ELEVENTH EDITION

ADAMS AND VICTOR'S

Principles of Neurology

ALLAN H. ROPPER • MARTIN A. SAMUELS
JOSHUA P. KLEIN • SASHANK PRASAD

Mc Graw Hill

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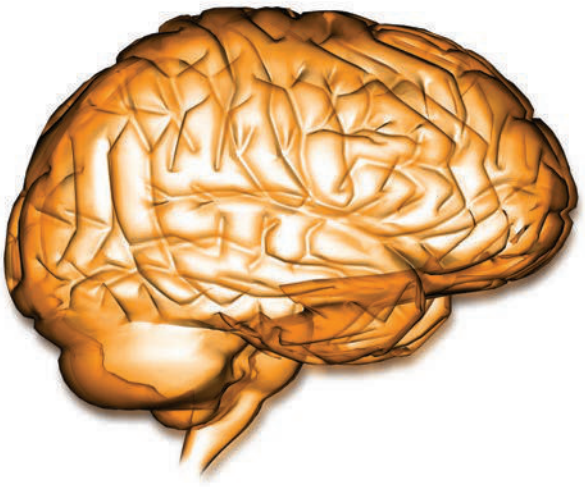

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Preface

We are very pleased to bring you the 11th edition of *Adams and Victor's Principles of Neurology*. To provide the context for the continued importance and relevance of a textbook that aspires to such breadth and depth, it may be compelling to review a patient's story; an event that took place between the last edition of this book and this one. Neurologists have always been particularly attracted to the case history as a method to imprint the fine points as well as the broad principles that can be gleaned in a clinical encounter. The originators of this book, Raymond D. Adams and Maurice Victor, insisted that the basis of the practice of neurology necessarily differs from that of neuroscience in that neurology is a medical discipline and must always be related back to the patient. Here is the story:

A 19-year-old college sophomore began to show paranoid traits. She became convinced that her roommate was listening in on her phone conversations and planning to alter her essays. She became reclusive and spent most of her time locked in her room. After much difficulty, her teachers convinced her to be seen by the student health service. It was believed she was beginning to show signs of schizophrenia and she was admitted to a psychiatric hospital, where she was started on antipsychotic medications. While in the hospital, she had a generalized seizure which prompted her transfer to our service. Her spinal fluid analysis showed 10 lymphocytes per mL^3. She was found to have an anti-NMDA receptor antibody, which prompted an ultrasound examination of the pelvis. The left ovary was thought to show a benign cyst. Because of the neurological syndrome, the ovarian cyst was resected and revealed a microscopic ovarian teratoma. The neuropsychiatric syndrome resolved. She has since graduated and obtained an advanced degree.

This class of disease, autoimmune encephalitis, appeared briefly in the last edition of this book, and not at all in the previous one, but has become a major field of modern neurology, now expanded to include antibodies to many other antigens, occurring de novo or in association with an array of tumors. What of the patients whose stories approximate this one but do not have one or two essential components? One wonders how many other patients harbor curious autoimmune disorders, which will be uncovered in future editions of *Principles of Neurology*.

The clinical features of conditions such as cerebral amyloid angiopathy, posterior reversible encephalopathy syndrome, the neuromyelitis optica spectrum, and toxicity of treatments such as adaptive cell therapy have all been expanded. The novel treatments now being applied to cerebrovascular disease, multiple sclerosis, muscular dystrophy, amyloidosis, and inborn enzyme deficiencies are among a list of triumphs of science that can only be applied by careful clinicians. In the present edition there is hardly a category of disease that has not begun to yield to the molecular biology and genetics.

Outside the laboratory, clinical trials have continued to build the background of information that applies to large groups of patients with neurological disease. Clinicians are very aware, however, that the results of a trial have less certain meaning for an individual patient. It is the skillful use of this information that this book aims to inform. Will the single patient be helped or harmed? Because medicine deals with the realities and complexities of illness, the clinician makes a best approximation of the correct course. The wise application of science, evidence from trials, and the traditional virtues of the neurological history and examination—essentially the craft of neurology—are the main purpose of this edition of *Principles of Neurology*.

As has been our tradition, the book is written in a conversational style and we do not eschew stating our personal preferences when they are based on experience. We continue to find that readers value the uniformity of voice and approach of a few individual authors, rather than a discursive list of topics and writers. We thank Drs. Edward Stim, Mehrnaz Fallah, and Tim Lachman for invaluable assistance in proofreading the text.

For this edition we introduce as a coauthor Dr. Sashank Prasad, a seasoned general neurologist with special training in neuro-ophthalmology and a director of our neurology training program. We hope that reading the book will feel akin to attending our ward rounds, clinics, or morning report, thus giving the reader an intimate window into demands of practice, without being prescriptive. We hope this edition allows the physician to use the material as a basis for continued professional growth and enjoyment. Welcome to our world.

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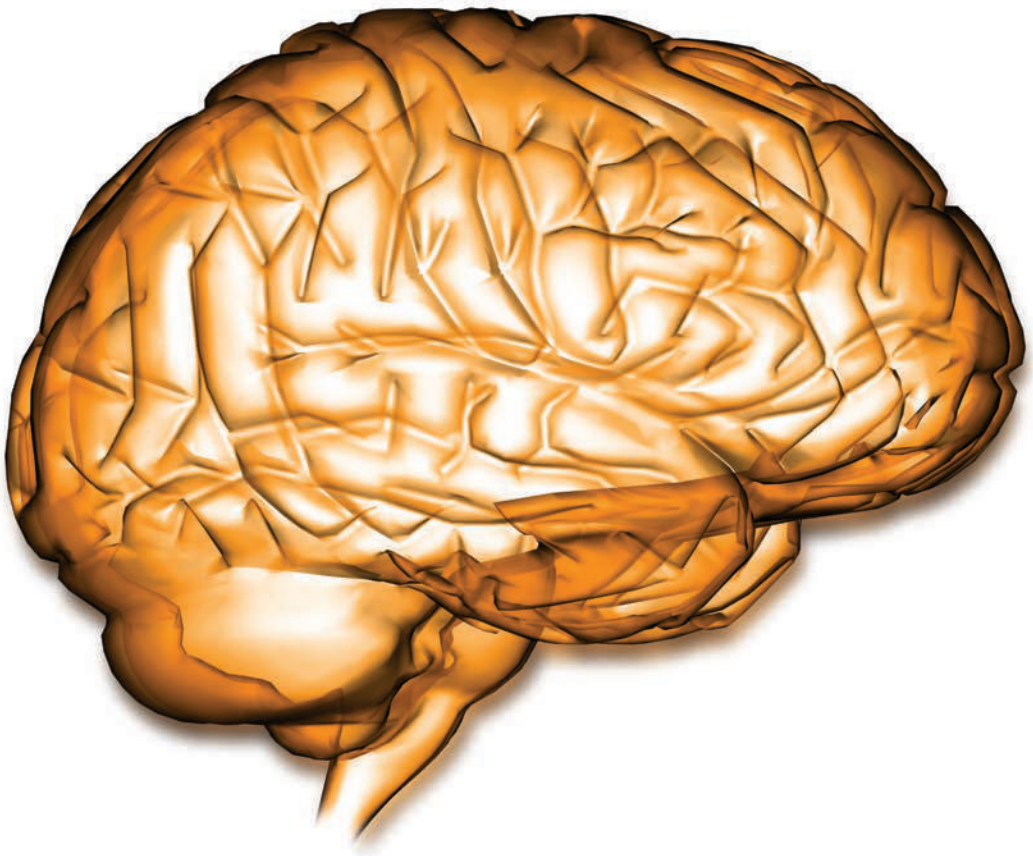
PART 1

THE CLINICAL METHOD OF NEUROLOGY



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1

Approach to the Patient With Neurologic Disease

INTRODUCTION

Neurology is the practice and study of diseases of the nervous system. It is among the most complex and exacting medical specialties and yet it is perhaps the most rewarding, encompassing as it does all aspects of human behavior, cognition, memory, movement, pain, sensory experience, and the homeostatic functions of the body that are under nervous control. Among the provocative aspects of neurology is the manner in which diseases disrupt the functions of the mind, but the field also encompasses study of the diseases of nerves, muscles, spinal cord, and cerebral hemispheres.

The neurologist occupies a special role by using extensive synthetic and analytical skill to explain neurological symptoms and findings. Neurology is distinctive in allowing a type of detailed interpretation of signs and symptoms that, as a result of the fixed structure of the nervous system, provides certainty in diagnosis that is not possible in other fields. This is the method of *localization* that is almost unique to neurology.

Part of the excitement of modern neurology is the incorporation of advances in imaging, and in the neurosciences including neurogenetics, neurochemistry, neuroepidemiology, and neuropathology, which now offer deep insights into the fundamental nature of disease. The close connections among neurology and the fields of internal medicine, psychiatry, neuropathology, developmental medicine and pediatrics, critical care, neurorehabilitation, and neurosurgery extend the purview of clinical neurology. As has occurred in other branches of medicine, increased understanding of disease and therapeutic options has led to the emergence of numerous subspecialties of neurology (Table 1-1).

Neurological symptoms, of course, do not present themselves as immediately referable to a part of the nervous system and the neurologist must therefore be knowledgeable in all aspects of nervous system function and disease. The authors believe that a successful application of medical knowledge is attained by adhering to the principles of the clinical method, which has been retained to a greater degree in neurology than in other fields of medicine. Even the experienced neurologist faced with a complex clinical problem uses this basic approach.

THE CLINICAL METHOD

In most cases, the clinical method consists of an orderly series of steps:

1. The symptoms and signs are secured with as much confidence as possible 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—i.e., one identifies the disorder of function and the anatomic structures that are implicated.
3. These analyses permit the physician to localize the disease process, i.e., to name the parts of the nervous system affected. This is the *anatomic*, or *topographic* diagnosis, which often allows the recognition of a characteristic clustering of symptoms and signs, constituting a syndrome.
4. From the anatomic diagnosis and other specific medical data—particularly the mode of onset and speed of evolution of the illness, the involvement of nonneurologic organ systems, the relevant past and family medical histories, and the imaging and laboratory findings—one deduces the *etiologic diagnosis* and its *pathogenesis*.
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 (*prognosis*).

The likely causes of a neurologic disease are judged in the context of a patient's personal and demographic characteristics, including their age, sex, race, ethnicity, and geographic circumstances. Knowledge of the incidence and prevalence of diseases among populations defined by these factors (base rates) is a valuable component of the diagnostic process. These change over time as for example, during epidemics, and may differ even within neighborhoods or regions of one country.

In recent decades, some of these steps have been eclipsed by imaging methods that allow precise localization of a lesion and, furthermore, often characterize the category of disease. Parts of the elaborate examination that

Table 1-1

NEUROLOGICAL SUBSPECIALTY

SUBSPECIALTY	CHAPTER
Stroke and cerebrovascular disease	33
Neurological intensive care	29, 33, 34
Cognitive, behavioral neurology, and neuropsychiatry	19-22
Epilepsy	15
Cancer neurology	30
Neuro-ophthalmology	12–13
Neuromuscular	43–46
Movement disorders	4, 6, 38
Headache	9
Multiple sclerosis and neuroimmunology	35
Autonomic neurology	25
Neuroimaging	2
Hospital neurology	15,19, 20, 30–35
Interventional neurology	33
Oto- and vestibular neurology	14
Pediatric and developmental neurology	36, 37
Neurological infections	31, 32
Sleep	18
Pain	7–10
Neuroendocrinology	26

Table 1-2

THE MAJOR CATEGORIES OF NEUROLOGIC DISEASE

Genetic–congenital
Traumatic
Degenerative
Vascular
Toxic
Metabolic
  Inherited
  Acquired
Neoplastic
Inflammatory–immune
Psychogenic
Iatrogenic

were intended to localize lesions are no longer necessary in every patient. Nonetheless, insufficient appreciation of the history and examination and the resulting overdependence on imaging leads to diagnostic errors and has other detrimental consequences. A clinical approach is usually more efficient and far more economical than is resorting to imaging. Images are also replete with spurious or unrelated findings, which elicit unnecessary further testing and needless worry on the part of the patient.

