs are a particularly sensitive means of detecting lesions of the eighth cranial nerve (acoustic neuroma and other tumors of the cerebellopontine angle) and of the auditory pathways of the brainstem. Almost one-half of patients with definite multiple sclerosis and a lesser number with a possible or probable diagnosis of this disease will show abnormalities of the BAEPs (usually a prolongation of interwave latencies I to III or III to V), even in the absence of clinical symptoms and signs of brainstem disease. The BAEPs are also useful in assessing hearing in infants who have been exposed to ototoxic drugs, in young children who cannot cooperate with audiometry, and in hysterical patients who feign deafness

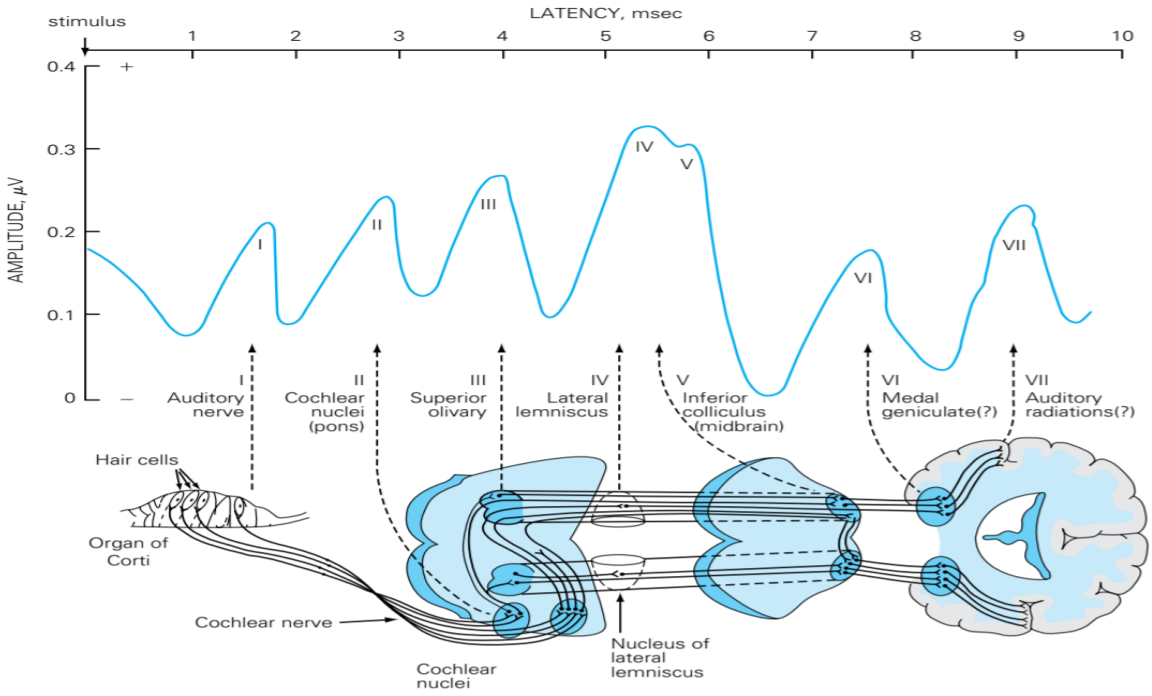

Figure 2-5. Short-latency brainstem auditory evoked responses (BAERs). Diagram of the proposed electrophysiologic-anatomic correlations in human subjects. Waves I through V are the ones measured in clinical practice.

Somatosensory Evoked Potentials

Somatosensory evoked potentials (SEPs) are used in most clinical neurophysiology laboratories to confirm lesions in the somatic sensory systems. The technique consists of applying 5-per-second painless transcutaneous electrical stimuli to the median, peroneal, and tibial nerves and recording the evoked potentials (for the upper limb) as they pass the brachial plexus over Erb's point above the clavicle, over the C2 vertebra and over the opposite parietal cortex, and (for the lower limb) sequentially over the lumbar roots of the cauda equina, the nuclei over the cervical spine, and the opposite parietal cortex. The impulses generated in large touch fibers by 500 or more stimuli and averaged by computer can be traced through the peripheral nerves, spinal roots, and posterior columns to the nuclei of Burdach and Goll in the lower medulla, through the medial lemniscus to the contralateral thalamus, and thence to the sensory cortex of the parietal lobe. Delay between the stimulus site and Erb's point or lumbar spine indicates peripheral nerve disease;delay from Erb's point (or lumbar spine) to C2 implies an abnormality in the appropriate nerve roots or more frequently in the posterior columns;the presence of lesions in the medial lemniscus and thalamoparietal pathway can be inferred from delays of subsequent waves recorded from the parietal cortex (Fig. 2-6). The normal waveforms are designated by the symbols P (positive) and N (negative), with a number indicating the interval of time in milliseconds from stimulus to recording (e.g., N 11, N 13, P 13, P 22, etc.). As shorthand for the polarity and approximate latency, the summated wave that is recorded at the cervicomedullary junction is termed N/P 13, and the cortical potential from median nerve stimulation is seen in two contiguous waves of opposite polarity is called N 19–P 22. The corresponding cortical wave after tibial or peroneal nerve stimulation is call ed N/P 37. For purposes of clinical interpretation, the SEPs are assumed to be linked in series, so that interwave abnormalities

in latency indicate a conduction defect between the generators of the two peaks involved (Chiappa and Ropper). Normal values are shown in Table 2-4. Recordings with pathologically verified lesions at these levels are to be found in the monograph by Chiappa. This test has been most helpful in establishing the existence of lesions in spinal roots, posterior columns, and brainstem in disorders such as the Guillain-Barre´ syndrome, ruptured lumbar and cervical discs, multiple sclerosis, and lumbar and cervical spondylosis when the clinical data are uncertain. The central counterpart also pertains— namely, that obliteration of the cortical waves (assuming that all preceding waves are unaltered) reflects profound damage to the somatosensory pathways in the hemisphere or to the cortex itself. As corollaries, the bilateral absence of cortical somatosensory waves after cardiac arrest is a powerful predictor of a poor clinical outcome;the persistent absence of a cortical potential after stroke usually indicates such profound damage that only a limited clinical recovery is to be expected.

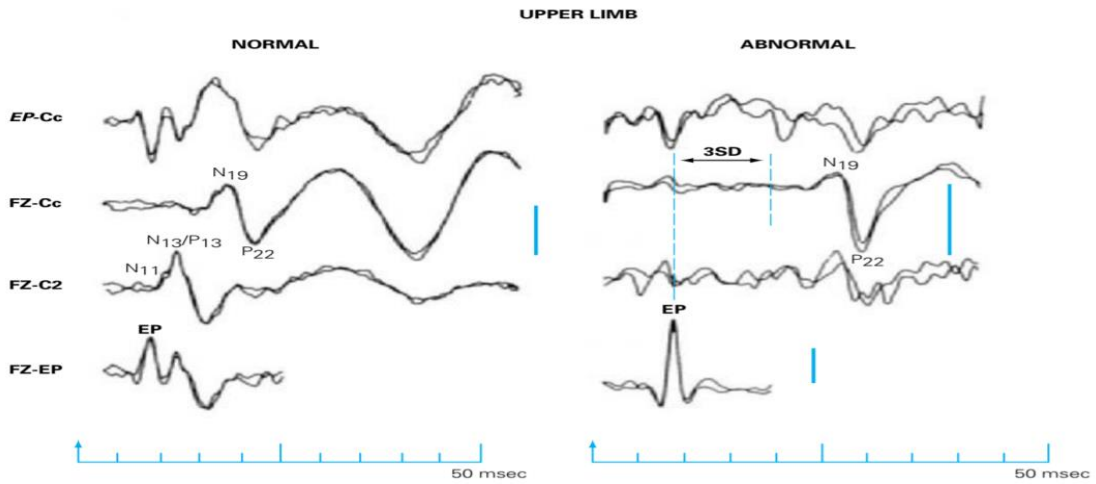

Figure 2-6. Short-latency SSEPs produced by stimulation of the **median nerve** at the wrist. The set of responses shown at left is from a normal subject; the set at right is from a patient with multiple sclerosis who had no sensory symptoms or signs. In the patient, note the preservation of the brachial-plexus component (EP), the absence of the cervical-cord (N 11) and lower-medullary components (N/P 13), and the latency of the thalamocortical components (N 19 and P 22), prolonged markedly above the normal mean 13 S.D. for the separation from the brachial plexus. Unilateral stimulation occurred at a frequency of 5 per second. Each trace is the averaged response to 1024 stimuli; the superimposed trace represents a repetition to demonstrate waveform consistency. Recording electrode locations are as follows: FZ denotes midfrontal; EP, Erb's point (the shoulder); C2, the middle back of the neck over the C2 cervical vertebra; and Cc, the scalp overlying the sensoriparietal cortex contralateral to the stimulated limb.

CLASSIFICATION OF SEIZURES

Seizures have been classified in several ways: according to their supposed etiology, i.e., idiopathic (primary) or symptomatic (secondary); their site of origin; their clinical form (generalized or focal); their frequency (isolated, cyclic, or repetitive, or the closely spaced sequence of status epilepticus); or their electrophysiologic correlates. A distinction must be made between the classification of seizures (the clinical manifestations of epilepsy: grand mal, petit mal, myoclonic, partial, and others), considered below, and the classification of the epilepsies, or epileptic syndromes, which are disease constellations, most of which may manifest several seizure types. These are discussed later in the chapter. The classification to be followed here was first proposed by Gastaut in 1970 and was then refined repeatedly by the Commission on Classification and Terminology of the International League Against Epilepsy (1981). This classification, based mainly on the clinical form of the seizure and its electroencephalographic (EEG) features, has been adopted worldwide and is generally referred to as the International Classification. A modified version of it is reproduced in Table 16-1. The strength of the International Classification lies in its easy applicability to patients with epilepsy and its universal

adoption. The main value of classifying a seizure by its clinical and EEG features is the reasonable predictability of response to specific medications and to some extent in prognosis. Basically, this classification divides seizures into two types—partial, in which a focal or localized onset can be discerned, and generalized, in which the seizures appear to begin bilaterally. It is also useful clinically and etiologically to separate epilepsies that originate as truly generalized electrical discharges in the brain from those which spread secondarily from a focus to become generalized. The primary generalized epilepsies are a group of somewhat diverse, age-dependent phenotypes that are characterized by generalized 2.5- to 4-Hz bifrontally predominant spikes or polyspike-and-slow-wave discharges that arise without underlying structural abnormalities. In most instances, these individuals have normal intelligence. What is most significant is that a genetic component underlies many of these disorders (see below). By contrast, seizures that begin locally and evolve into generalized tonic-clonic seizures, termed secondary generalized seizures, generally have no such genetic component and are usually the result of underlying brain disease, either acquired or due to congenital malformations or metabolic defects. Quite often, the initial focal phase is missed, leading to misdiagnosis.

Individuals with secondary generalized epilepsies tend to have more diffuse brain dysfunction and may have a progressive course. These seizures may be of different types, including atonic, myoclonic, and tonic-clonic seizures. An increasing frequency and severity of this group of disorders with age reflects the accumulation of focal insults from trauma, strokes, and other damage. Partial or focal seizures are further classified as simple when consciousness is undisturbed and complex when consciousness is altered or impaired. Simple partial seizures are further classified according to their main clinical manifestations—motor, sensory, autonomic, or psychic. When one of these subjective manifestations precedes the progression of the attack to a loss of consciousness, it is referred to as an aura and has commonly been regarded as a premonitory sign or warning of the impending seizure. In reality, the aura represents the initial phase of a focal seizure; in some instances it may constitute the entire epileptic attack. Generalized seizures are of two types—convulsive and nonconvulsive. The common convulsive type is the tonic-clonic (grand mal) seizure. Less common is a purely tonic, purely clonic, or clonic-tonic-clonic generalized seizure.

The classic nonconvulsive generalized seizure is the brief lapse of consciousness or absence (petit mal); included also under this heading are minor motor phenomena such as brief myoclonic, atonic, or tonic seizures. The classification of seizures and of the epilepsies is constantly being modified. In one of the latest versions, the so-called syndromic classification (Epilepsia 30:389, 1989), an attempt has been made to incorporate all of the seizure types and epileptic syndromes and to categorize them not only as partial and generalized but also according to their age of onset, their primary or secondary nature, the evidence of cortical loci of the epileptogenic lesions, and the many clinical settings in which they occur. This classification is semantically difficult and, in our view, too complicated as yet for general clinical application. Since many epileptic syndromes share overlapping features, it is often not possible to fit a newly diagnosed case of epilepsy into a specific category in this new classification (Manford et al). The commission is engaged in an extensive revision of terminology and classification in the field of epilepsy. Until this revision is widely adopted, we propose to begin our discussion with the 1981 classification of seizures, with certain modifications and additions, to be followed by a consideration of a number of well-defined epilepsies and epileptic syndromes. In the discussions that follow, the various types of seizures are viewed largely in the context of the age at which they occur. An approximation of the distribution of the seizure types for

each age epoch, obtained and aggregated from several sources, is shown in Fig. 16-1. There has also been substantial progress in defining the molecular basis of familial and hereditary epilepsies over the last decade; it is highly likely that these new insights will lead to further modification of both the clinical classifications and the therapeutic management of the epilepsies (see further on).

GENERALIZED SEIZURES

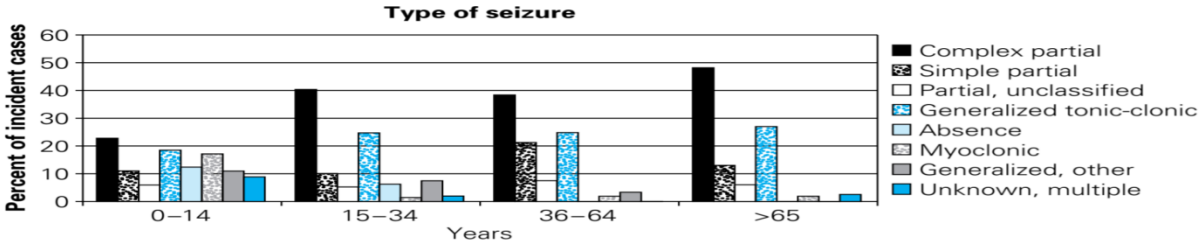

Figure 16-1. The distribution of the main types of epilepsy by age. Apparent is the overrepresentation of absence and myoclonic seizures in childhood and of complex partial seizures in older individuals. (Adapted from Hauser and Annegers and the texts of Engel and of Pedley.)

The Generalized Tonic-Clonic Seizure (Grand Mal) As has already been pointed out, it is important, whenever possible, to distinguish between a primary (generalized) type of seizure, with widespread EEG abnormalities at the onset, and a secondarily generalized type, which begins as a focal or partial seizure and then becomes generalized. The patient sometimes senses the approach of a seizure by one of several subjective phenomena (a prodrome). For some hours, the patient may feel apathetic, depressed, irritable, or, very rarely, the opposite—ecstatic. One or more myoclonic jerks of the trunk or limbs on awakening may herald a seizure later in the day. In more than half the cases, there is some type of movement for a few seconds before consciousness is lost (turning of the head and eyes or whole body or intermittent jerking of a limb), although the patient fails to form a memory of this and such information is obtained only from an observer.

Abdominal pains or cramps, a sinking, rising, or gripping feeling in the epigastrium, pallor or redness of the face, throbbing headache, constipation, or diarrhea have also been given prodromal status, but we have not found them consistently enough to be helpful. Most often, the seizure strikes “out of the blue,” i.e., without warning, beginning with a sudden loss of consciousness and fall to the ground. The initial motor signs are a brief flexion of the trunk, an opening of the mouth and eyelids, and upward deviation of the eyes. The arms are elevated and abducted, the elbows semiflexed, and the hands pronated. These are followed by a more protracted extension (tonic) phase, involving first the back and neck, then the arms and legs. There may be a piercing cry as the whole musculature is seized in a spasm and air is forcibly emitted through the closed vocal cords. Since the respiratory muscles are caught up in the tonic spasm, breathing is suspended, and after some seconds the skin and mucous membranes may become cyanotic. The pupils are dilated and unreactive to light. The bladder may empty at this stage or later, during the postictal coma. This is the tonic phase of the seizure and lasts for 10 to 20 s. There then occurs a transition from the tonic to the clonic phase of the convulsion. At first there is a mild generalized tremor, which is, in effect, a repetitive relaxation of the tonic contraction. It begins at a rate of eight per second and coarsens to four per second; then it rapidly gives way to brief, violent flexor spasms that come in rhythmic salvos and agitate the entire

body. The face becomes violaceous and contorted by a series of grimaces, and often the tongue is bitten. Autonomic signs are prominent: the pulse is rapid, blood pressure is elevated, pupils are dilated, and salivation and sweating are abundant; bladder pressure may increase sixfold during this phase. The clonic jerks decrease in amplitude and frequency over a period of about 30 s. The patient remains apneic until the end of the clonic phase, which is marked by a deep inspiration. Instead of the whole dramatic sequence described above, the seizures may be abbreviated or limited in scope by anticonvulsive medications. In the terminal phase of the seizure, all movements have ended and the patient lies still and limp, in a deep coma.

The pupils, equal or unequal, now begin to contract to light. Breathing may be quiet or stertorous. This state persists for several minutes, after which the patient opens his eyes, begins to look about, and is obviously bewildered and confused and may be quite agitated. The patient may speak and later not remember anything that he said. Undisturbed, he becomes drowsy and falls asleep, sometimes for several hours, then sometimes awakens with a pulsatile headache. When fully recovered, such a patient has no memory of any part of the spell but knows that something has happened because of the strange surroundings (in ambulance or hospital); the obvious concern of those around him; and a sore, bitten tongue and aching muscles from the violent contractions. The latter, if violent enough, may crush a vertebral body or result in a serious injury; a fracture, periorbital hemorrhages, subdural hematoma, or burn may have been sustained in the fall. Each of these phases of the generalized tonic-clonic seizure has its characteristic EEG accompaniment. Initially, movement artifacts obscure the EEG changes; sometimes there are repetitive spikes or spike-wave discharges lasting a few seconds, followed by an approximately 10-s period of 10-Hz spikes. As the clonic phase asserts itself, the spikes become mixed with slow waves and then the EEG slowly assumes a polyspike-and-wave pattern. When all movements have ceased, the EEG tracing is nearly flat for a variable time, and then the brain waves resume their preseizure pattern.

Convulsions of this type ordinarily come singly or in groups of two or three and may occur when the patient is awake and active or during sleep, or frequently when falling asleep or awakening. Some 5 to 8 percent of such patients will at some time have a prolonged series of such seizures without resumption of consciousness between them; this is called convulsive status epilepticus and demands urgent treatment. Sometimes the first outburst of seizures takes the form of convulsive status. Few clinical states closely simulate a grand mal convulsion, but several are worthy of mention. One is a clonic jerking of the extended limbs (usually less severe than those of a grand mal seizure) that occurs with vasodepressor syncope or a Stokes-Adams attack. In contrast to an epileptic type of EEG, the brain waves are slow and flat during the jerking movements. A rarer phenomenon that may be indistinguishable from a generalized convulsion occurs as part of basilar artery occlusion (Ropper). This presumably has its basis in ischemia of the corticospinal tracts in the pons; a similar ischemic mechanism in the cortex has been invoked for “limbshaking TIAs” (transient ischemic attacks), in which there are clonic movements of one limb or one side of the body during an episode of cerebral ischemia. Hysterical (nonepileptogenic, “psychogenic”) seizures, as discussed further on, are often difficult to distinguish from a true seizure. Rarely, in adults, an attack of panic (page 438) or the rare entity of rapid-eye-movement (REM) sleep.