All of these steps are undertaken in the service of effective treatment, an ever-increasing aspect in neurology. As is emphasized repeatedly in later chapters, there is always a premium in the diagnostic process on the discovery of treatable diseases. Even when specific treatment is not available, accurate diagnosis may in its own right function as a therapy, as uncertainty about the cause of a neurologic illness may be as troubling to the patient than the disease itself.

Of course, the solution to a clinical problem need not always be schematized in this way. The clinical method offers several alternatives 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 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 vertigo, cerebellar ataxia, unilateral Horner syndrome, paralysis of a vocal cord, and analgesia of the face occur with acute onset, the cause is an occlusion of the vertebral artery, because all the involved structures lie in the lateral medulla, within the territory of this artery. Thus, the anatomic diagnosis determines and limits the etiologic possibilities. Some signs themselves are almost specific for a particular disease. Nonetheless, one is cautious in calling any single sign pathognomonic as exceptions are found regularly.

Ascertaining 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 speed of onset, course, laboratory and imaging characteristics, and natural history of a multiplicity of diseases. 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 division of diseases in all branches of medicine, as summarized in Table 1-2.

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 is found later that the symptoms or signs were incorrectly interpreted in the first place. Repeated examinations may be necessary to establish the fundamental clinical findings beyond doubt. Hence the aphorism: In a difficult neurologic case, a second examination is the most helpful diagnostic test.

It is advantageous to focus the clinical analysis on the principal symptom and signs and avoid being distracted by minor signs and uncertain clinical data. Of course, as mentioned, if the main sign has been misinterpreted—if a tremor has been taken for ataxia or fatigue for weakness—the clinical method is derailed from the start.

Expert diagnosticians make successively more accurate estimates of the likely diagnosis, utilizing pieces of the history and findings on the examination to either affirm or exclude specific diseases. It is perhaps not surprising that the method of successive estimations works well; evidence from neuroscience reveals that this is the mechanism that the nervous system uses to process information. As the lessons of cognitive psychology have been applied to medical diagnosis, several heuristics (cognitive shortcuts) have been identified as both necessary to the diagnostic process and as pitfalls for the unwary clinician (see Tversky and Kahneman). Awareness of these heuristics offers the opportunity to incorporate corrective strategies. We openly discuss these heuristics and their pitfalls with our

colleagues and trainees in order to make them part of clinical reasoning. Investigators such as Redelmeier have identified the following categories of cognitive mistakes that are common in arriving at a diagnosis:

1. The framing effect reflects excessive weighting of specific initial data in the presentation of the problem.
2. Anchoring heuristic, in which an initial impression cannot be subsequently adjusted to incorporate new data.
3. Availability heuristic, in which experience with recent cases has an undue impact on the diagnosis of the case at hand.
4. Representative heuristic refers to the lack of appreciation of the frequency of disease in the population under consideration, a restatement of the Bayes theorem.
5. Blind obedience, in which there is undue deference to authority or to the results of a laboratory test.

With our colleague Vickery, we have reviewed the workings of these heuristics in neurological diagnosis. Any of these shortcuts produce a tendency to come to early closure in 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.

When several of the main features of a disease in its typical 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 (another paraphrasing of the Bayes theorem). Should the disease be in a stage of transition, time will allow the full picture to emerge and the diagnosis to be clarified.

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 appreciate 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. To achieve expert performance in all areas, cognitive, musical, and athletic, a prolonged period of focused attention to the subject and to personal experience is required.

PREVALENCE AND INCIDENCE OF NEUROLOGIC DISEASE

To offer the physician the broadest perspective on the relative frequency of neurologic diseases, estimates of their approximate impact in the world, taken from the Global Burden of Disease Study, commissioned by the World Health Organization and World Bank, published in *Lancet* and updated in 2010 are summarized in Fig. 1-1. The main analysis was of disability-adjusted life years (DALYs), which represent the years or life lost from premature death summed with the years of life lived with disability. Neurologic disease accounts for 8.6 percent of the total global DALY (including infections such as meningitis and encephalitis, and noncommunicable diseases such as stroke, epilepsy, dementia, and headache, but excluding traumatic brain injury). In summary, hemorrhagic stroke, ischemic stroke, and meningitis together account for approximately two-thirds of the total global burden caused by neurologic conditions. In relative terms, conditions such as Parkinson disease and multiple sclerosis were smaller contributors to the total global burden. Of course, these statistics differ markedly between developing and developed areas of the world. In addition, many neurologic conditions encountered in daily practice are not accounted for in these surveys and these frequencies of disease throughout the world were ascertained by various methods and must be considered approximations.

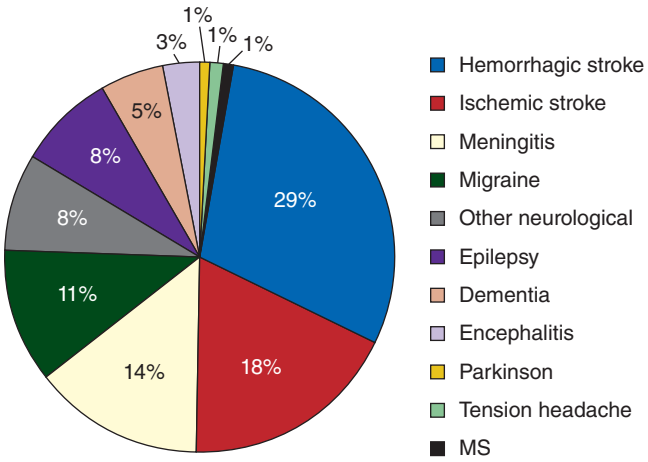

Figure 1-1. Contribution of neurologic conditions to the global burden of neurologic disease. The analysis, from WHO, includes communicable and noncommunicable diseases, but does not include traumatic brain injury or spine disease. (Modified from Chin and Vora.)

Donaghy and colleagues have provided a more detailed listing of the incidence of various neurologic diseases that are likely to be seen in the outpatient setting by a physician practicing in the United Kingdom. They note stroke as far and away the most commonly encountered condition. More focused surveys, such as the one conducted by Hirtz and colleagues, give similar rates of prevalence, with migraine, epilepsy, and multiple sclerosis being the most common neurologic disease in the general population (121, 7.1, and 0.9 per 1,000 persons in a year); stroke, traumatic brain injury, and spinal injury occurring in 183, 101, and 4.5 per 100,000 per year; and Alzheimer disease, Parkinson disease, and amyotrophic lateral sclerosis (ALS) among older individuals at rates of 67, 9.5, and 1.6 per 100,000 yearly. Data such as these assist in allocating societal resources, and they may be helpful in leading the physician to the correct diagnosis insofar as they emphasize the oft-stated dictum that "common conditions

Table 1-3

PREVALENCE OF THE MAJOR NEUROLOGIC DISORDERS IN THE UNITED STATES

	INDIVIDUALS AFFECTED
Degenerative diseases	
Amyotrophic lateral sclerosis	5×10^4
Huntington disease	5×10^4
Parkinson disease	5×10^6
Alzheimer disease	5×10^6
Macular degeneration	5×10^7
Autoimmune neurologic diseases	
Multiple sclerosis	4×10^5
Stroke, all types	5×10^6
Central nervous system trauma	
Head	2×10^6
Spinal cord	2.5×10^5
Metabolic	
Diabetic retinopathy	2×10^6
Headache	3×10^7
Epilepsy	3×10^6
Back pain	5×10^7
Peripheral neuropathy	
Total	2.5×10^7
Inherited	1×10^4
Diabetic neuropathy	2×10^6
Mental retardation	
Severe	1×10^6
Moderate	1×10^7
Schizophrenia	3×10^6
Manic depressive illness	3×10^6

occur commonly" and therefore should be considered a priori to be more likely diagnoses (Table 1-3).

TAKING THE HISTORY

In neurology, the physician is highly dependent on the cooperation of the patient for a reliable history, especially for a description of those symptoms that are unaccompanied by observable signs of disease. 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 history and examination procedure. 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. When the patient's cooperation is not possible, as for example in a comatose or confused individual or in a young child, an attempt should be made to acquire the necessary information from other sources.

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. 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 a simple description—being asked, for example, to choose a word that best describes his pain and to report precisely what he means by a particular term such as dizziness, imbalance, or vertigo. Otherwise there is disposition on the part of the patient to emphasize aspects of the history that support a superficially plausible diagnosis. This problem is now amplified by the wide array of medical information available to patients through various sources such as the Internet. The patient who is given to highly circumstantial and rambling accounts can be kept on the subject of his illness by directive questions that draw out essential points. One should avoid suggesting terms to the patient, particularly those that prematurely confirm the physician's preconceived diagnoses ("leading the witness").
2. The setting in which the illness occurred, its mode of onset and evolution, and its course are of major 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, such as the typical sudden onset of stroke. 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.
3. In general, one tends to be careless in estimating the mental capacities of patients. Attempts are sometimes made to take histories from patients who are cognitively impaired or so confused that they have no idea why they are in a doctor's office or a hospital. Young physicians and students have a natural tendency to "normalize" the patient's cognitive performance, often collaborating with a hopeful family in the misperception that no real problem exists. This attempt at sympathy does not serve the patient and may delay the diagnosis of a potentially treatable disease. 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.
4. Asking the patient to give his own interpretation of the possible meaning of symptoms sometimes exposes concern, depression, anxiety, suspiciousness, or even delusional thinking. This also may allow the patient to articulate fears about certain diseases such as brain tumor, dementia, motor neuron disease, or multiple sclerosis. Exposing these fears allows the physician to allay these concerns forthrightly.

THE NEUROLOGIC EXAMINATION

The neurologic examination begins with observations in the waiting room, and continues as the patient proceeds to the examination room and 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. A more extensive examination of attention, memory, cognitive ability, and language is undertaken if the history or the manner in which it is given indicates the problem lies in those spheres. Otherwise, asking the date and place, repeating and recalling words, and simple arithmetic are adequate screening procedures. One then proceeds from an examination of the cranial nerves to the testing of motor, reflex, and sensory functions of the upper and lower limbs. This is followed by an assessment of gait and station (standing position) are observed before or after the rest of the examination.

The thoroughness and focus of the neurologic examination must be governed by the type of clinical problem presented by the patient. To spend a half hour or more testing cerebral, cerebellar, cranial nerve, and sensorimotor function in a patient seeking treatment for a simple compression palsy of an ulnar nerve is pointless and uneconomical. Conversely, if the main problem relates to hand function, a detailed examination of the motor, sensory and higher order functions of the hand are undertaken. The examination must also be modified according to the condition of the patient. Obviously, many parts of the examination cannot be carried out in a comatose patient; also, infants and small children, as well as patients with psychiatric disease, must be examined in special ways. Similarly, the examination in acute situations that require urgent resolution must be necessarily compressed to address to essential minimum that allows intelligent initial steps.

When an abnormal finding is detected, whether cognitive, motor, or sensory, it becomes necessary to analyze the problem in a more elaborate fashion. Details of these sensitive examinations are addressed in appropriate chapters of the book and, cursorily, below.

The neurologic examination is ideally performed and recorded in a relatively uniform manner in order to avoid omissions and facilitate the subsequent analysis of records. Some variation in the order of examination from physician to physician is understandable, but each examiner over time establishes a consistent pattern. If certain portions are intentionally not performed, these omissions should be stated so that those reading the description at a later time are not left wondering whether an abnormality was not previously detected.

Portions of the general physical examination that may be particularly informative in the patient with neurologic disease should be included. For example, examination of the heart rate and blood pressure, as well as carotid and cardiac auscultation, may be essential in a patient with stroke. Likewise, the skin and eyes can reveal a number of conditions that pertain to congenital, metabolic, and infectious causes of neurologic disease. Aspects of general appearance, such as obesity or cachexia, may offer guidance to the likelihood of certain systemic illnesses.

The Detailed Examination of Patients With Neurologic Symptoms

An inordinately large number of tests of neurologic function have been devised, and it is not proposed to review all of them here. Many tests are of doubtful value or are repetitions of simpler ones and to perform all of them on one patient would be unproductive. The danger with all clinical tests is to regard them as indicators of a particular disease rather than as ways of uncovering disordered functioning of the nervous system. The following approaches are relatively simple and provide the most useful information.