Idiopathic Nonconvulsive Seizures (Absence, Petit Mal)

In contrast to major generalized seizures, absence seizures (formerly referred to as petit mal or pykno-epilepsy) are notable for their brevity and the paucity of motor activity. Indeed, they may be so brief that the patients themselves are sometimes not aware of them; to an onlooker, they resemble a moment of absentmindedness or daydreaming. The attack, coming without warning, consists of a sudden interruption of consciousness, for which the French word absence ("not present," "not in attendance") has been retained. The patient stares and briefly stops talking or ceases to respond. Only about 10 percent of such patients are completely motionless during the attack; in the remainder, one observes a brief burst of fine clonic movements of the eyelids, facial muscles, or fingers or synchronous movements of both arms at a rate of three per second. This rate corresponds to that of the EEG abnormality, which takes the form of a generalized three-per-second spike-andwave pattern (Fig. 2-3E, page 26). Minor automatisms—in the form of lip-smacking, chewing, and fumbling movements of the fingers—are common during an attack but do not assume prominence.

Postural tone may be slightly decreased or increased, and occasionally there is a mild vasomotor disorder. As a rule, such patients do not fall; they may even continue such complex acts as walking or riding a bicycle. After 2 to 10 s, occasionally longer, the patient re-establishes full contact with the environment and resumes preseizure activity. Only a loss of the thread of conversation or the place in reading betrays the occurrence of the momentary "blank" period (the absence). In many such patients, voluntary hyperventilation for 2 to 3 min is an effective way of inducing absence attacks. Typical absence seizures constitute the most characteristic epilepsy of childhood; rarely do the seizures begin before 4 years of age or after puberty. Another attribute is their great frequency (hence the old term pykno, meaning "compact" or "dense"). As many as several hundred may occur in a single day, sometimes in bursts at certain times of the day. Most often they relate to periods of inattention and may appear in the classroom when the child is sitting quietly rather than participating actively in his lessons. If frequent, they may disturb attention and thinking to the point that the child's performance in school is impaired. Such attacks may last for hours with no interval of normal mental activity between them— so-called absence or petit mal status. Small, subtle threeper-second myoclonic movements are the only motor display (myoclonic petit mal), and are accompanied by a continuous threeper-second spike-wave abnormality in the EEG. Most cases of absence status have been described in adults with frontal lobe epilepsy (see below). Such attacks may begin or end with a generalized tonic-clonic seizure or a burst of seizures.

Absence may be the only type of seizure during childhood. The attacks tend to diminish in frequency in adolescence and then often disappear, only to be replaced in many instances by major generalized seizures. Absence or Petit Mal Variants To be distinguished from typical absence seizures are varieties in which the loss of consciousness is less complete or in which myoclonus is prominent, and others in which the EEG abnormalities are less regularly of a 3-per-second spike-and-wave type (they may occur at the rate of 2 to 2.5 per second or take the form of 4- to 6-Hz polyspike-and-wave complexes). Atypical petit mal is a term that was coined to describe long runs of slow spike-and-wave activity, usually with no apparent loss of consciousness. External stimuli such as asking the patient to answer a question or to count will interrupt the run of abnormal EEG activity. About one-third of children with absence attacks will, in addition, display symmetrical or asymmetrical myoclonic jerks without loss of consciousness, and about half will also at some time have major generalized (tonic-clonic) convulsions. As described further on, a common and relatively benign variety of myoclonic

seizure occurs in late childhood and adolescence (juvenile myoclonic epilepsy). In sharp contrast to the aforementioned epilepsies is a form that has its onset between 2 and 6 years of age and is characterized by atonic, or astatic, seizures (i.e., falling attacks), often succeeded by various combinations of minor motor, tonic-clonic, and partial seizures and by progressive intellectual impairment in association with a distinctive, slow (1- to 2-Hz) spike-and-wave EEG pattern. This is the Lennox-Gastaut syndrome. Often it is preceded in earlier life by infantile spasms, a characteristic EEG picture (3-Hz "hypsarrhythmia"), and an arrest in mental development, a triad sometimes referred to as the West syndrome (see further on). The early onset of atonic seizures with abrupt falls, injuries, and associated abnormalities nearly always has a grave implication— namely, the presence of serious neurologic disease. Prematurity, perinatal injury, and metabolic diseases of infancy are the most common underlying conditions. This is essentially a symptomatic generalized epilepsy, in contrast to the foregoing idiopathic types. The LennoxGastaut syndrome may persist into adult life and is one of the most difficult forms of epilepsy to treat. The notion that absence, myoclonic, and akinetic seizures constitute a petit mal triad, as originally proposed by Lennox, has been generally abandoned. Akinesia (motionlessness) is not unique to any seizure type. The typical absence, with or without myoclonic jerks, rarely causes the patient to fall and should be considered a separate entity because of its relative benignity.

Myoclonic Seizures

The phenomenon of myoclonus has already been discussed in Chap. 6, where the relationship to seizures was indicated. Characterized by a brusque, brief, muscular contraction, some myoclonic jerks are so small as to involve only one muscle or part of a muscle; others are so large as to implicate a limb on one or both sides of the body or the entire trunk musculature. Many are brief, lasting 50 to 100 ms. They may occur intermittently and unpredictably or present as a single jerk or a brief salvo. As mentioned earlier, an outbreak of several small, rhythmic myoclonic jerks may appear with varying frequency as part of absence seizures and as isolated events in patients with generalized clonic-tonic-clonic or tonic-clonic seizures. As a rule, these types of myoclonus are quite benign and respond well to medication. In contrast, disseminated myoclonus (polymyoclonus), having its onset in childhood, raises the suspicion of acute viral encephalitis, the myoclonus-opsoclonus-ataxia syndrome of Kinsbourne, lithium or other drug toxicity, or, if lasting a few weeks, subacute sclerosing panencephalitis. Chronic progressive polymyoclonus with dementia characterizes the group of juvenile lipidosis, Lafora- type familial myoclonic epilepsy, certain mitochondrial disorders, or other chronic familial degenerative diseases of undefined type (paramyoclonus multiplex of Friedreich, dyssynergia cerebellaris myoclonica of Ramsay Hunt). In middle and late adult years, disseminated myoclonus joined with dementia usually indicates the presence of so-called Creutzfeldt-Jakob disease (page 653) and rarely of Alzheimer disease. A few late-onset cases of Lafora disease have been reported (Messouak et al), but this remains mainly a childhood process, autosomal recessive in transmission, characterized by a triad of progressive dementia, myoclonus, and episodes of generalized seizures, some of which are visual in nature. Intraneuronal cortical inclusions of amyloid are found, and similar inclusions are found in muscle, liver, and skin (polyglucosan body disease is another process associated with these changes). Myoclonus is usually the main manifestation of juvenile myoclonic epilepsy, as discussed below. Uremia at any age gives rise to myoclonus, twitching, and sometimes seizures

Juvenile Myoclonic Epilepsy

This is the most common form of idiopathic generalized epilepsy in older children and young adults. It begins in adolescence, typically about age 15, with a range that essentially spans all of the teenage years. The patient comes to attention because of a generalized seizure, often upon awakening or because of myoclonic jerks in the morning that involve the entire body; sometimes absence seizures are prominent. The family reports that the patient has occasional myoclonic jerks of the arm and upper trunk that become prominent with fatigue, during early stages of sleep, or after alcohol ingestion. A few patients in our experience have had only the myoclonic phenomena and rare absence seizures that persisted unnoticed for years. The EEG characteristically shows bursts of 4- to 6-Hz irregular polyspike activity. A linkage has been established to chromosome 6 in some cases of this illness and in some other forms of juvenile-onset epilepsy, but no mendelian pattern of inheritance has been established. The disorder does not impair intelligence and tends not to be progressive, but a proclivity to infrequent seizures usually continues throughout life. Valproic acid in particular and some other anticonvulsants have been highly effective in eliminating the seizures and myoclonus; they should be continued indefinitely.

PARTIAL OR FOCAL SEIZURES

As indicated earlier, the International Classification divides all seizures into two types— generalized (described above), in which the clinical and EEG manifestations indicate bilateral and diffuse cerebral cortical involvement from the onset, and focal or partial (more recently termed localization-related), in which the seizure is often the product of a demonstrable focal lesion or EEG abnormality in some part of the cerebral cortex (or perhaps in the diencephalon). As noted, partial seizures vary with the locale of the lesion and are conventionally divided into two groups, simple and complex, depending on whether consciousness is retained or impaired. Simple partial seizures most often arise from foci in the sensorimotor cortex. Complex partial seizures most often have their focus in the temporal lobe on one side or the other, but a frontal localization is also well known. The sites of the offending lesions and the types of seizures to which they give rise are listed in Table 16-2. These relationships are so helpful in diagnosis that they should be familar to all neurologists.

Frontal Lobe Partial Seizures (Focal Motor and Jacksonian Seizures)

Focal or partial motor seizures are attributable to a discharging lesion of the opposite frontal lobe. The most common type, originating in the supplementary motor area, takes the form of a turning movement of the head and eyes to the side opposite the irritative focus, often associated with a tonic contraction of the trunk and limbs on that side. This may constitute the entire seizure, or it may be followed by generalized clonic movements; the extension of the seizure may occur just before or simultaneously with loss of consciousness. On the other hand, a lesion in one frontal lobe may give rise to a major generalized convulsion without an initial turning of the head and eyes. It has been postulated that in both types of seizure, the one with and the one without turning movements, there is an immediate spread of the discharge from the frontal lobe to integrating centers in the thalamic or high midbrain reticular formation, accounting for the loss of consciousness. Seizures that begin with forceful, sustained deviation of the head and eyes, and sometimes of the entire body, are referred to

as versive or adversive. Since the turning movements are usually to the side opposite the irritative focus (sometimes to the same side), contraversive and ipsiversive, respectively, would be preferable terms. Nonforceful, unsustained, or seemingly random lateral head movements during the ictus do not have localizing value. The same is true for the head and eye turning that occurs at the end of the generalized tonic-clonic phase of versive seizures (Wylie et al). Contraversive deviation of only the head and eyes can be induced most consistently by electrical stimulation of the superolateral frontal region (area 8), just anterior to area 6 (see Fig. 22-1). Less dependably, the same movements can be obtained by stimulating the more anterior portions of the frontal cortex, or the supplementary motor area, and the temporal or occipital cortex— presumably through propagation of the ictal discharge to the frontal contraversive area. In seizures of temporal lobe origin, early in the seizure, there may be head turning ipsilaterally followed by forceful, contraversive head (and body) turning. These head and body movements, if they occur, are preceded by quiet staring and other automatisms. The jacksonian motor seizure begins with a tonic contraction of the fingers of one hand, the face on one side, or the muscles of one foot. This transforms into clonic movements in these parts in a fashion analogous to that in a generalized clonic-tonic-clonic convulsion. Sometimes a series of clonic movements of increasing frequency build up to a tonic contraction.

The movements may remain localized or spread ("march") from the part first affected to other muscles on the same side of the body. In the latter, or "classic," jacksonian form, which is relatively uncommon, the seizure spreads from the hand, up the arm, to the face, and down the leg; or, if the first movement is in the foot, the seizure marches up the leg, down the arm, and to the face, usually in a matter of 20 to 30 s. Interestingly, spontaneously occurring focal motor seizures, e.g., those beginning in the toes or fingers, may sometimes be arrested (inhibited) by applying a ligature above the affected part or, in the case of focal sensory seizures, by applying a vigorous sensory stimulus ahead of the advancing sensory aura. Rarely, the first muscular contraction is in the abdomen, thorax, or neck. In some cases, the one-sided seizure activity is followed by turning of the head and eyes to the convulsing side, occasionally to the opposite side, and then by a generalized seizure with loss of consciousness. Consciousness is not lost if the sensorimotor symptoms remain confined to one side.

Following convulsions that have a prominent focal motor signature, there may be a transient paralysis of the affected limbs. This "Todd's paralysis" persists for minutes or at times for hours after the seizure, usually in proportion to the duration of the convulsion. Continued focal paralysis beyond this time usually indicates the presence of a focal brain lesion as the underlying cause of the seizure. A similar phenomenon is found in cases of focal epilepsy that involve the language, somesthetic, or visual areas; here the persistent deficit corresponds to the region of brain affected. The high incidence of onset of focal motor epilepsy in the face, hands, and toes is probably related to the disproportionately large cortical representation of these parts. The disease process or focus of excitation is usually in or near the rolandic (motor) cortex, i.e., area 4 of Brodmann (Figs. 3-3 and 22-1); in some cases, and especially if there is a sensory accompaniment, it has been found in the postrolandic convolution. Lesions confined to the motor cortex are reported to assume the form of clonic contractions, and those confined to the premotor cortex (area 6), tonic contractions of the contralateral arm, face, neck, or all of one side of the body. Tonic elevation and extension of the contralateral arm ("fencer's posture") and choreoathetotic and dystonic postures have been associated with high medial frontal lesions (area 8 and supplementary motor cortex), as have complex, bizarre, and flailing movements of a contralateral limb, but this always raises the suspicion of hysterical seizure. Perspiration and piloerection occur occasionally in parts of the body involved in a

focal motor seizure, suggesting that these autonomic functions have a cortical representation in or adjacent to the rolandic area.

Focal motor and jacksonian seizures have essentially the same localizing significance. Seizure discharges arising from the cortical language areas may give rise to a brief aphasic disturbance (ictal aphasia) and ejaculation of a word, or, more frequently, a vocal arrest. Ictal aphasia is usually succeeded by other focal or generalized seizure activity but may occur in isolation, without loss of consciousness, in which case it can later be described by the patient. Postictal aphasia is more common and has much the same localizing value. Vocalization at the onset of a seizure has no such significance. These disturbances should be distinguished from the stereotyped repetition of words or phrases or the garbled speech that characterizes some cases of complex partial seizures or the postictal confusional state. As pointed out by Manford and colleagues, relatively few focal seizures can be localized precisely from clinical data alone. However, when combined with scalp and intracranial EEG recording and MRI, the data are reasonably accurate.

Somatosensory, Visual, and Other Types of Sensory Seizures

Somatosensory seizures, either focal or "marching" to other parts of the body on one side, are nearly always indicative of a focus in or near the postrolandic convolution of the opposite cerebral hemisphere. Penfield and Kristiansen found the seizure focus in the postcentral or precentral convolution in 49 of 55 such cases. The sensory disorder is usually described as numbness, tingling, or a "pins-and-needles" feeling and occasionally as a sensation of crawling (formication), electricity, or movement of the part. Pain and thermal sensations may occur but are exceedingly rare. In the majority of cases, the onset of the sensory seizure is in the lips, fingers, or toes, and the spread to adjacent parts of the body follows a pattern determined by sensory arrangements in the postcentral (postrolandic) convolution of the parietal lobe. If the sensory symptoms are localized to the head, the focus is in or adjacent to the lowest part of the convolution, near the sylvian fissure; if the symptoms are in the leg or foot, the upper part of the convolution, near the superior sagittal sinus or on the medial surface of the hemisphere, is involved. Visual seizures are relatively rare but also have localizing significance. Lesions in or near the striate cortex of the occipital lobe usually produce elemental visual sensations of darkness or sparks and flashes of light, which may be stationary or moving and colorless or colored.

According to Gowers, red is the most frequently reported color, followed by blue, green, and yellow. These images may be referred to the visual field on the side opposite of the lesion or may appear straight ahead. If they occur on one side of the visual field, patients perceive that only one eye is affected (the one opposite the lesion), probably because most persons are aware of only the temporal half of a homonymous field defect. Curiously, a seizure arising in one occipital lobe may cause momentary blindness in both fields. It has been noted that lesions on the lateral surface of the occipital lobe (Brodmann's areas 18 and 19) are likely to cause a sensation of twinkling or pulsating lights. More complex or formed visual hallucinations are usually due to a focus in the posterior part of the temporal lobe, near its junction with the occipital lobe, and may be associated with auditory hallucinations. The localizing value of visual auras has been confirmed recently by Bien and colleagues in a group of 20 surgically treated patients with intractable seizures. They found that elementary visual hallucinations and visual loss were typical of occipital lobe epilepsy but could also occur with

seizure foci in the anteromedial temporal and occipitotemporal regions. Auditory hallucinations are infrequent as an initial manifestation of a seizure. Occasionally a patient with a focus in one superior temporal convolution will report a buzzing or roaring in the ears. A human voice, sometimes repeating unrecognizable words, or the sound of music, has been noted a few times with lesions in the more posterior part of one temporal lobe. Vertiginous sensations of a type suggesting a vestibular origin may on rare occasions be the first symptom of a seizure.

The lesion is usually located in the superoposterior temporal region or the junction between parietal and temporal lobes. In one of the cases reported by Penfield and Jasper, a sensation of vertigo was evoked by stimulating the cortex at the junction of the parietal and occipital lobes. Occasionally with a temporal focus, the vertigo is followed by an auditory sensation. Giddiness, or light-headedness, is a frequent prelude to a seizure, but this symptom, as discussed in Chap. 15, has so many different connotations that it is of little diagnostic value. Olfactory hallucinations are often associated with disease of the inferior and medial parts of the temporal lobe, usually in the region of the parahippocampal convolution or the uncus (hence Jackson's term uncinate seizures, pages 199 and 398). Usually the perceived odor is exteriorized, i.e., projected to someplace in the environment, and is described as disagreeable or foul, though otherwise unidentifiable. Gustatory hallucinations have also been recorded in proven cases of temporal lobe disease (see page 201) and with lesions of the insula and parietal operculum; salivation and a sensation of thirst may be associated. Electrical stimulation in the depths of the sylvian fissure, extending into the insular region, has produced peculiar sensations of taste. Vague and often indefinable visceral sensations arising in the thorax, epigastrium, and abdomen are among the most frequent of auras, as already indicated. Most often they have a temporal lobe origin, although in several such cases the seizure discharge has been localized to the upper bank of the sylvian fissure; in a few others, the focus was located in the upper or middle frontal gyrus or in the medial frontal area near the cingulate gyrus. Palpitation and acceleration of the pulse at the beginning of the attack have also been related to a temporal lobe focus.

Complex Partial Seizures (Psychomotor Seizures, Temporal Lobe Seizures)

These differ from the major generalized and absence seizures discussed above in that (1) the aura (i.e., the initial event in the seizure) may be either a focal seizure of simple type or a hallucination or perceptual illusion, indicating (usually) a temporal lobe origin, and (2) instead of a complete loss of control of thought and action, there is a period of altered behavior and consciousness, for which the patient is later found to be amnesic. Although it is difficult to enumerate all the psychic experiences that may occur during complex partial seizures, they may be categorized into a somewhat arbitrary hierarchy of illusions, hallucinations, dyscognitive states, and affective experiences. Sensory illusions, or distortions of ongoing perceptions, are the most common. Objects or persons in the environment may shrink or recede into the distance, or they may enlarge (micropsia and macropsia), or perseverate as the head is moved (palinopsia). Tilting of the visual environment has been reported. Hallucinations are most often visual or auditory, consisting of formed or unformed visual images, sounds, and voices; less frequently, they may be olfactory (usually unpleasant, unidentifiable sensations of smell), gustatory, or vertiginous. The term dyscognitive state refers to feelings of increased reality or familiarity (de´ja` vu) or of strangeness or unfamiliarity (jamais vu) or a sense of depersonalization. Fragments of certain old memories or scenes may insert themselves into the

patient's mind and recur with striking clarity, or there may be an abrupt interruption of memory. (See Gloor for a more detailed description of the experiential phenomena of temporal lobe epilepsy.) Associated epigastric and abdominal sensations have been alluded to above. Emotional experiences, while less common, may be dramatic— sadness, loneliness, anger, happiness, and sexual excitement have all been recorded. Fear and anxiety are the most common affective experiences, while occasionally the patient describes a feeling of rage or intense anger as part of a complex partial seizure. Ictal fear may have no apparent connection to objective experience and is generally not related to the situation in which the patient finds himself during the seizure. Each of these subjective psychic states may constitute the entire seizure (simple partial seizure), or some combination may occur and proceed to a period of unresponsiveness.