Numerous guides to the examination of the nervous system are available (see the references at the end of this chapter). For a full account of these methods, the reader is referred to monographs on the subject, including those of Biller and colleagues (DeMyer's), Spillane (Bickerstaff's) Campbell (DeJong's *The Neurological Examination*), and of the staff members of the Mayo Clinic, each of which approaches the subject from a different point of view.

Testing of Higher Cortical Functions

Broadly speaking, the mental status examination has two main components, although the separation is somewhat artificial: the psychiatric aspects, which incorporate affect, mood, and normality of thought processes and content; and the cognitive aspects, which include the level of consciousness, awareness (attention), language, memory, visuospatial, and other executive abilities. These functions are tested in detail if the patient's history or behavior has provided a reason to suspect some defect.

Questions are first 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. The patient's account of his recent illness, dates of hospitalization, and day-to-day recollection of recent incidents are excellent tests of memory; the narration of the illness and the patient's choice of words (vocabulary) and syntax provide information about language ability and coherence of thinking. There are many useful bedside tests of attention, concentration, memory and cognition, for example, repetition of a series of digits in forward and reverse order, serial subtraction of 3s or 7s from 100, and recall of three items of information or a short story after an interval of 3 min. More detailed examination procedures appear in Chaps. 19–21.

If there is any suggestion of a speech or language disorder, the nature of the patient's spontaneous speech should be noted. In addition, the accuracy of reading, writing, and spelling, executing spoken commands, repeating words and phrases spoken by the examiner, naming objects, and parts of objects should be assessed.

The ability to carry out commanded tasks (praxis) is pertinent to the evaluation of several aspects of cortical function. For example, commonly used tests are carrying out commanded and imitated gestures such as hammering a nail, blowing out a candle, throwing dice and copying sequential hand positions. Visuospatial abilities may be tested by asking the patient to bisect a line, draw the numbers and hands of a clock face or the floor plan of one's home or a map of one's country, and copying figures.

Recognition (gnosis) is tested by naming of objects or pictures and describing their use.

Testing of Cranial Nerves

The function of the cranial nerves is tested as a component of most examinations, in part because defects in their function are so easily recognizable and because certain abnormalities allow precise localization of a lesion. If one suspects a lesion in the anterior cranial fossa, the sense of smell should be tested and it should be determined whether odors can be discriminated. Visual fields can be outlined by having the patient indicate when the examiner's finger moves or by counting fingers at the periphery of vision (confrontation testing), ideally by testing each eye separately. If an abnormality is suspected, perimetry provides a more sensitive method of confirming and mapping the defect. Pupil size and reactivity to light, direct, consensual, and during convergence, the position of the eyelids, and the range of ocular movements should next be observed. Details of these tests and their interpretations are given in Chaps. 11–13.

Sensation over the face is tested with a pin and wisp of cotton. Also, the presence or absence of the corneal reflexes, direct and consensually, may be determined. Care must be taken to avoid eliciting blinking by a visual stimulus.

Facial movements should be observed in repose and as the patient speaks and smiles, for a slight weakness may be more evident in these circumstances than on movements to command. Direct testing of facial power can be accomplished by asking the patent to forcefully close the eyes, purse the lips and raise the brow.

The auditory meatus and tympanic membranes should be inspected with an otoscope if there is a problem with hearing. A high-frequency (512 Hz) tuning fork held next to the ear and compared to applying it to the mastoid discloses hearing loss and distinguishes middle-ear (conductive) from neural deafness. An additional test of impaired bone or air conduction is performed by placing a high-frequency tuning fork in the center of the forehead and having the patient report any asymmetry in the sound. Audiograms and other special tests of auditory and vestibular function are needed if there is any suspicion of disease of the vestibulocochlear nerve or of the cochlea or labyrinths (see Chap. 14).

The vocal cords may 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 an asymmetrical response; 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, but a major deviation represents under action of the hypoglossal nerve and muscle on that side. The pronunciation of words should be noted. The jaw jerk (masseter tendon reflex) should be evaluated in order to localize the source of dysphagia, dysarthria, or dysphonia. In adults, abnormal reactions to tactile contact (reflexes) of the mouth and lips (such as sucking, snouting, rooting) reflect the reemergence of developmental reflexes and usually indicate disease of the frontal lobes. Failure to inhibit blinking in response to repetitive tapping of the brow (glabella) may indicate extrapyramidal or frontal disorders.

The abnormal quality of speech and articulation, dysarthria, may give indications of weakness or other disorders of the lips, tongue, larynx, and pharynx. Certain patterns also conform to disorders of the cerebellum and parts of the brainstem and cerebrum. The abnormal speech patterns of spastic, ataxic, extrapyramidal, and neuromuscular disorders are elaborated mainly in Chap. 22.

Testing of Motor Function

In the assessment of motor function, the most informative aspects are observations of the speed, power, muscle bulk, tone, and coordination. The maintenance of the supinated arms against gravity is a useful test; the weak arm, tiring first, soon begins to sag, or, in the case of a corticospinal lesion, to resume the more natural pronated position ("pronator drift"). An additional sign of subtle weakness of one side is the asymmetric "orbiting" of one forearm around the other when the patient is asked to rotate the fists or index fingers around the other. The strength of the legs can be tested with the patient prone and the knees flexed and observing downward drift of the weakened leg. In the supine position at rest, weakness due to an upper motor neuron lesion causes external rotation of the hip. In testing the power of the legs, it should be kept in mind that the hip flexors and quadriceps of most adults are stronger than the arm of the examiner.

It is useful to have the limbs exposed and to inspect them for atrophy and fasciculations. Abnormalities of movement and posture as well as tremors may be revealed by observing the limbs at rest and in motion (see Chaps. 4 to 5). This is accomplished by watching the patient maintain the arms and move them from the prone to the 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 may be 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 limbs are observed to determine if during natural activities, there is excessive or reduced quantity, speed or excursion of movement, tremor, and if normal postural adjustments. The resistance of muscles during passive

movement by the examiner (tone) gives information about spasticity and extrapyramidal rigidity.

Testing of Reflexes

Testing of the tendon reflexes at the biceps, triceps, supinator-brachioradialis, patellar, and Achilles tendon are an adequate sampling of reflex activity. Underactive or barely elicitable reflexes can be facilitated by voluntary contraction of other muscles, such as pulling the grasped hands against each other (Jendrassik maneuver).

The plantar reflexes, particularly the elicitation of the Babinski sign by stroking the lateral sole of the foot from heel to toe, are an essential part of most examinations. The sign is a dependable marker of damage to the corticospinal system as described in Chap. 3. The main features of the Babinski sign are dorsiflexion of the large toe and fanning of the other toes. Interpretation of the plantar response poses some difficulty because reactions besides the Babinski sign can be evoked. These include a quick withdrawal response of the foot and leg that does not signify disease; and a pathologic slower, spinal flexor reflex (flexion of knee and hip and dorsiflexion of toes and foot, "triple flexion") that has similar significance to the Babinski sign. Avoidance and withdrawal responses interfere with the interpretation of the Babinski sign and can sometimes be overcome by utilizing alternative stimuli (e.g., squeezing the calf or Achilles tendon, flicking the fourth toe, downward scraping of the shin, lifting the straight leg, and others) or by having the patient scrape his own sole.

Absence of the superficial cutaneous reflexes of the abdominal, cremasteric, and other muscles are useful ancillary tests for detecting corticospinal lesions, particularly when unilateral.

Testing of Sensory Function

Because this part of the examination is attainable only through the subjective responses of the patient, it requires considerable cooperation. At the same time, it is subject to overinterpretation and suggestibility. Usually, sensory testing is reserved for the end of the examination and, if the findings are to be reliable, should not be prolonged. Each test should be explained briefly; too much discussion with a meticulous, introspective patient encourages the reporting of meaningless 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. Moving the stimulus from an area of diminished sensation into a normal area is recommended because it enhances the perception of a difference. The finding of a zone of heightened sensation ("hyperesthesia") also calls attention to a disturbance of superficial sensation.

The ability to perceive vibration may be tested by comparing the thresholds at which the patient and examiner lose perception at comparable bony prominences. We suggest recording the number of seconds for which the examiner appreciates vibration at the malleolus, toe, or finger after the patient reports that the fork has stopped buzzing. Joint position and the perception of movement of a digit can be tested by holding the body part at the sides and making small excursion at the adjacent joint.

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. Sensory testing is considered in greater detail in Chaps. 7 and 8.

Testing of Gait and Stance

The examination is completed by observing the patient arise from a chair, stand and walk. An abnormality of stance or gait may be the most prominent or only neurologic abnormality, as in certain cerebellar or frontal lobe syndromes; and an impairment of posture and highly automatic adaptive movements in walking may provide diagnostic clues in the early stages of diseases such as Parkinson disease. Having the patient walk in tandem on a straight line may bring out a lack of balance and walking on the sides of the soles may elicit dystonic postures in the hands and trunk. Hopping or standing on one foot may also betray a lack of balance or weakness. Standing with feet together and eyes closed will bring out disequilibrium due to sensory loss (Romberg test) that is usually attributable to a disorder of the large diameter sensory fibers in the nerves and posterior columns of the spinal cord. Disorders of gait are discussed in Chap. 6.

The Screening Neurological Examination

In the situation of a patient without neurologic symptoms, brevity is desirable but any test that is undertaken should be done carefully and recorded. Accurate recording of negative data may be useful in relation to some future illness that requires examination. As indicated in Table 1-4, the patient's orientation, insight, judgment, and the integrity

Table 1-4

BRIEF NEUROLOGIC EXAMINATION IN THE GENERAL MEDICAL OR SURGICAL PATIENT

1. Orientation, insight into illness, language assessed during taking of the history
2. Size of pupils, reaction to light, visual and auditory acuity
3. Movement of eyes, face, tongue
4. Examination of the outstretched hands for atrophy, pronating or downward drift, tremor, power of grip, and wrist dorsiflexion
5. Biceps, supinator, and triceps tendon reflexes
6. Inspection of the legs during active flexion and extension of the hips, knees, and feet
7. Patellar, Achilles, and plantar reflexes
8. Vibration sensibility in the fingers and toes
9. Finger-to-nose and heel-to-shin testing of coordination
10. Gait

of language function are readily assessed in the course of taking the history. With respect to the cranial nerves, the size of the pupils and their reaction to light, ocular movements, visual and auditory acuity, and movements of the face, palate, and tongue should be tested. Observing the bare outstretched arms for atrophy, weakness (pronator drift), tremor, or abnormal movements; checking the strength of the extended and outstretched fingers; inquiring about sensory disturbances; and eliciting the biceps, brachioradialis, and triceps reflexes are usually sufficient for the upper limbs. Inspection of the legs while the feet, toes, knees, and hips are actively flexed and extended; elicitation of the patellar, Achilles, and plantar reflexes; testing of vibration and position sense in the fingers and toes; and assessment of coordination by having the patient alternately touch his nose and the examiner's finger and run his heel up and down the front of the opposite leg, and observation of walking complete the essential parts of the neurologic examination.

This entire procedure adds only a few minutes to the physical examination but the routine performance of these simple tests provides clues to the presence of disease of which the patient is not aware. For example, the finding of absent Achilles reflexes and diminished vibratory sense in the feet and legs alerts the physician to the possibility of diabetic or nutritional neuropathy, even when the patient does not report symptoms.

THE COMATOSE PATIENT

Although subject to obvious limitations, careful examination of the stuporous or comatose patient yields considerable information concerning the function of the nervous system. It is remarkable that, with the exception of cognitive function, almost all parts of the nervous system, including the cranial nerves, can be evaluated in the comatose patient. The demonstration of signs of focal cerebral or brainstem disease or of meningeal irritation is useful in the differential diagnosis of diseases that cause stupor and coma. The adaptation of the neurologic examination to the comatose patient is described in Chap. 16.