Patients call these "auras," but they represent electrical seizures and have the same significance as a motor convulsion. The motor components of the seizure, if they occur, do so during the latter phase and take the form of automatisms such as lip-smacking, chewing or swallowing movements, salivation, fumbling of the hands, or shuffling of the feet. Patients may walk around in a daze or act inappropriately (undressing in public, speaking incoherently, etc.). Certain complex acts that were initiated before the loss of consciousness— such as walking, chewing food, turning the pages of a book, or even driving—may continue. However, when asked a specific question or given a command, the patients are obviously out of contact with their surroundings. There may be no response at all, or the patient may look toward the examiner in a perplexed way or utter a few stereotyped phrases. In a very small number of patients with temporal lobe seizures (7 of 123 patients studied by Ebner et al), some degree of responsiveness (to simple questions and motor commands) is preserved in the presence of prominent automatisms such as lip-smacking and swallowing. Interestingly, in this small group of partially responsive patients, the seizures originate in the right temporal lobe.

The patient, in a confused and irritable state, may resist or strike out at the examiner. The violence and aggression that are said to characterize patients with temporal lobe seizures usually take this form of nondirected oppositional resistance in response to restraint during the period of automatic behavior (so called be- cause the patient presumably acts like an automaton) or, more often, in the postictal period. Unprovoked assault or outbursts of intense rage or blind fury are very unusual; Currie and associates found such outbursts in only 16 of 666 patients (2.4 percent) with temporal lobe epilepsy. Penfield once commented that he had never observed a rage state as a result of temporal lobe stimulation. It is exceedingly unlikely that an organized violent act requiring several sequential steps in its performance, such as obtaining a gun and using it, could represent a temporal lobe seizure. Rarely, laughter may be the most striking feature of an automatism (gelastic epilepsy). A particular combination of gelastic seizures and precocious puberty has been traced to a hamartoma of the hypothalamus. Or the patient may walk repetitively in small circles (volvular epilepsy), run (epilepsia procursiva), or simply wander aimlessly, either as an ictal or postictal phenomenon (poriomania). These forms of seizure are actually more common with frontal lobe than with temporal lobe foci. Dystonic posturing of the arm and leg contralateral to the seizure focus is found to be a frequent accompaniment if sought—again, the origin is more often in the frontal than the temporal lobes, localizing particularly to the supplementary motor area. After the attack, the patient usually has no memory or only fragments of recall for what was said or done. Any type of complex partial seizures may proceed to other forms of secondary generalized seizures. The tendency to generalization holds true for all types of partial or focal epilepsy. The patient with temporal lobe seizures may exhibit only

one of the foregoing manifestations of seizure activity or various combinations of them. In a series of 414 patients studied by Lennox, 43 percent displayed some of the motor changes; 32 percent, automatic behavior; and 25 percent, alterations in psychic function.

Because of the frequent concurrence of these symptom complexes, he referred to them as the psychomotor triad. Probably the clinical pattern varies with the precise locality of the lesion and the direction and extent of spread of the electrical discharge. Because of their focal origin and complex symptomatology, all these types of seizures are best subsumed under the heading of complex partial seizures. This term is preferable to temporal lobe seizures, since typical complex partial seizures sometimes arise from a focus in the medial-orbital part of the frontal lobe. Also, seizures originating in the parietal or occipital lobes may be manifested as complex partial seizures because of seizure spread into the temporal lobes. Often the brief ictal aura is not reflected in cortical epileptic activity and therefore may be missed by routine surface EEG recordings. Complex partial seizures are not peculiar to any period of life, but they do show an increased incidence in adolescence and the adult years. In the series of Ounsted and coworkers, about onethird of such cases could be traced to the occurrence of severe febrile convulsions in early life (see further on). As a corollary, about 5 percent of all their patients with febrile seizures continued to have seizures during adolescence and adult life; in the latter group there were many in whom the seizures were of the temporal lobe type. Also, in Falconer's series in which a temporal lobectomy was performed for intractable epilepsy, there were many patients who had previously had this complicated type of febrile seizure. Neonatal convulsions, head trauma, and various other nonprogressive perinatal neurologic disorders are antecedents that place a child at risk of developing complex partial seizures (Rocca et al).

Two-thirds of patients with complex partial seizures also have generalized tonic-clonic seizures or have had them at some earlier time, and it has been theorized that the generalized seizures may have led to secondary ischemic damage to the hippocampal portions of the temporal lobes. In the latter cases, carefully performed and quantitated MRI in the coronal plane may disclose a loss of volume in the hippocampi and adjacent gyri on one or both sides—i.e., medial temporal sclerosis (Fig. 16-2). Complex partial seizures are notably variable in duration. Behavioral automatisms rarely last longer than a minute or two, although postictal confusion and amnesia may persist for a considerably longer time. Some complex partial seizures consist only of a momentary change in facial expression and a blank spell, resembling an absence. Almost always, however, the former are characterized by distinct ictal and postictal phases, whereas patients with absence attacks usually have an instantaneous return of full consciousness following the ictus. Postictal behavior after partial complex seizures is often accompanied by widespread slowing in the EEG. With seizures of left-sided origin there is likely to be global and nonfluent aphasia. Prolonged disorientation for time and place suggests a right-sided source. Automatisms in the postictal period have no lateralizing connotation (Devinsky et al). However, postictal posturing and paresis of an arm (Todd's paralysis) or an aphasic difficulty are helpful in determining the side of the lesion (Cascino). Also, postictal nose wiping is carried out by the hand ipsilateral to the seizure focus in 97 percent of patients, according to Leutzmezer and colleagues, but we are in no position to confirm this.

Amnesic Seizures

Rarely, brief, recurrent attacks of transient amnesia are the only manifestations of temporal lobe epilepsy, although it is unclear whether the amnesia in such patients represents an ictal or postictal phenomenon. These attacks of pure amnesia have been referred to as transient epileptic amnesia, or TEA (Palmini et al; Zeman et al). If the patient functions at a fairly high level during the attack, as may happen, there is some resemblance to transient global amnesia (page 379). However, the brevity and frequency of the TEA spells, their tendency to occur on awakening, the impaired performance on complex cognitive tasks, and, of course, a history of epilepsy and associated seizure discharges in the EEG help to make the distinction.

Behavioral and Psychiatric Disorders

Some comments are in order concerning the issues of personality, behavioral, and psychiatric disorders in patients with complex partial seizures. Data as to prevalence of these disorders are limited and have been derived mainly from studies of selected groups of patients attending university hospitals and other specialty clinics that tend to treat the most difficult and complicated cases. In one such study (Victoroff), about one-third of the patients had a history of major depressive illness, and an equal number had symptoms of anxiety disorder; psychotic symptoms were found in 10 percent. Similar figures, also from a university-based epilepsy center, have been reported by Blumer et al. It must be emphasized that these remarkable rates of psychiatric morbidity do not reflect the prevalence in the entire population of epileptics. The postictal state in patients with temporal lobe epilepsy sometimes takes the form of a protracted paranoid-delusional or amnesic psychosis lasting for days or weeks. The EEG during this period may show no seizure discharge, though this does not exclude repeated or sustained seizure activity in the amygdala and other deep temporal lobe structures. This disorder, virtually indistinguishable from schizophrenia in form (but not in temporal evolution), may also present in the interictal period. An excess of psy chosis has been reported only in studies emanating from specialized centers; epidemiologic studies provide only limited evidence of an association with psychosis in the overall population of epileptics (see Trimble and Schmitz and the review by Trimble for a critical discussion of this subject). Again, the frequency of this association with temporal lobe epilepsy is uncertain.

Epileptic Personality Disorder

It has long been observed that some patients with temporal lobe seizures may exhibit a number of abnormalities of behavior and personality during the interictal period. Often they are slow and rigid in their thinking, verbose, circumstantial and tedious in conversation, inclined to mysticism, and preoccupied with rather naive religious and philosophical ideas. Also, they are often subject to outbursts of bad temper and aggressiveness. Obsessionalism, humorless sobriety, emotionality (mood swings, sadness and anger), and a tendency to paranoia are other frequently described traits. Diminished sexual interest and potency in men and menstrual problems in women, not readily attributable to anticonvulsant drugs, are common among patients with complex partial seizures of temporal lobe origin. Geschwind proposed that a triad of behavioral abnormalities— hyposexuality, hypergraphia, and hyperreligiosity—constitute a characteristic syndrome in such patients.

The Electroencephalogram in Epilepsy

The EEG provides confirmation of Hughlings Jackson's concept of epilepsy—that it represents a recurrent, sudden, excessive discharge of cortical neurons. The EEG is undoubtedly the most sensitive, indeed indispensable, tool for the diagnosis of epilepsy; but like other ancillary tests, it must be used in conjunction with clinical data. In patients with idiopathic generalized seizures and in a high proportion of their relatives, interictal spike-and-wave abnormalities without any clinical seizure activity are common, especially if the EEG is repeated several times. Contrariwise, a proportion of epileptic patients have a perfectly normal interictal EEG; occasionally, using standard methods of scalp recording, the EEG may even be normal during a simple or complex partial seizure. Furthermore, a small number of healthy persons (approximately 2 to 3 percent) show paroxysmal EEG abnormalities; some of them have a family history of epilepsy (particularly of absence seizures) and may themselves later develop seizures. EEG abnormalities that characterize a spreading epileptogenic focus and generalization of seizure activity, both the grand mal and absence types, have been described in the preceding section and are illustrated in Chap. 2. At first there was thought to be a characteristic EEG picture for seizures, but further studies have not confirmed this, many patterns being possible. One consistent observation, however, has been that the region of earliest spike activity corresponds best to the epileptogenic focus. This rule guides epilepsy surgery.

The postseizure or postictal state following generalized seizures also has its EEG correlate, taking the form of random generalized slow waves. Following partial or focal seizures, the EEG shows focal slowing. With clinical recovery, the EEG returns to normal or to the preseizure state. A single EEG tracing obtained during the interictal state is abnormal to some degree in 30 to 50 percent of epileptic patients; this figure rises to 60 to 70 percent if patients are subjected to three or more studies utilizing standard activating measures (hyperventilation, photic stimulation, and sleep; see Chap. 2). With structural lesions, focal slow and sharp activity, which is not clearly epileptiform, may be the only clue to a seizure focus. A higher yield of abnormalities and a more precise definition of seizure types can be obtained by the use of several special EEG procedures. Overnight EEG recording is particularly helpful because focal abnormalities, particularly in the temporal lobes, may become prominent in stage II sleep. Sphenoidal leads have been used to detect inferomedial temporal seizure activity, but they are uncomfortable and probably add little more information than can be obtained by the placement of additional subtemporal scalp electrodes. In our experience, nasopharyngeal electrode recordings are too contaminated by artifact to be clinically useful. Activating procedures such as hyperventilation, photic stroboscopic stimulation, and sleep increase the yield of EEG recordings, as detailed in Chap. 2. Beyond dependably identifying artifacts in the EEG recording, one of the main challenges for the electroencephalographer is to differentiate between normal patterns that simulate seizures and true epileptic discharges. These paroxysmal but ostensibly normal patterns appear mostly during sleep, each with a highly characteristic morphology. These include small sharp spikes, "14 and 6" polyspike activity, lambda and posterior occipital mu rhythm, and occipital sharp transients. These are pictured in most standard textbooks on the subject of EEG.

SLEEP AND ITS ABNORMALITIES

Sleep, that familiar yet inexplicable condition of repose in which consciousness is in abeyance, is obviously not abnormal, yet it is most appropriately considered in connection with abnormal phenomena because there are a number of interesting and common irregularities of sleep, some of which approach serious extremes. Everyone has had a great deal of personal experience with sleep, or lack of it, and has observed people in sleep, so it requires no special knowledge to understand something about this condition or to appreciate its importance to health and well-being. The psychologic and physiologic benefits of sleep have seldom been so eloquently expressed as in the words of Tristram Shandy: Tis the refuge of the unfortunate—the enfranchisement of the prisoner, the downy lap of the hopeless, the weary, the broken-hearted; of all the soft delicious functions of nature this is the chiefest; what a happiness it is to man, when the anxieties and passions of the day are over. Physicians are often consulted by patients who suffer some derangement of sleep. Most often the problem is one of sleeplessness, but sometimes it concerns excessive sleep or some peculiar phenomenon occurring in connection with sleep. Certain points concerning normal sleep and the sleep-wake mechanisms are worth reviewing, since familiarity with them is necessary for an understanding of disorders of sleep. A great deal of information about sleep and sleep abnormalities is now available as a result of the development, in relatively recent years, of the subspecialty of sleep medicine and the creation of a large number of centers for the diagnosis and treatment of sleep disorders. Most disorders of sleep can be readily recognized and managed if one attends closely to the patient's description of his sleep disturbance. Only complex or odd cases or those requiring the documentation of apneic episodes or seizures and other motor disorders during sleep need study in special sleep laboratories.

Physiology of Sleep and Sleep-Wake Mechanisms

Sleep, as everyone knows, is an elemental phenomenon of life and an indispensable phase of human existence. It represents one of the basic 24-h (circadian) rhythms, traceable through all mammalian, avian, and reptilian species. The neural control of circadian rhythms is thought to reside in the ventral-anterior region of the hypothalamus—more specifically, in the suprachiasmatic nuclei. Lesions in these nuclei result in a disorganization of the sleep-wake cycles as well as of the rest-activity, temperature, and feeding rhythms. The ancillary role of melatonin and the pineal body in modulating this cyclic activity is described in Chap. 27. Effects of Age Observations of the human sleep-wake cycle show it to be age-linked. The newborn baby sleeps from 16 to 20 h a day and the child, 10 to 12 h. Total sleep time drops to 9 to 10 h at age 10 and to about 7 to 7.5 h during adolescence. A gradual decline to about 6.5 h develops in late adult life. However, there are wide individual differences in the length and depth of sleep, due apparently to genetic factors, early-life conditioning, the amount of physical activity, and particular psychologic states. The pattern of sleeping, which in terrestrial life is adjusted to the 24-h day, also varies in the different epochs of life. The circadian rhythm, with predominance of daytime wakefulness and nighttime sleep, begins to appear only after the first few weeks of postnatal life of the full-term infant; as the child matures, the morning nap is omitted, then the afternoon nap; by the fourth or fifth year, sleep becomes consolidated into a single long nocturnal period. (Actually, a large part of the world's population continue to have an afternoon nap, or siesta, as a lifelong sleep-wake pattern.) This alternating pattern of sleeping and waking persists throughout

the adolescent and adult years unless it is altered by emotional or physical disease; fragmentation of the sleep pattern begins in late adult life. Over ensuing years, night awakenings tend to increase in frequency and the daytime waking period tends to be interrupted by episodic sleep lasting seconds to minutes (microsleep) as well as by longer naps. From about 35 years of age onward, women tend to sleep slightly more than men. Stages of Sleep Seminal contributions to our understanding of the physiology of sleep were made by Loomis and associates and by Aserinsky, Dement, and Kleitman through EEG and polygraphic analysis. As a result of their studies, five stages of sleep, representative of two alternating physiologic mechanisms, were defined. In each stage, the electrical activity of the brain occurs in organized and recurring cycles, referred to as the architecture of sleep. These findings put to rest the antiquated ideas that sleep is a purely passive state and simply reflects fatigue and reduction in environmental stimuli, and that sleep and coma have fundamentally the same anatomic-physiologic basis. As the electrophysiologic stages of sleep progress, sleep becomes deeper, meaning that arousal requires a more intense stimulus.

Relaxed wakefulness with the eyes closed is accompanied in the electroencephalogram (EEG) by posterior sinusoidal alpha waves of 9 to 11 Hz (cycles per second) and low-voltage fast activity of mixed frequency. Except for the facial muscles, the electromyogram (EMG) is silent when the patient is sitting or lying quietly. With drowsiness, as the first stage of sleep sets in, the eyelids begin to droop, the eyes may rove slowly from side to side, and the pupils become smaller. As the early stage of sleep evolves, the muscles relax and the EEG pattern changes to one of progressively lower voltage and mixed frequency with a loss of alpha waves; this is associated with slow, rolling eye movements and is called stage 1 sleep. As this changes into stage 2 sleep, 1/2- to 2-s bursts of biparietal 12- to 14-Hz waves (sleep spindles) and intermittent high-amplitude, central-parietal sharp slow-wave complexes appear (vertex waves) (Fig. 19-1). The deep sleep of stages 3 and 4, also called slow-wave sleep, is composed of an increasing proportion of high-amplitude (.75-mV), delta (1- to 2-Hz) waves in the EEG. If the eyelids are raised gently, the globes are usually

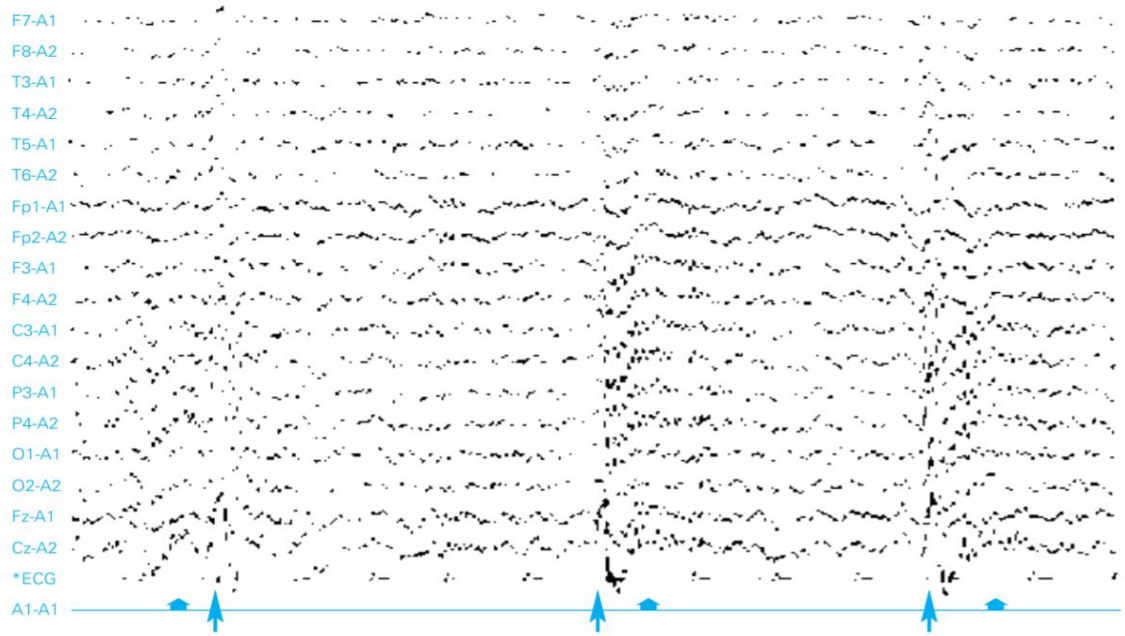

Figure 19-1. Conventional EEG (30 mm/s) of a young healthy woman in stage 2 sleep showing vertex waves (*large arrows*) and sleep spindles (*small arrows*), best seen in the central regions.

seen to be exotropic and the pupils are even smaller than before, but with retained responses to light. The last stage of the sleep cycle, which follows the others intermittently throughout the night, is associated with further reduction in muscle tone except in the extraocular muscles and with bursts of rapid eye movements (REM; thus the term REM sleep designates this stage) behind the closed lids. The EEG becomes desynchronized, i.e., it has a lowvoltage, high-frequency discharge pattern. The first four stages of sleep are called non– rapid eye movement (NREM) sleep or quiet or synchronized sleep; the last stage is variously designated as rapid-eye-movement (REM), fast-wave, nonsynchronized, or desynchronized sleep. These features are illustrated in Fig. 19-2. In the first portion of a typical night's sleep, the normal young and middle-aged adult passes successively through stages 1, 2, 3, and 4 of NREM sleep. After about 70 to 100 min, a large proportion of which consists of stages 3 and 4 sleep, the first REM period occurs, usually heralded by a transient increase in body movements and a shift in the EEG pattern from that of stage 4 to stage 2.