THE ANXIOUS, DEPRESSED, PSYCHOTIC, OR HYSTERICAL PATIENT

One is compelled in the examination of psychiatric patients to be unusually critical of their statements and reports or symptoms. Many people, even those without psychiatric conditions, are highly suggestible and may display changes in sensory and motor function. The depressed patient, for example, may perceive impaired memory or weakness when actually there is neither amnesia nor reduced power, or the sociopath or hysteric may feign paralysis. The opposite is as often true: psychotic patients may make accurate observations of their symptoms, only to have them ignored because of their mental state. It is well to keep in mind that patients with even the most extreme psychiatric disease are subject to all of the neurologic conditions typical of others of their age.

By the manner in which the patient expresses ideas and responds to spoken or written requests, it is possible to determine whether there are hallucinations or delusions, defective memory, or other recognizable symptoms of brain disease merely by watching and listening to the patient. On occasion, mute and resistive patients judged to be psychotic prove to have some widespread cerebral disease.

INFANTS AND SMALL CHILDREN

The reader is referred to the special methods of examination described by Volpe and the staff members of the Mayo Clinic, which are listed in the references and described in Chap. 27. Many of these tests address the developmental aspects of the child's nervous system, and although some signs may be difficult to obtain because of the age of the patient, they still stand as the best reflections of the child's neurologic state.

THE GENERAL MEDICAL EXAMINATION

The general medical examination often reveals evidence of an underlying systemic disease that has secondarily affected the nervous system. In fact, many of the most serious neurologic problems are of this type. Two common examples will suffice: adenopathy or a lung infiltrate implicates neoplasia or sarcoidosis as the cause of multiple cranial nerve palsies, and the presence of low-grade fever, anemia, a heart murmur, and splenomegaly in a patient with unexplained stroke points to a diagnosis of bacterial endocarditis with embolic occlusion of cerebral arteries. The examination of a patient with stroke is includes a determination of blood pressure, auscultation for carotid bruits, heart murmurs, and palpation of the pulse for heart rhythm.

INTEGRATION OF NEUROANATOMY, NEUROPHYSIOLOGY, MOLECULAR GENETICS, NEUROIMAGING, AND NEUROPATHOLOGY WITH THE CLINICAL METHOD

Once the technique of obtaining reliable clinical data is attained, knowledge of the basic sciences of neurology is necessary to determine the cause of disease and its treatment. For this reason, each of the later chapters dealing with the motor system, sensation, special senses, consciousness, memory, and language is introduced by a review of the anatomic and physiologic facts that are necessary for understanding the associated clinical disorders.

Physicians wishing to master neurology should be familiar with the anatomy of the corticospinal tract; motor unit (anterior horn cell, nerve, and muscle); basal ganglionic and cerebellar motor connections; main sensory

pathways; cranial nerves; hypothalamus and pituitary; reticular formation of brainstem and thalamus; limbic system; areas of cerebral cortex and their major connections; visual, auditory, and autonomic systems; and cerebrospinal fluid pathways. A working knowledge of neurophysiology should include an understanding of neural excitability and nerve impulse propagation, neuromuscular transmission, and contractile process of muscle; spinal reflex activity; central neurotransmission; processes of neuronal excitation, inhibition, and release; and cortical activation and seizure production. The genetics and molecular biology of neurologic disease have assumed increasing importance in the past few decades. The practitioner should be familiar with the terminology of mendelian and mitochondrial genetics and the main aberrations in the genetic code that give rise to neurologic disease.

The physician must be familiar with the imaging characteristics of the multitude of clinical diseases encountered in practice, and the risk and pitfalls of each technique, including computed tomography (CT), magnetic resonance imaging (MRI), radiographs, including those incorporating contrast agents, and ultrasound as discussed in Chap. 2.

We believe the neurologist is greatly aided by knowledge of the neuropathologic changes that are produced by processes such as infarction, hemorrhage, demyelination, physical trauma, inflammation, neoplasm, and infection, to name the more common ones. Experience with the gross and microscopic appearances of these disease processes greatly enhances one's ability to explain their clinical effects. The ability to visualize the abnormalities of disease in nerve and muscle, brain and spinal cord, meninges, and blood vessels gives one a strong sense of which clinical features to expect of a particular process and which features are untenable or inconsistent with a particular diagnosis. An additional advantage of being exposed to neuropathology is, of course, that the clinician is able to intelligently evaluate pathologic changes and reports of material obtained by biopsy. For many conditions there is a parallel representation of neuropathology through various imaging techniques. This allows the clinician to deduce the pathology from the imaging appearance and vice versa.

From the foregoing description of the clinical method, it is evident that the use of laboratory aids, including imaging in the diagnosis of diseases of the nervous system, is ideally preceded by rigorous clinical examination. As in all of medicine, laboratory study can be planned intelligently only on the basis of clinical information. To reverse this process is wasteful of medical resources and prone to the discovery of irrelevant information, and in some cases exposes a patient to unnecessary risk.

In the prevention of neurologic disease, however, one resorts to two other approaches, namely, the use of genetic information and laboratory screening tests. Biochemical screening tests are applicable to an entire population and permit the identification of neurologic diseases in individuals, mainly infants and children, who have yet to show their first symptom; in some diseases, treatment can be instituted before the nervous system has suffered damage. Similarly in adults, screening for atherosclerosis and its underlying metabolic causes is profitable in certain populations as a way of preventing stroke. Genetic information enables the neurologist to arrive at the diagnosis of certain illnesses and to identify patients and relatives at risk of developing certain diseases.

The laboratory methods that are available for neurologic diagnosis are discussed in the next chapter and in Chap. 2, on clinical electrophysiology. The relevant principles of genetic and laboratory screening methods for the prediction of disease are presented in the discussion of the disease to which they are applicable.

THERAPEUTICS IN NEUROLOGY

There are a growing number of neurologic diseases for which specific therapy is available. Through advances in neuroscience, their number is steadily increasing. Among the most sweeping changes, now that many infectious diseases of the nervous system are being addressed, have been entirely novel medications for stroke, multiple sclerosis, Parkinson disease, migraine, neuropathy, brain tumor, and epilepsy as summarized in a review of 200 years of neurology by Ropper. These therapies and the dosages, timing, and manner of administration of particular drugs are considered in later chapters in relation to the description of individual diseases and detailed in Samuels's *Manual of Neurologic Therapeutics*, cited in the references. The neurologist should also be familiar with the proper application of surgical treatment when it is an integral part of the amelioration or cure of disease, as it is for brain tumor, degenerative and neoplastic diseases of the spine, cerebral aneurysm, extracranial arterial stenosis, and some congenital disease of the brain and spinal cord. There are, in addition, many diseases in which neurologic function can be restored to a varying degree by appropriate rehabilitation measures or by the judicious use of therapeutic agents.

Randomized controlled trials play an ever-increasing role in therapeutic decisions. Claims for the effectiveness of a particular therapy based on statistical analysis of large-scale clinical studies must be treated circumspectly. Was the study well conceived as reflected in a clearly stated hypothesis and outcome criteria; was there adherence to the plans for randomization and admission of cases into the study; were the statistical methods appropriate; and were the controls truly comparable? It has been our experience that the original results must be accepted with caution and it is prudent to wait until further studies confirm the benefits that have been claimed.

There are, of course, many instances in which evidence is not available or is not applicable to difficult individual therapeutic decisions. This is in part true because small albeit statistically significant effects in large groups may be of little consequence when applied to an individual patient. It goes without saying that data derived from trials must be used in the context of a patient's overall physical and mental condition and age. Furthermore, for many neurologic conditions there is, at the moment, inadequate evidence on which to base treatment. Here, the physician

makes judgments based on partial or insufficient data. Even deciding purposefully to wait before committing to an intervention displays wisdom.

Even when no effective treatment is possible, neurologic diagnosis is more than an intellectual pastime. The first step in the scientific study of any disease process is its identification in the living patient.

In closing this introductory chapter, a comment regarding the extraordinary burden of diseases of the nervous system is appropriate. It is not just that conditions such as brain and spinal cord trauma, stroke, epilepsy, developmental delay, psychiatric diseases, and dementia are ubiquitous, but that these are highly disabling and often chronic in nature, altering in a fundamental way the lives of affected individuals. Furthermore, the promise of cure or amelioration by new techniques such as molecular biology, genetic therapy, and brain–computer interfaces has excited vast interest, for which reason aspects of the current scientific insights are included in appropriate sections of the book.

References

Biller J, Greuner G, Brazis P: *DeMyer's: Technique of the Neurologic Examination: A Programmed Text*, 6th ed. New York, McGraw-Hill, 2011.

Campbell WW: *DeJong's The Neurological Examination*, 7th ed. Philadelphia, Lippincott Williams & Wilkins, 2012.

Chimowitz MI, Logigian EL, Caplan LP: The accuracy of bedside neurological diagnoses. *Ann Neurol* 28:78, 1990.

Chin JH, Vora N: The global burden of neurologic diseases. *Neurology* 83:349, 2014.

Donaghy M, Compston A, Rossor M, Warlow C: Clinical diagnosis. In: *Brain's Diseases of the Nervous System*, 11th ed. Oxford, Oxford University Press, 2001, pp 11–60.

Global Burden of Disease Study 2010. *Lancet* 380:2053, 2012.

Hirtz D, Thurman DJ, Gwinn-Hardy K, et al: How common are the "common" neurologic disorders? *Neurology* 68:326, 2007.

Holmes G: *Introduction to Clinical Neurology*, 3rd ed. Revised by Bryan Matthews. Baltimore, Williams & Wilkins, 1968.

Mayo Clinic Examinations in Neurology, 7th ed. St. Louis, Mosby-Year Book, 1998.

Redelmeier DA: Improving patient care. The cognitive psychology of missed diagnoses. *Ann Intern Med* 142:115, 2005.

Ropper AH: Two centuries of neurology and psychiatry in the Journal. *New Engl J Med* 367:58, 2012.

Samuels MA, Ropper AH: *Samuels's Manual of Neurologic Therapeutics*, 8th ed. Philadelphia, Lippincott Williams & Wilkins, 2010.

Spillane JA: *Bickerstaff's Neurological Examination in Clinical Practice*, 6th ed. Oxford, Blackwell Scientific, 1996.

Tversky A, Kahneman D: Judgment under uncertainty; heuristics and biases. *Science* 185:1124, 1974.

Vickery B, Samuels MA, Ropper AH: How neurologists think: A cognitive psychology perspective on missed diagnoses. *Ann Neurol* 67:425, 2010.

Volpe JJ: *Neurology of the Newborn*, 5th ed. Philadelphia, Saunders, 2008.

2

Diagnostic Testing in Neurologic Disease

Neurologic diagnosis is frequently determined solely on the basis of careful history and examination. In that case, ancillary testing is unnecessary or simply corroborates the clinical impression. It also happens that the diagnoses can be reduced to a few possibilities but that testing is necessary to arrive at the correct one. The aim of the neurologist is to arrive at a diagnosis by artful integration of clinical data with laboratory procedures. Commonly the clinician already has at his disposal some laboratory information when the patient presents for a consultation. This may orient or distract from the correct course of action.

Only a few decades ago, the only laboratory tests available to the neurologist were examination of a sample of cerebrospinal fluid, radiography of the skull and spinal column, contrast myelography, pneumoencephalography, and electrophysiologic tests. The physician's armamentarium has been expanded to include a multitude of neuroimaging modalities, biochemical and immunologic assays, and genetic analyses. Some of these new methods give the impression of such accuracy that there is a temptation to substitute them for a detailed history and physical examination. Moreover, it is common in practice for laboratory testing to reveal abnormalities that are of no significance to the problem at hand. Consequently, the physician should always judge the relevance and significance of laboratory data only in the context of clinical findings. Hence, the neurologist must be familiar with all laboratory procedures relevant to neurologic disease, their reliability, and their hazards.

What follows is a description of laboratory tests that have application to a diversity of neurologic diseases. Certain procedures that are pertinent to a particular category of disease—e.g., audiography to study deafness; electronystagmography (ENG) in cases of vertigo; as well as nerve and muscle biopsy, where there is neuromuscular disease—are presented in the chapters devoted to these disorders.

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 processes that alter intracranial pressure. Patterns of findings, or "formulas," in the CSF generally denote particular classes of disease; these are summarized in Table 2-1. The fluid is most often obtained by lumbar puncture, the technique and indications for which are described below.