This NREM-REM cycle is repeated at about the same interval four to six times during the night, depending on the total duration of sleep. The first REM period may be brief; the later cycles have less stage 4 sleep or none at all. In the latter portion of a night's sleep, the cycles consist essentially of two alternating stages—REM sleep and stage 2 (spindle-K-complex) sleep. Newborn full-term infants spend about 50 percent of their sleep in the REM stage (although their EEG and eye movement characteristics differ from those of adults). The newborn sleep cycle lasts about 60 min (50 percent REM, 50 percent NREM, generally alternating through a 3- to 4-h interfeeding period); with age, the sleep cycle lengthens to 90 to 100 min. About 20 to 25 percent of total sleep time in young adults is spent in REM sleep, 3 to 5 percent in stage 1, 50 to 60 percent in stage 2, and 10 to 20 percent in stages 3 and 4 combined. The amount of sleep in stages 3 and 4 decreases with age, and persons more than 70 years of age have virtually no stage 4 sleep and only small amounts of stage 3 sleep (Fig. 19-3). The 90- to 100-min cycle is fairly stable in any one person and is believed to continue to operate to a less perceptible degree during wakefulness in relation to cyclic gastric motility, hunger, degrees of alertness, and capacity for cognitive activity.

Physiologic Changes and Dreaming in NREM and REM Sleep

- A comparison of the physiologic changes in NREM and REM sleep is instructive.
- Cortical neurons tend to discharge in synchronized bursts during NREM sleep and in nonsynchronized bursts in the wakeful states; in REM sleep, the EEG pattern is generally asynchronous as well.
- Most complex visual dreaming has been found to occur in the REM period, with the qualifications noted below, and is recalled most consistently if the subject is awakened at this time.

Tonic muscle activity is minimal during REM sleep, although small twitches in facial and digital muscles (hand and foot) can still be detected

The Function of Sleep and Dreams

This has been pondered almost endlessly by physiologists and psychiatrists. Parkes has reviewed the main theories— body restitution, facilitation of motor function, consolidation of learning and memory—and tends to agree with the ungrammatical but unambiguous conclusion of Popper and

Eccles that “Sleep is a natural repeated unconsciousness that we do not even know the reason for.” There is no convincing proof, for example, of the popular notion that we stabilize learned material while asleep, nor can one logically entertain the notion that the function of sleep is to produce dreams, at least until the utility and meaning of dreams become known. On the basis of plausibility and logic, we favor the simple notion that sleep restores strength and physical and mental energy. Regarding neurophysiologic changes during dreaming, Braun and colleagues, who used positron emission tomography (PET) to study REM sleep, observed selective activation of the extrastriate visual cortices and limbic-paralimbic regions, with concomitant attenuation of activity in the primary visual cortex and frontal association areas. The relation of these findings to the nature of dreams is discussed below. Based on these and similar studies, several authors have speculated that the suppression of frontal lobe activity during dreaming, at a time when visual association areas and their paralimbic connections are activated, might explain the uncritical acceptance of the bizarre visual content, the disordered temporal relationships, and the heightened emotionality that characterize dreams, as mentioned earlier. This would be in keeping with Hobson’s expressed view of dreams as a form of delirium. (This is an interesting idea and one that we find appealing, but it explains little, since the nature of delirium is also obscure.) As an alternative that links dreams to inherent meaning for the individual, Solms has suggested that activation of frontal dopaminergic systems, the same pathways that participate in most biologic drives, implies that dreams express latent wishes and drives—the classic psychoanalytical interpretation expressed by Freud in his book The Interpretation of Dreams. We remain skeptical of these views.

The Effects of Total and Partial Sleep Deprivation

Deprived of sleep, experimental animals will die within a few weeks, no matter how well they are fed, watered, and housed (Rechtschaffen et al); but whether a similar degree of sleep deprivation leads to death in humans is unknown. Nevertheless, humans being deprived of sleep do suffer a variety of unpleasant symptoms quite distinct from the effects of the usual types of insomnia. Despite many studies of the deleterious emotional and cognitive effects of sleeplessness, we still know little about them. If deprived of sleep (NREM and REM) for periods of 60 to 200 h, human beings experience increasing sleepiness, fatigue, irritability, and difficulty in concentration. Performance of skilled motor activities also deteriorates:if the tasks are of short duration and slow pace, the subject can manage them; but if speed and perseverance are demanded, he cannot. Self-care is neglected, incentive to work wanes, sustained thought and action are interrupted by lapses of attention, judgment is impaired, and the subject becomes less and less inclined to communicate. With sustained deprivation, sleepiness becomes increasingly more intense, momentary periods of sleep (“microsleep”) become more intrusive, and the tendency to all types of errors and accidents becomes more marked. Eventually, subjects fail to perceive accurately and to maintain their orientation. Illusions and hallucinations, mainly visual and tactile ones, intrude into consciousness and become more persistent as the period of sleeplessness is prolonged. Neurologic signs to be noted include a mild and inconstant nystagmus, impairment of saccadic eye movements, loss of accommodation, exophoria, a slight tremor of the hands, ptosis of the eyelids, expressionless face, and thickness of speech, with mispronunciations and incorrect choice of words. The EEG shows a decrement of alpha waves, and closing of the eyes no longer generates alpha activity. The seizure threshold is reduced and seizure

foci in the EEG may be activated. The concentration of 17-hydroxycorticosteroids increases in the blood, and catecholamine output rises.

SLEEP DISORDERS:

(1)Insomnia

- The term insomnia signifies a chronic inability to sleep despite adequate opportunity to do so; it is used popularly to indicate any impairment in the duration, depth, or restorative properties of sleep.
- There may be difficulty in falling asleep or remaining asleep, awakening may come too early, or a combination of these complaints may be made.
- **Primary Insomnia** This term should be reserved for the condition in which nocturnal sleep is disturbed for prolonged periods and none of the symptoms of neurosis, depression, or other psychiatric or medical diseases can be invoked to explain the sleep disturbance.
- **Secondary or Situational Insomnia** This type of insomnia, which is usually transitory, can often be ascribed to pain or some other recognizable bodily disorder, such as drug or alcohol abuse or, most commonly, to anxiety, worry, or depression.
- **"Restless Legs," Periodic Leg Movements of Sleep, and Related Disorders** The disorder known as the restless legs syndrome (anxietas tibiarum) may regularly delay the onset of sleep or occur in its early stages.
- The patient complains of unpleasant aching and drawing sensations in the calves and thighs, often associated with creeping or crawling feelings.
- **Other Causes of Secondary Insomnia** Acroparesthesias, a predominantly nocturnal tingling and numbness of the fingers and palms due to tight carpal ligaments (carpal tunnel syndrome), may awaken the patient at night (see further on, under "Sleep Palsies").

- Cluster headaches characteristically awaken the patient within 1 to 2 h after falling asleep.
- Among the secondary insomnias, those due to some type of psychologic disturbance are particularly common.
- The depressive illnesses characteristically produce early-morning waking and inability to return to sleep; the quantity of sleep is reduced, and nocturnal motility is increased; REM sleep, although not always reduced, comes earlier in the night.

Treatment of Insomnia

- In general, a sedative-hypnotic drug fo the management of insomnia should be prescribed only as a shortterm adjuvant during an illness or some unusual circumstance.
- The ones most commonly used have been flurazepam (Dalmane), 15 to 30 mg; triazolam (Halcion), 0.25 to 0.5 mg; lorazepam (Ativan) 0.5 mg; and the nonbenzodiazepine hypnotic zolpidem (Ambien), 10 mg.
- All of these drugs are more or less equally effective in inducing and maintaining sleep, although they affect sleep stages somewhat differently.
- Flurazepam reduces stage 4 but not REM sleep, whereas the barbiturates reduce both stage 4 and REM sleep.

- Melatonin (300 to 900 mg) is sometimes as effective as the sedative-hypnotics and may cause fewer short-term side effects.
- Amitriptyline (25 to 50 mg at bedtime) appears to be a sleep-enhancing drug even in those who are not anxious or depressed.

(2)Disorders of Sleep Due to Neurologic Disease

- Many neurologic conditions seriously derange the total amount and patterns of sleep.
- Lesions in the upper pons, near the locus ceruleus, are particularly prone to do so.
- The clinical abnormality took the form of diminished NREM sleep and near abolition of REM sleep lasting for weeks or months.
- Bilateral lacunar infarctions in the pontine tegmentum, demonstrable by magnetic resonance imaging (MRI), also appear to be the basis of some instances of the socalled REM sleep behavior disorder.
- Major head injury is an important cause of sleep disturbance.
- The abnormalities, which may persist for months or years, consist mainly of a decrease in stages 1 and 2 of NREM sleep and less than the expected amounts of REM sleep and dreaming.
- Migraine, cluster headaches, and paroxysmal hemicrania all have been linked to certain sleep stages.