Lumbar Puncture

The lumbar puncture (LP) is performed to obtain pressure measurements and procure a sample of the CSF for cellular, cytologic, chemical, bacteriologic, and other examination. It is also utilized in special circumstances to aid in therapy by the instillation of anesthetics, antibiotics, antitumor agents, or for drainage in order to reduce CSF pressure. Another diagnostic use is the injection of radiopaque substances, as in myelography, or radioactive agents, as in radionuclide cisternography.

It is advisable to determine that the patient's coagulation function is adequate for safe LP. In general, it is safe to perform LP on patients without history or overt signs of coagulopathy and those who are not taking anticoagulant medications. An international normalized ratio (INR) less than or equal to 1.4 and platelet count greater than 50,000/mm^3 are generally acceptable, as is the use of aspirin in conventional doses. Individuals with impaired platelet function from diseases such as alcoholism or uremia may have bleeding complications. For patients receiving heparin by continuous intravenous infusion, the LP is best performed after the infusion has been discontinued for a period of time, and if possible, the partial thromboplastin time has been determined to be in a safe range. There are circumstances, however, where these provisions are not practical.

LP carries some risks if the CSF pressure is very high (evidenced mainly by headache and papilledema), for it increases the possibility of a fatal cerebellar or transtentorial herniation. The risk is considerable when there is an intracranial mass that distorts and displaces brain tissue, particularly asymmetric mass lesions near the tentorium or foramen magnum. The risk is much lower in patients with subarachnoid hemorrhage, in hydrocephalus with communication among all the ventricles, or with pseudotumor cerebri. Indeed, these are conditions in which repeated LPs may be employed as a therapeutic measure. In patients with purulent meningitis, there is also a small

Table 2-1

CHARACTERISTIC CSF FORMULAS

CONDITION	CELLS	PROTEIN	GLUCOSE	OTHER FEATURES
Bacterial infection	WBC >50/mm^3, often greatly increased	100–250 mg%	20–50 mg%; usually lower than half of blood glucose level	Gram stain shows organisms; pressure increased
Viral, fungal, spirochetal infection	WBC 10–100/mm^3	50–200 mg%	Normal or slightly reduced	Special culture techniques required; pressure normal or slightly increased
Tuberculous infection	WBC >25/mm^3	100–1,000 mg%	<50, often markedly reduced	Special culture techniques and PCR may be needed to detect organisms
Subarachnoid hemorrhage	RBC >500/mm^3; slight increase in WBC	60–150 mg%	Normal; slightly reduced later	Must be distinguished from traumatic lumbar puncture by presence of xanthochromia of spun sample; greatly increased pressure
Cerebral hemorrhage, trauma	RBC 50–200/mm^3; higher if ventricular rupture of blood	50–150 mg%	Normal	Pressure may be elevated
Ischemic stroke	Normal or few WBC	Normal	Normal	Normal pressure unless brain swelling
Multiple sclerosis	Normal or few WBC	Normal or slightly increased	Normal	Increased IgG fraction and oligoclonal bands
Meningeal cancer	WBC 10–100/mm^3	Usually elevated	Normal or depressed	Neoplastic cells in CSF; elevation of certain protein markers (e.g., β_2-microglobulin)

IgG, immunoglobulin G; PCR, polymerase chain reaction; RBC, red blood cells; WBC, white blood cells.

risk of herniation, but this is outweighed by the need for a definitive diagnosis and the institution of appropriate treatment at the earliest moment. With this last exception, LP should generally be preceded by computed tomography (CT) or magnetic resonance imaging (MRI) whenever an elevation of intracranial pressure is suspected.

If imaging procedures disclose a mass lesion that poses a risk of herniation, yet it is considered essential to have the information yielded by CSF examination, the LP may be performed—with certain precautions. If the pressure proves to be very high, one should obtain the smallest necessary sample of fluid, adequate for the diagnosis of the suspected disease, administer mannitol or another hyperosmolar agent, and ideally 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. Corticosteroids are particularly useful in situations in which the increased intracranial pressure is caused by vasogenic cerebral edema (e.g., tumor-associated edema).

Cisternal (foramen magnum) puncture and lateral cervical subarachnoid puncture are infrequently performed, but are safe in the hands of an expert. LP is preferred except in obvious instances of spinal block requiring a sample of cisternal fluid or for myelography above the lesion. In critical care practice, CSF is often obtained from external ventricular drain, and care is taken to maintain a closed drainage system and antiseptic technique.

Technique and Complications of LP

Experience teaches the importance of meticulous technique and proper positioning of the patient. LP should be done under locally sterile conditions. The patient is placed in the lateral decubitus position, preferably on the left side for right-handed physicians, with hips and knees flexed, and the head as close to the knees as comfort permits. The patient's hips should be vertical, the back aligned near the edge of the bed. The puncture is usually easiest to perform at the L3-L4 interspace, which corresponds in many individuals to the axial plane of the iliac crests, or at the interspace above or below. In infants and young children, in whom the spinal cord may extend to the level of the L3-L4 interspace, lower levels should be used.

Xylocaine is typically injected in and beneath the skin to reduce local discomfort. Warming of the analgesic by rolling the vial between the palms seems to diminish the burning sensation that accompanies cutaneous infiltration. The bevel of the LP needle should be oriented in the longitudinal plane of the dural fibers (see below regarding atraumatic needles). It is usually possible to appreciate a palpable "give" as the needle approaches the dura, followed by a subtle "pop." At this point, the trocar should be removed slowly from the needle to avoid sucking a nerve rootlet into the lumen and causing radicular pain. Sciatic pain during the insertion of the needle indicates that it is placed too far laterally. If the flow of CSF slows, the head of the bed can be elevated slowly. Rarely, 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 usually can 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 the result of an improperly placed needle than of obliteration of the subarachnoid space by a compressive lesion of the cauda equina or by adhesive arachnoiditis. In an obese patient,

in whom palpable spinal landmarks cannot be appreciated, or after several unsuccessful attempts in any patient, fluoroscopy can be employed to position the needle.

LP has few serious complications. The most common is headache, estimated to occur in one-third of patients, but in severe form in far fewer. A history of migraine headaches may increase the incidence of prolonged or severe post-LP headache. The headache becomes apparent when the patient assumes the upright posture and is presumably the result of a reduction of CSF pressure from leakage of fluid at the puncture site and tugging on cerebral and dural vessels. Prolonged recumbency immediately after the procedure has not been shown to prevent headache, but is often implemented nonetheless. Strupp and colleagues have found that the use of an atraumatic needle almost halved the incidence of headache. Curiously, headaches are twice as frequent after diagnostic LP as they are after spinal anesthesia. Severe headache can be associated with vomiting and mild neck stiffness. Unilateral or bilateral sixth nerve palsy occur rarely after LP, even at times without headache, and rare cases of hearing loss, facial numbness, or facial palsy have been reported. The syndrome of low CSF pressure, its treatment by "blood patch," and other complications of LP are considered further in Chap. 29.

Bleeding into the spinal meningeal or epidural spaces after LP can occur in patients with abnormal coagulation, as discussed earlier. Treatment of bleeding complications is by reversal of the coagulopathy and, in rare cases, surgical evacuation of the clot. Purulent meningitis and disc space infections rarely complicate LP.

Examination Procedures for CSF

Once the subarachnoid space has been entered, the pressure and fluctuations with respiration of the CSF are observed, and samples of fluid are obtained. The gross appearance of the fluid is noted, after which the CSF, in separate tubes, can be examined for a number of features. The standard determinations are of the number and type of cells, protein and glucose content, and microscopy and bacterial culture. In addition, the following can be studied: (1) tumor cells (cytology and flow cytometry); (2) presence of oligoclonal bands or content of gamma globulin; (3) serologic (immunological) tests; (4) substances elaborated by some tumors (e.g., β_2 microglobulin); and (5) markers pertaining to certain infections such as fungi, cryptococcal and other antigen and India ink preparations, mycobacteria, DNA of herpesvirus, cytomegalovirus and other organisms (by polymerase chain reaction), markers of certain infections (e.g., 14-3-3 protein), and viral isolation.

Pressure

With the patient in the lateral decubitus position, the CSF pressure is measured by a manometer attached to the needle in the subarachnoid space. In the normal adult, the opening pressure varies from 100 to 180 mm H_2O, or 8 to 14 mm Hg. In children, the pressure is in the range of 30 to 60 mm H_2O. A pressure above 200 mm H_2O with the patient relaxed and legs straightened generally reflects increased intracranial pressure. In an adult, a pressure of 50 mm H_2O or below indicates intracranial hypotension, generally caused by leakage of spinal fluid or systemic dehydration (see Avery and colleagues). When measured with the needle in the lumbar sac and the patient in a sitting position, the fluid in the manometer rises to the level of the cisterna magna (pressure is approximately double that obtained in the recumbent position). It fails to reach the level of the ventricles because the latter are in a closed system under slight negative pressure, whereas the fluid in the manometer is influenced by atmospheric pressure. Normally, with the needle properly placed in the subarachnoid space, the fluid in the manometer oscillates through a few millimeters in response to the pulse and respiration and rises promptly with coughing, straining, and with jugular vein or abdominal compression. An apparent low pressure can also be the result of a needle aperture that is not fully within the subarachnoid space; this is evidenced by the lack of expected fluctuations in pressure with these maneuvers.

The presence of a spinal subarachnoid block was in the past confirmed by jugular venous compression (Queckenstedt test, which tests for a rapid rise in CSF pressure after application of the pressure on the vein). The maneuver risks worsening of a spinal block or of raised intracranial pressure and is of historical interest.

Gross Appearance and Pigments

Normally, the CSF is clear and colorless. Minor degrees of color change are best detected by comparing test tubes of CSF and water against a white background (by daylight rather than by fluorescent illumination) or by looking down into the tubes from above. The presence of red blood cells imparts a hazy or ground-glass appearance; at least 200 red blood cells (RBCs) per cubic millimeter (mm^3) must be present to detect this change. The presence of 1,000 to 6,000 RBCs per cubic millimeter imparts a hazy pink to red color, depending on the amount of blood; centrifugation of the fluid or allowing it to stand causes sedimentation of the RBCs. Several hundred or more white blood cells (WBCs) in the fluid (pleocytosis) may cause a slight opaque haziness.

A traumatic tap, in which blood from the epidural venous plexus has been introduced into the spinal fluid, may seriously confuse the diagnosis if it is incorrectly interpreted as indicating a preexistent subarachnoid hemorrhage. To distinguish between these two types of "bloody taps," two or three serial samples of fluid may be collected. With a traumatic tap, there is usually a decreasing number of RBCs in the subsequent tubes. Also with a traumatic tap, the CSF pressure is usually normal, and if a large amount of blood is mixed with the fluid, it will clot or form fibrinous webs. These changes are not seen with preexistent hemorrhage because the blood has been greatly diluted with CSF and defibrinated by enzymes in the CSF. In subarachnoid hemorrhage, the RBCs begin to hemolyze within a few hours, imparting a pink-red discoloration (erythrochromia) to the supernatant fluid; if the spinal fluid is sampled more than a day following the hemorrhage, the fluid

will have become yellow-brown (xanthochromia). Prompt centrifugation of bloody fluid from a traumatic tap will yield a colorless supernatant; only with large amounts of venous blood (RBC >100,000/mm^3) will the supernatant fluid be faintly xanthochromic due to contamination with serum bilirubin and lipochromes.

The fluid from a traumatic tap should contain approximately one or two WBCs per 1,000 RBCs assuming that the hematocrit and white blood cell count are normal, but in reality this ratio varies. With subarachnoid hemorrhage, the proportion of WBCs rises as RBCs hemolyze, sometimes reaching a level of several hundred per cubic millimeter; but the vagaries of this reaction are such that it, too, cannot be relied upon to distinguish traumatic from preexistent bleeding. The same can be said for crenation of RBCs, which occurs in both types of bleeding. Why red corpuscles undergo rapid hemolysis in the CSF is not clear. It is surely not because of osmotic differences, as the osmolarity of plasma and CSF is essentially the same. Fishman suggested that the low protein content of CSF disequilibrates the red cell membrane in some way.

The pigments that discolor the CSF following subarachnoid hemorrhage are oxyhemoglobin, bilirubin, and methemoglobin as described by Barrows and colleagues. In pure form, these pigments are colored red (orange to orange-yellow with dilution), canary yellow, and brown, respectively. Oxyhemoglobin appears within several hours of hemorrhage, becomes maximal in approximately 36 h, and diminishes over a 7- to 9-day period. Bilirubin begins to appear in 2 to 3 days and increases in amount as the oxyhemoglobin decreases. Methemoglobin appears when blood is loculated or encysted and isolated from the flow of CSF. Spectrophotometric techniques can be used to distinguish the various hemoglobin breakdown products and thus determine the approximate time of bleeding.

Not all xanthochromia of the CSF is caused by hemolysis of RBCs. With severe jaundice, both conjugated and unconjugated bilirubin diffuses into the CSF. The quantity of bilirubin in the CSF ranges from one-tenth to one-hundredth that in the serum. Elevation of CSF protein from any cause results in a faint opacity and xanthochromia. Only at protein levels greater than 150 mg/100 mL does the coloration become visible to the naked eye. Hypercarotenemia and hemoglobinemia (through hemoglobin breakdown products, particularly oxyhemoglobin) also impart a yellow tint to the CSF, as do blood clots in the subdural or epidural space of the cranium or spinal column. Myoglobin does not appear in the CSF because a low renal threshold for this pigment permits rapid clearing from the blood.

Cellularity

During the first month of life, the CSF contains a larger number of mononuclear cells than in adults. Beyond this period, the CSF is normally nearly acellular (i.e., fewer than 5 lymphocytes or other mononuclear cells per cubic millimeter). An elevation of WBCs in the CSF always signifies a reactive process, either to infectious agents, blood, chemical substances, an immunologic inflammation, a neoplasm, or vasculitis. The WBCs can be counted in an ordinary counting chamber, but their identification requires centrifugation of the fluid, preferably with a Wright stain of the sediment. Identification of malignant cells by the cytology laboratory is usually done by cytocentrifugation or other semiautomated liquid-based method, followed by cell fixation and staining (Bigner and Den Hartog-Jage). One can recognize and differentially count neutrophilic and eosinophilic leukocytes (the latter being prominent in some parasitic infections, neurosyphilis, and cholesterol emboli), lymphocytes, plasma cells, mononuclear cells, macrophages, and tumor cells (see Bigner and also Den Hartog-Jaeger). Bacteria and fungi can be seen in routinely stained preparations. An India ink preparation helps to distinguish between lymphocytes and *Cryptococcus* organisms. Acid-fast bacilli will be found in appropriately stained samples. The monograph by Ali and Cibas is an excellent reference on CSF cytology. Flow cytometry permits the distinction between polyclonal and monoclonal proliferations, thus aiding in the detection of leukemia and lymphoma, and immunostaining techniques help identify metastatic solid tumors. These and other methods for the examination of cells in the CSF are discussed in the appropriate chapters.

Proteins

In contrast to the high-protein content of blood (5,500 to 8,000 mg/dL), that of the lumbar spinal fluid is 45 to 50 mg/dL or less in the adult. The protein content of CSF from the basal cisterns is 10 to 25 mg/dL and that from the ventricles is 5 to 15 mg/dL. Based on work by Fishman and colleagues, this gradient may reflect the fact that CSF proteins leak to a greater degree at the lumbar roots than at higher levels of the neuraxis. An alternative explanation derives from the manner in which the spinal fluid is an ultrafiltrate of blood made by the choroid plexus in the lateral and the fourth ventricles, analogous to the formation of urine by the glomerulus. The amount of protein in the CSF would then be proportional to the length of time the fluid is in contact with the blood–CSF barrier. Thus shortly after it is formed in the ventricles, the protein is low. More caudally in the basal cisterns, the protein is higher and in the lumbar subarachnoid space it is highest of all. In children, the protein concentration is somewhat lower at each level (<20 mg/dL in the lumbar subarachnoid space). Levels higher than normal indicate a pathologic process in or near the ependyma or meninges—in either the brain, spinal cord, or nerve roots—although the cause of modest elevations of the CSF protein, in the range of 75 mg/dL, frequently remains obscure.

As one would expect, bleeding into the ventricles or subarachnoid space results in spillage not only of RBCs but of serum proteins. If the serum protein concentrations are normal, the CSF protein should increase by about 1 mg/1,000 RBCs. The same holds for a traumatic puncture that allows seepage of venous blood into the CSF at the puncture site. However, in the case of subarachnoid hemorrhage, caused by the irritating effect of hemolyzed RBC upon the leptomeninges, the CSF protein may be increased by many times this ratio.

The protein content of the CSF in bacterial meningitis may reach 500 mg/dL or more. Viral infections induce a less intense and mainly lymphocytic reaction and a lesser elevation of protein—usually 50 to 100 mg/dL but sometimes up to 200 mg/dL; in some instances of viral meningitis and encephalitis the protein content is normal. Brain tumors, by opening the blood–CSF barrier, can raise the total protein. Protein values as high as 500 mg/dL are found in exceptional cases of the Guillain-Barré syndrome and in chronic inflammatory demyelinating polyneuropathy. Values in the lumbar CSF of 1,000 mg/dL or more usually indicate a block to CSF flow, typically in the spinal canal; the fluid is then deeply yellow and clots readily because of the presence of fibrinogen, a phenomenon called Froin syndrome. Partial CSF blocks by ruptured discs or tumor may elevate the protein to 100 to 200 mg/dL. Low CSF protein values are sometimes found in meningismus (a febrile illness in children with signs of meningeal irritation but normal CSF), in hyperthyroidism, or in conditions that produce low CSF pressure (e.g., after a recent LP as indicated in Chap. 29).

The quantitative partition of CSF proteins by electrophoretic and immunochemical methods demonstrates the presence of most of the serum proteins with a molecular weight of less than 150 to 200 kDa. The protein fractions that have been identified electrophoretically are prealbumin and albumin as well as alpha$_1$, alpha$_2$, beta$_1$, beta$_2$, and gamma globulin fraction, the last of these being accounted for mainly by immunoglobulins (the major immunoglobulin in normal CSF is IgG). The gamma globulin fraction in CSF is approximately 70 percent of that in serum. Table 2-2 gives the quantitative values of the different fractions. Immunoelectrophoretic methods have also demonstrated the presence of glycoproteins, ceruloplasmin, hemopexin, beta-amyloid, and tau proteins. Large molecules—such as fibrinogen, IgM, and lipoproteins—are mostly excluded from the CSF unless generated there by disease states.

There are other notable differences between the protein fractions of CSF and plasma. The CSF always contains a prealbumin fraction and the plasma does not. Although derived from plasma, this fraction, for an unknown reason, concentrates in the CSF, and its level is greater in ventricular than in lumbar CSF, perhaps because of its concentration by choroidal cells. Also, tau (also identified as beta$_2$-transferrin) is detected only in the CSF and not in other fluids; its concentration is higher in the ventricular than in the spinal fluid. The concentration of tau protein and in particular the ratio of tau to beta-amyloid, has found use in the diagnosis of Alzheimer disease, as discussed in Chap. 38. At present only a few of these proteins are known to be associated with specific diseases of the nervous system. The most important is IgG, which may exceed 12 percent of the total CSF protein in diseases such as multiple sclerosis, neurosyphilis, subacute sclerosing panencephalitis and other chronic viral meningoencephalitides. The serum IgG is not correspondingly increased, which means that this immune globulin originates in (or perhaps is preferentially transported into) the nervous system. However, an elevation of serum gamma globulin—as occurs in cirrhosis, sarcoidosis, myxedema, and multiple myeloma—will be accompanied by a rise in the CSF globulin. Therefore, in patients with an elevated CSF gamma globulin, it is necessary to determine the electrophoretic pattern of the serum proteins as well. Certain qualitative changes in the CSF immunoglobulin pattern, particularly the demonstration of several discrete (oligoclonal) electrophoretic "bands," each representing a specific immune globulin, and the ratio of IgG to total protein, are of special diagnostic importance in multiple sclerosis, as discussed in Chap. 36.

Table 2-2

AVERAGE VALUES OF CONSTITUENTS OF NORMAL CSF AND SERUM

	CEREBROSPINAL FLUID	SERUM
Osmolarity	295 mOsm/L	295 mOsm/L
Sodium	138.0 mEq/L	138.0 mEq/L
Potassium	2.8 mEq/L	4.1 mEq/L
Calcium	2.1 mEq/L	4.8 mEq/L
Magnesium	2.3 mEq/L	1.9 mEq/L
Chloride	119 mEq/L	101.0 mEq/L
Bicarbonate	23.0 mEq/L	23.0 mEq/L
Carbon dioxide tension	48 mm Hg	38 mm Hg (arterial)
pH	7.31–7.33	7.41 (arterial)
Nonprotein nitrogen	19.0 mg/dL	27.0 mg/dL
Ammonia	30.0 g/dL	70.0 g/dL
Uric acid	0.24 mg/dL	5.5 mg/dL
Urea	4.7 mmol/L	5.4 mmol/L
Creatinine	1.1 mg/dL	1.8 mg/dL
Phosphorus	1.6 mg/dL	4.0 mg/dL
Total lipid	1.5 mg/dL	750.0 mg/dL
Total cholesterol	0.4 mg/dL	180.0 mg/dL
Cholesterol esters	0.3 mg/dL	126.0 mg/dL
Glucose	60 mg/dL	90.0 mg/dL
Lactate	1.6 mEq/L	1.0 mEq/L
Total protein	15–50 mg/dL	6.5–8.4 g/dL
Prealbumin	1–7%	Trace
Albumin	49–73%	56%
Alpha$_1$ globulin	3–7%	4%
Alpha$_2$ globulin	6–13%	10%
Beta globulin (beta$_1$ plus tau)	9–19%	12%
Gamma globulin	3–12%	14%

Source: Reproduced by permission from Fishman.

The albumin fraction of the CSF increases in a wide variety of central nervous system (CNS) and craniospinal nerve root diseases that increase the permeability of the blood–CSF barrier, but no specific clinical correlations can be drawn. Certain enzymes that originate in the brain, especially the brain-derived fraction of creatine kinase (CK-BB) but also enolase and neopterin, are found in the CSF after stroke, global ischemic hypoxia, or trauma, and have been used as markers of brain damage in experimental work. Other special markers such as elevation of the 14-3-3 protein, which has some diagnostic significance in prion disease, β_2-microglobulin in meningeal lymphomatosis, neuron-specific enolase in traumatic and other severe brain injuries, and alpha fetoprotein in embryonal tumors of the brain, may be useful in specialized circumstances.

Glucose

The CSF glucose concentration is normally in the range of 45 to 80 mg/dL, that is, about two-thirds of that in the blood (0.6 to 0.7 of serum concentrations). Higher levels parallel the blood glucose in this proportion; but with marked hyperglycemia, the ratio of CSF to blood glucose is reduced (0.5 to 0.6). With extremely low serum glucose, the ratio becomes higher, approximating 0.85. In general, CSF glucose values below 35 mg/dL are abnormal. After the intravenous injection of glucose, 2 to 4 h is required to reach equilibrium with the CSF; a similar delay follows the lowering of blood glucose. For these reasons, samples of CSF and blood for glucose determinations should ideally be drawn simultaneously in the fasting state or the serum should be obtained a few hours before the puncture but (this is often not practical). Low values of CSF glucose (hypoglycorrhachia) in the presence of pleocytosis usually indicate bacterial, tuberculous, or fungal meningitis, although similar reductions are observed in some patients with widespread neoplastic infiltration of the meninges and occasionally with sarcoidosis, subarachnoid hemorrhage (usually in the first week) and in chemically induced inflammation.

For a long time it was assumed that in meningitis the bacteria lowered the CSF glucose by their active metabolism, but the fact that the glucose remains at a subnormal level for 1 to 2 wk after effective treatment of the meningitis suggests that another mechanism is operative. Theoretically at least, an inhibition of the entry of glucose into the CSF, because of an impairment of the membrane transfer system, can be implicated. As a rule, viral infections of the meninges and brain do not lower the CSF glucose, although low glucose values have been reported in a small number of patients with mumps meningoencephalitis, and rarely in patients with herpes simplex and zoster infections. The almost invariable rise of CSF lactate in purulent meningitis probably suggests that some of the glucose is undergoing anaerobic glycolysis by polymorphonuclear leukocytes and by cells of the meninges and adjacent brain tissue.