(3)Disorders of Sleep Associated with Changes in Circadian Rhythm

- Sleep is also disturbed and diminished when the normal circadian rhythm of the sleep-wake cycle is exogenously altered.
- Sleep is also disturbed and diminished when the normal circadian rhythm of the sleep-wake cycle is exogenously altered.
- The delayed-sleep-phase syndrome is a chronic inability to fall asleep and to arise at conventional clock times.
- The advanced-sleep-phase syndrome is characterized by an earlyevening sleep onset (8 to 9 P.M.) and early-morning awakening.
- Still other persons show a completely irregular sleep-wake pattern; sleep consists of persistent but variable short or long naps throughout the night and day, with a nearly normal 24-h accumulation of sleep.

(4)Parasomnic Disturbances

- Included under this title are several diverse disorders, the distinctive feature of which is their occurrence only during sleep:somnolescent starts, sensory paroxysms, nocturnal paroxysmal dystonia, sleep paralysis, night terrors and nightmares, somnambulism, and REM sleep behavior disorder.
- Somnolescent (Sleep, Hypnic) Starts As sleep comes on, certain motor centers may be excited to a burst of insubordinate activity.
- It may involve one or both legs or the trunk (less often, the arms) and may be associated with a frightening dream or sensory experience.
- **Sensory Paroxysms** Sensory centers may be disturbed in a similar way to the above described sleep starts, either as an isolated phenomenon or in association with motor phenomena.

- **Nocturnal Paroxysmal Dystonia** This is yet another parasomnic disorder, characterized by paroxysmal bursts of generalized choreoathetotic, ballistic, and dystonic movements occurring during NREM sleep.

- **Night Terrors and Nightmares** The night terror (pavor nocturnus) is mainly a problem of childhood. It usually occurs soon after falling asleep, during stage 3 or 4 sleep. The child awakens abruptly in a state of intense fright, screaming or moaning, with marked tachycardia (150 to 170 beats per minute) and deep, rapid respirations.
- **Sleep Paralysis** Curious paralytic phenomena, referred to as preand postdormital paralyses, may occur in the transition from the sleeping to the waking state.
- **Somnambulism and Sleep Automatism** This condition occurs far more commonly in children (average age, 4 to 6 years) than in adults and is often associated with nocturnal enuresis and night terrors, as indicated above.
- It is estimated that 15 percent of children have at least one episode of sleepwalking, and that 1 in 5 sleepwalkers has a family history of this disorder.
- **Somnabulism in Adults** The onset of sleepwalking or night terrors in adult life is most unusual and suggests the presence of psychiatric disease or drug intoxication.
- **REM Sleep Behavior Disorder** This is a more recently recognized parasomnic disorder, occurring in adult life, most commonly in older men without a history of childhood sleepwalking.
- It is characterized by attacks of vigorous and often dangerous motor activity accompanied by vivid dreams.

(5)Nocturnal Epilepsy

- This is such a frequent occurrence tha the practice of inducing sleep has been adopted as an activatin EEG procedure to obtain confirmation of epilepsy. Seizures ma occur soon after the onset of sleep or a any time during the night but mainly in stage 4 of NREM sleep or in REM sleep.
- Sleeping epileptic patients attract attention to their seizures by a cry, violent motor activity, unusual but stereotyped actions, such as sitting up and crossing the arms over the chest, or labored breathing.
- Rarely, epilepsy occurs in conjunction with night terrors and somnambulism; the question then arises whether the latter disorders represent postepileptic automatisms.

(6)Excessive Sleep (Hypersomnia) and Reversal of Sleep-Wake Rhythm

- Protracted sleep lasting for days to weeks was such a prominent symptom of this disease that it was called sleeping sickness.
- The patient appeared to be in a state of continuous sleep, or somnosis, and could be kept awake only by constant stimulation.
- “Sleep drunkenness” is the name given to a special form of hypersomnia, characterized by a failure of the patient to attain full alertness for a protracted period after awakening.
- Unsteadiness, drowsiness, disorientation, and automatic behavior are the main features.
- **Kleine-Levin Syndrome** Kleine in 1925 and Levin in 1936 described an episodic disorder characterized by somnolence and overeating. For days or weeks, the patients, mostly adolescent boys, sleep 18 h or more a day, awakening only long enough to eat and attend to

toilet needs. They appeared dull, often confused, and restless and were sometimes troubled by hallucinations.

(7)Sleep Apnea and Excessive Daytime Sleepiness

- Excessive daytime sleepiness is a common complaint in general medical practice (Table 19-1). Certainly the most frequent cause is the use of any one of the large variety of medications that are not prescribed primarily for their sedative effect.
- Abuse of alcohol and illicit drugs should also be included in this category.
- *Central sleep apnea* has been observed in patients with a variety of severe and life-threatening lower brainstem lesions.
- Patients with primary *hypoventilation syndromes* are usually of normal body habitus. Awakenings during the night are frequent, usually after an apneic period, and insomnia is a common complaint.
- Apnea of the obstructive type is more common than the purely central variety. *Obstructive apnea* is often associated with obesity and less frequently with acromegaly, myxedema, micrognathia, and myotonic dystrophy.

Treatment

- In central apnea, any underlying abnormality, such as congestive heart failure or nasal obstruction, should, of course, be treated insofar as possible.
- In the treatment of obstructive apnea, continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BIPAP) is the most useful measure.

(8)Narcolepsy and Cataplexy

- This clinical entity has long been known to the medical profession. Gelineau gave it the name narcolepsy in 1880.
- Other emotional states; this was referred to as cataplectic inhibition by Henneberg (1916) and later as cataplexy by Adie (1926).
- Sometimes sleep paralysis is accompanied or just preceded by vivid and terrifying hallucinations (hypnagogic hallucinations), which may be visual, auditory, vestibular (a sense of motion), or somatic.
- These four conditions— narcolepsy, cataplexy, hypnagogic paralysis, and hallucinations—constitute a clinical tetrad.
- Nocturnal sleep is often disrupted and reduced in amount. The number of hours in a 24-h day spent in sleep by the narcoleptic is no greater than that of a normal individual.
- Cataplexy refers to a sudden loss of muscle tone brought on by strong emotion—that is, circumstances in which hearty laughter or, more rarely, excitement, surprise, anger, or intense athletic activity cause the patient's head to fall forward, the jaw to drop, the knees to buckle, even with sinking to the ground—all with perfect preservation of consciousness.
- **Diagnosis** The greatest difficulty in diagnosis relates to the problem of separating narcolepsy from the daytime sleepiness of certain sedentary, obese adults who, if unoccupied, doze readily after meals, while watching television, or in the theater.
- **Treatment** No single therapy will control all the symptoms.
- The narcolepsy responds best to

(1) strategically placed 15- to 20-min naps (during lunch hour, before or after dinner, etc.);

(2) the use of stimulant drugs—modafinil (Provigil), dextroamphetamine sulfate (Dexedrine), methylphenidate hydrochloride (Ritalin), or pemoline (Cylert)—to heighten alertness; and

(3) a tricyclic antidepressant (protriptyline, imipramine, or clomipramine) for control of cataplexy.

(8)Idiopathic Hypersomnia (Essentia Hypersomnolence; Independen Narcolepsy)

- As has been indicated, recurrent daytime sleepiness may be the presenting symptom in a varied number of disorders other than narcolepsy and cataplexy.
- When chronic daytime sleepiness occurs repeatedly and persistently without known cause, it is classified as essential or idiopathic hypersomnolence.
- **Treatment**, however, is the same as that for narcolepsy. Idiopathic hypersomnia, as defined in this manner, proves to be a rare syndrome once narcolepsy and all other causes of daytime sleepiness have been excluded.

(9)Pathologic Wakefulness

- The commonest causes of asomnia in hospital practice are delirium tremens and certain drugwithdrawal psychoses. Drug-induced psychoses and mania (bipolar disease) may induce a similar state.
- None of the various treatments we have tried has been successful in suppressing this state. Fortunately, it was transitory in the traumatic cases.

(10)Sleep Palsies and Acroparesthesias

- Several types of paresthetic disturbances, sometimes distressing in nature, may arise during sleep. Everyone is familiar with the phenomenon of an arm or leg “falling asleep.”
- Immobility of the limbs and maintenance of uncomfortable postures, without any awareness of them, permit undue pressure to be applied on peripheral nerves.
- *Acroparesthesias* are frequent in adult women and are not unknown in men. The patient, after being asleep for a few hours, is awakened by numbness or a tingling, prickling, “pins-and-needles” feeling in the fingers and hands.

(11)Bruxism

- Nocturnal grinding of the teeth, sometimes diurnal as well, occurs at all ages and may be as distressing to the bystander as it is to the patient.
- It may also cause serious dental problems unless the teeth are protected in some way.

(12)Nocturnal Enuresis

- Nocturnal bedwetting with daytime continence is a frequent disorder during childhood, which may persist into adult life. Approximately 1 of 10 children 4 to 14 years of age is affected.
- The incidence is much higher if one or both parents were enuretic.

(13)Relation of Sleep to Other Medical Illnesses

- As already mentioned, cluster headache and migraine have an intricate relationship to sleep, the former almost always occurring during or soon after the first REM period and the latter often curtailed by a sound sleep.
- Patients with duodenal ulcer secrete more HCl during sleep (peaks coincide with REM sleep) than normal subjects.
- Patients with coronary arteriosclerosis may show ECG changes during REM sleep, and nocturnal angina has been recorded at this time.
- Snoring is strongly associated with hypertension.
- Patients with hypothyroidism have shown a decrease of stages 3 and 4 NREM sleep and a return to a normal pattern when they become euthyroid.

- Alcohol, barbiturates, and other sedative-hypnotic drugs, which suppress REM sleep, permit extraordinary excesses of it to appear during withdrawal periods, which may in part account for the hyperactivity and confusion and perhaps the hallucinosis seen in these states.