Serologic and Virologic Tests

CSF testing for cryptococcal surface antigen has become widely available as a rapid method if this infection is suspected. On occasion, a false-positive reaction is obtained in the presence of high titers of rheumatoid factor or antitreponemal antibodies, but otherwise the test is diagnostically more dependable than the formerly used India ink preparation. The nontreponemal antibody tests of the blood—Venereal Disease Research Laboratories (VDRL) slide flocculation test and rapid plasma reagin (RPR) agglutination test—can also be performed on the CSF. When positive, these tests are usually diagnostic of neurosyphilis, but false-positive reactions may occur with collagen diseases, malaria, and yaws, or with contamination of the CSF by seropositive blood. Tests that depend on the use of treponemal antigens, including the Treponema pallidum immobilization test and the fluorescent treponemal antibody test, are more specific and assist in the determination of false-positive RPR and VDRL reactions. The value of CSF examinations in the diagnosis and treatment of neurosyphilis is discussed in Chap. 31, but testing of CSF for treponemal antibodies is no longer routine. Serologic tests for the Lyme spirochete are useful in circumstances of suspected infection of the CNS with this agent.

The utility of serum serologic tests for viruses is limited by the time required to obtain results, but they are useful in determining retrospectively the source of meningitis or encephalitis. More rapid tests that use the polymerase chain reaction (PCR) in CSF, which amplifies viral DNA fragments, are now widely available for diagnosis, particularly for herpesviruses, cytomegalovirus, and JC virus. These tests are most useful in the first week of infection, when the virus is being reproduced and its genomic material is most prevalent; after this time, serologic techniques for viral infection are more sensitive. Amplification of DNA by PCR is particularly useful in the rapid detection of tubercle bacilli in the CSF, the conventional culture of which takes several weeks at best. Tests for the detection of 14-3-3 protein that reflects the presence of prion agents in the spinal fluid are available and may aid in the diagnosis of the spongiform encephalopathies, but the results have been erratic (Chap. 32). Testing for anti-Hu and anti-NMDA and other antibodies has become practical for paraneoplastic and non-paraneoplastic encephalitides (Chap. 30).

Changes in Solutes and Other Components

The average osmolality of the CSF (295 mOsm/L) is identical to that of plasma. As the osmolality of the plasma is increased by the intravenous injection of hypertonic solutions such as mannitol or urea, there is a delay of up to several hours in the rise of osmolality of the CSF. It is during this period that the hyperosmolality of the blood maximally dehydrates the brain and decreases the volume of CSF. Table 2-2 lists the CSF and serum levels of sodium, potassium, calcium, and magnesium. Neurologic disease does not alter the CSF concentrations of these constituents in any characteristic way. The low CSF concentration of chloride that occurs in bacterial meningitis is not specific but a reflection of hypochloremia and, to a slight degree, of a greatly elevated CSF protein. Acid–base balance in the CSF is of interest in relation to metabolic acidosis and alkalosis but pH is not routinely measured. Normally, the pH of the CSF is approximately 7.33—that is, somewhat lower than that of arterial blood, which is 7.41. The PCO_2 in the CSF is in the range of 45 to 49 mm Hg—that is, higher than in arterial blood (about 40 mm Hg). The bicarbonate levels of the two fluids are about the same, 23 mEq/L. The pH of the CSF is precisely regulated, and it tends to remain relatively unchanged even in the face of severe systemic acidosis and alkalosis. Acid–base changes in the lumbar CSF do not necessarily reflect the presence of similar changes in the brain, nor are the CSF data as accurate an index of the systemic changes as direct measurements of arterial blood gases.

The ammonia content of the CSF is one-third to one-half that of the arterial blood; it is increased in

hepatic encephalopathy, the inherited hyperammonemias, and the Reye syndrome; the concentration corresponds roughly with the severity of the encephalopathy. The uric acid content of CSF is approximately 5 percent of that in serum and varies with changes in the serum level (high in gout, uremia, and meningitis, and low in Wilson disease). The urea concentration in the CSF is slightly lower than that in the serum; in uremia, it rises in parallel with that in the blood. An intravenous injection of urea raises the blood level immediately and the CSF level more slowly, exerting an osmotic dehydrating effect on the central nervous tissues and CSF. All 24 amino acids have been isolated from the CSF. The concentration of amino acids in the CSF is approximately one-third that in plasma. Elevations of glutamine are found in all the portosystemic encephalopathies, including hepatic coma and the Reye syndrome. Concentrations of phenylalanine, histidine, valine, leucine, isoleucine, tyrosine, and homocystine are increased in the corresponding aminoacidurias.

Many of the enzymes found in serum are known to rise in CSF under conditions of disease, usually in relation to a rise in the CSF protein. None of the enzyme changes has proved to be a specific indicator of neurologic disease with the possible exception of lactic dehydrogenase, especially isoenzymes 4 and 5, which are derived from granulocytes and are elevated in bacterial meningitis but not in aseptic or viral meningitis. Lactic dehydrogenase is also elevated in cases of meningeal tumor infiltration, particularly lymphoma, as is carcinoembryonic antigen; the latter, however, is not elevated in bacterial, viral, or fungal meningitis. As to lipids, the quantities in CSF are small and their measurement is difficult.

The catabolites of the catecholamines can be measured in the CSF. Homovanillic acid (HVA), the major catabolite of dopamine, and 5-hydroxyindoleacetic acid (5-HIAA), the major catabolite of serotonin, are normally present in the spinal fluid; both are five or six times higher in the ventricular than the lumbar CSF. The levels of both catabolites are reduced in patients with idiopathic and drug-induced parkinsonism.

IMAGING TECHNIQUES

A century ago, Harvey Cushing introduced the use of plain x-ray films of the cranium as part of the study of the neurologic patient. Plain skull films demonstrate fractures, changes in contour of the skull, bony erosions and hyperostoses, infection in paranasal sinuses and mastoids, and changes in the basal foramina. Calcified structures such as the pineal gland were time-honored landmarks of midline structures, allowing measurements of the displacement of intracranial contents. Plain films of the spine are able to demonstrate destructive lesions resulting from degenerative processes as well neoplastic, dysplastic, and infectious diseases. It also detects fracture dislocations, spondylolistheses, and spinal instability, utilizing images acquired during flexion and extension maneuvers. However, refinements of imaging techniques have greatly increased the yield of valuable information. Without question the most important advances in neuroradiology have come about with the development of CT and MRI.

Computed Tomography

In this procedure, x-radiation is attenuated as it passes successively through the scalp, 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 two-dimensional images are reconstructed by computer. This major achievement in methodology, attributed to Hounsfield and others, permitted the technologic advance from plain radiographs of the skull to reconstructed images of the cranium and its contents in any plane. The differing densities of bone, CSF, blood, and gray and white matter are distinguishable in the resulting picture with great clarity. One can see and measure the sizes of hemorrhage, infarction, contusion, edematous brain, abscess, tumor, and also determine the shape and position of the ventricles and midline structures. The radiation exposure is only modestly greater than that from plain skull films. The machinery can be manipulated to reduce radiation exposure where this limitation is desirable, for example, in children.

As illustrated in Fig. 2-1, in transverse (axial) section of the brain, one sees the cortex and underlying subcortical white matter, the caudate and lenticular nuclei and the internal capsules and thalami. The position and width of all the major sulci and fissures 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. Intravenous administration of radiopaque material (contrast) can be used with CT to visualize regions where the blood–brain barrier has been disrupted from tumors, demyelination, and infection.

In imaging of the head, CT has a number of advantages over MRI, the most important being safety when metal may be present in the body, shorter examination time, and the clarity of blood from the moment of bleeding. Other appealing aspects are its broader availability, lower cost, larger aperture of the machine that reduces patient claustrophobia, and equivalent or superior visualization of calcium, fat, and bone, particularly of the skull base and vertebrae (see Fig. 2-1*D*). If constant monitoring and use of life support equipment is required during the imaging procedure, it is accomplished more readily by CT than by MRI. Advances in CT technology have greatly increased the speed of the scanning procedure and have also made possible the visualization, with great clarity, of the cerebral vasculature (CT angiography; see further on).

CT also demonstrates the bony structures of the vertebral column in greater detail than is available with conventional x-ray. Herniated lumbar and cervical discs, cervical spondylotic bars and bony spurs encroaching on the spinal

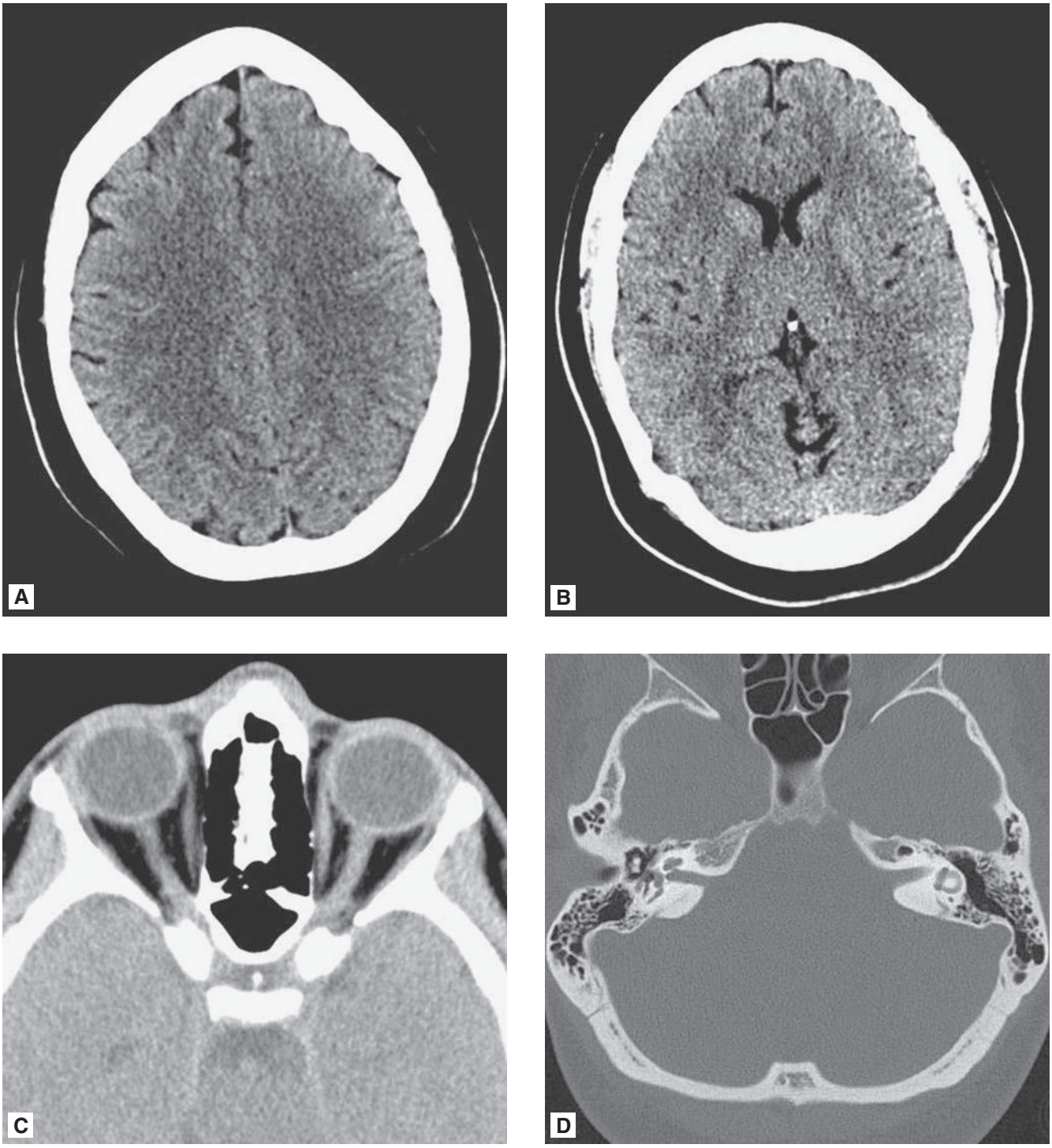

Figure 2-1. Normal CT in the axial plane of the brain, orbits, and skull base. *A*. Image through the cerebral hemispheres at the level of the corona radiata. The dense bone of the calvarium is white, and fat-containing subcutaneous tissue is dark. Gray matter appears denser than white matter due to its lower lipid content. *B*. Image at the level of the lenticular nuclei. The caudate and lenticular nuclei are denser than the adjacent internal capsule. CSF within the frontal horns of the lateral ventricles as well as surrounding the slightly calcified pineal body appears dark. *C*. Image through the mid-orbits. The sclera appears as a dense band surrounding the globe. The optic nerves are surrounded by dark orbital fat. The medial and lateral rectus muscles lie along the orbital walls and have a fusiform shape. Air within the nasopharynx and paranasal sinuses appears dark. *D*. Image at the base of the skull, digitally adjusted to visualize bone ("bone window"), showing the basal occipital and temporal bones, clivus, the bony structures of the posterior nasopharynx, aerated mastoid air cells, internal auditory canals and inner ear structures, as well as the sutures in the occipital bone.

cord or roots, and spinal cord tumors can be visualized with clarity. MRI provides even sharper visualization of the spinal canal and its contents as well as the vertebrae and intervertebral discs as discussed further on.

Contrast Myelography

Myelography utilizes intrathecal contrast material to demonstrate the contours of the spinal cord and spinal roots. It can be accomplished either by conventional fluoroscopy or by CT. By injecting water-soluble radiopaque contrast through an LP needle and then placing the patient in the Trendelenberg position, the entire spinal subarachnoid space can be visualized (Fig. 2-2*A–C*). The procedure is almost as harmless as the LP except for cases of complete spinal block, in which high concentrations of contrast near the block can cause pain and regional myoclonus. Iophendylate (Pantopaque), a formerly used fat-soluble dye, is still approved by the FDA but is now employed only in special circumstances (visualizing the upper level of a spinal canal lesion that completely obstructs the flow of water soluble dye). If iophendylate is left in the subarachnoid space, particularly in the presence of blood or inflammatory exudate, it may incite arachnoiditis of the spinal cord and brain. MRI, because of its ability to clearly demonstrate intrathecal structures has largely supplanted contrast myelography as discussed in a later section.

Risks of CT

The primary risk of CT is radiation exposure, and overexposure can have clinical consequences ranging from relatively benign alopecia to leukomalacia and neoplasia. The interested reader should refer to FDA guidelines on the subject (http://www.fda.gov/Radiation-emittingProducts/RadiationEmittingProductsandProcedures/MedicalImaging/MedicalX-Rays/ucm115317.htm). Given the need for repeated CT examinations in certain patients, tracking of total radiation exposure may be advisable and may find greater use in the future. CT is usually deferred during pregnancy unless the mother's health is at imminent risk (i.e., following trauma). The potential harm to a fetus from radiation depends on gestational age and total absorbed dose. It is noteworthy that the fetal radiation dose from maternal cranial CT is lower than from maternal pelvic CT.

The risks of contrast infusion include allergic reactions and nephropathy, which is most often transient and reversible, but can be more severe in patients with underlying renal dysfunction. Intravenous contrast in generally withheld if the glomerular filtration rate (calculated GFR) is less than 30 mL/min/1.73 m^2; if GFR is 30 to 60, hydration and, discontinuation of potentially nephrotoxic medications should precede the administration of contrast, particularly nonsteroidal anti-inflammatory agents, cisplatin-containing chemotherapy and aminoglycoside antibiotics. Repeated infusions of contrast should be done cautiously.

Magnetic Resonance Imaging

Many engineers, mathematicians, and physicists made contributions to the technology of nuclear MRI, and a Nobel Prize was awarded to Lauterbur and Mansfield for its development. MRI provides images in any plane, and it has the advantage over CT in using nonionizing energy and providing higher resolution views, and improved contrast between different structures within the nervous system. For visualization of many neurologic lesions, MRI is the preferred procedure.

Nuclear magnetic resonance can be detected from several isotopes, but current technology uses mainly signals derived from hydrogen atoms because hydrogen is the most abundant element in tissue and yields the strongest magnetic signal as discussed by Horowitz. 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. MRI is accomplished by placing the patient within a powerful magnetic field, causing certain endogenous isotopes to be aligned 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. When the RF pulse ceases, the atoms return to their original alignment and the RF energy that was absorbed is then emitted by the isotopes, producing an electric signal that is detected by 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 that allows reconstruction of two-dimensional images.

The terms T1- and T2-weighting refer to the time constants for proton relaxation; these may be altered to highlight certain features of tissue structure. In T1-weighted images, CSF appears dark and gray matter is hypointense to white matter. In T2-weighted images, CSF appears bright, and gray matter is hyperintense to white matter. Lesions within the white matter, such as the demyelination of multiple sclerosis, are more easily seen on T2-weighted images, appearing hyperintense against normal white matter (Table 2-3).

A high degree of contrast is seen between white and gray matter on both T1- and T2-weighted images, allowing the identification of many discrete structures (Fig. 2-3). Lesions near the skull base and within the posterior fossa, in particular, are seen with greater clarity on MRI compared to CT, unmarred by signals from adjacent skeletal structures. The products of disintegrated RBCs—oxyhemoglobin, deoxyhemoglobin, methemoglobin, and hemosiderin—can be recognized, enabling one to approximate the age of hemorrhages and to follow their resolution, as discussed in Chaps. 33 and 34. Gradient-echo (GRE), or susceptibility weighted imaging (SWI), is especially sensitive to blood and its breakdown products that appear hypointense.

As mentioned earlier, MRI of the spine provides clear images of the vertebral bodies, intervertebral discs, spinal

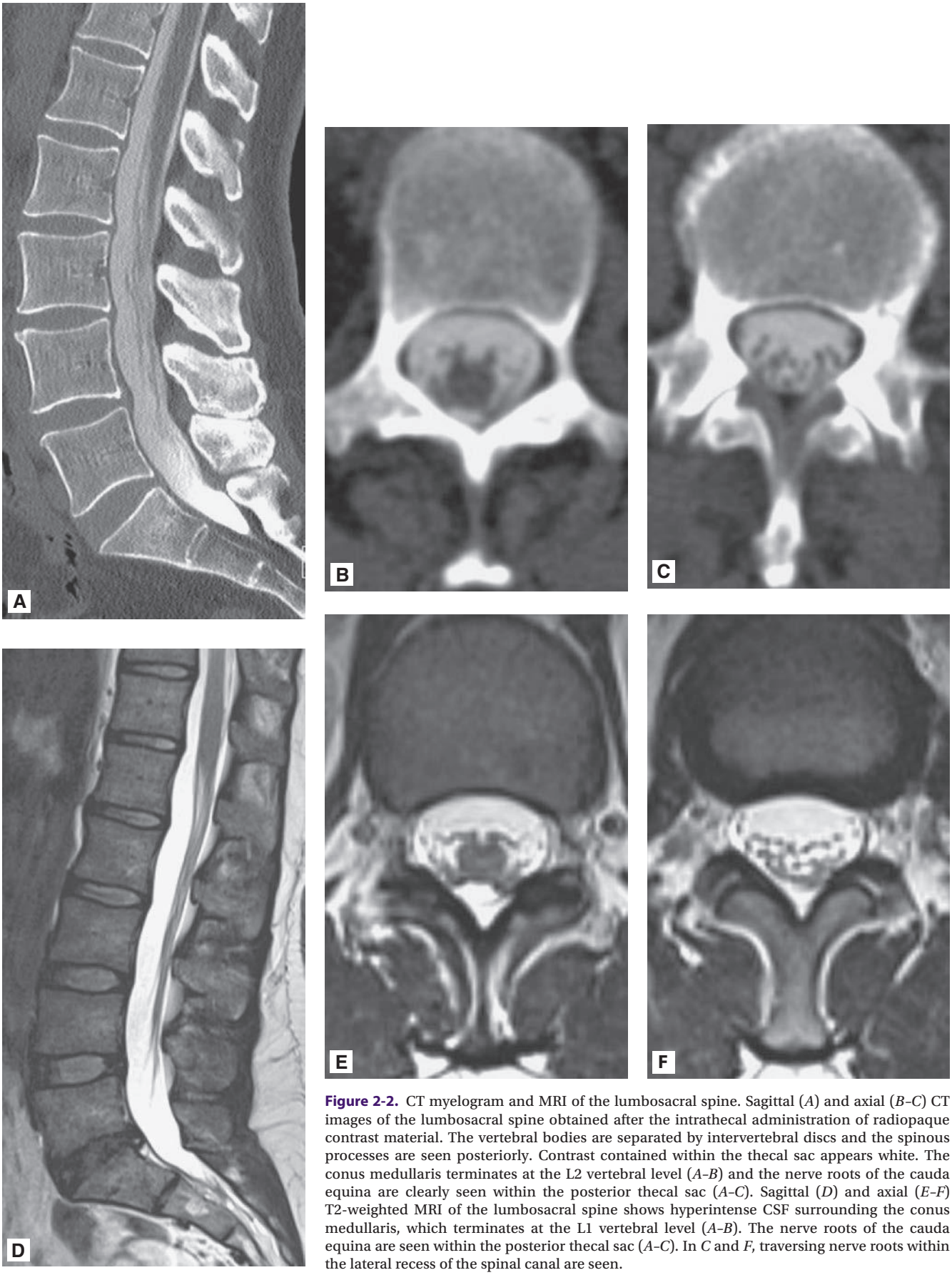

Figure 2-2. CT myelogram and MRI of the lumbosacral spine. Sagittal (*A*) and axial (*B–C*) CT images of the lumbosacral spine obtained after the intrathecal administration of radiopaque contrast material. The vertebral bodies are separated by intervertebral discs and the spinous processes are seen posteriorly. Contrast contained within the thecal sac appears white. The conus medullaris terminates at the L2 vertebral level (*A–B*) and the nerve roots of the cauda equina are clearly seen within the posterior thecal sac (*A–C*). Sagittal (*D*) and axial (*E–F*) T2-weighted MRI of the lumbosacral spine shows hyperintense CSF surrounding the conus medullaris, which terminates at the L1 vertebral level (*A–B*). The nerve roots of the cauda equina are seen within the posterior thecal sac (*A–C*). In *C* and *F*, traversing nerve roots within the lateral recess of the spinal canal are seen.

Table 2-3

CT AND MRI IMAGING CHARACTERISTICS OF VARIOUS TISSUES

TISSUE	CT GRAY SCALE	MRI T1 SIGNAL	MRI T2 SIGNAL
Brain	Gray	Gray	Gray
Air	Black	Black	Black
CSF	Black	Black	White
Fat	Black	White	Less white
Calcium	White	Black	Black
Bone	Very white	Black	Black
Extravasated blood	White	White	Black
Inflammation	Contrast enhancing	Gray, gadolinium enhancing	White
Edema	Dark gray	Gray	White
Tumor	Gray or white and contrast enhancing	Gray or white and gadolinium enhancing	White

cord, and cauda equina (Fig. 2-2*D–F*). Abnormalities such as syringomyelia, herniated discs, tumors, epidural or subdural hemorrhages, areas of demyelination, and abscesses are well delineated (see Modic).

Additional radiofrequency pulses can be applied to T1- and T2-weighted images in order to selectively suppress signal from fluid or fat. The FLAIR (fluid-attenuated inversion recovery) sequence is a T2-weighted sequence in which the bright signal of fluid that is not contained within tissues is suppressed. This is a particularly useful sequence for visualizing lesions located near CSF compartments. Fat suppression, which can be applied to T1 or T2 sequences, can be used to improve the demonstration of inflammation of the optic nerve, visualize pathologic inflammation within the vertebral bodies, and show thrombus within the false lumen of a cervical dissection.

Diffusion-weighted imaging (DWI) is a technique that measures the free diffusion of water molecules within tissue. Preferential movement of water molecules along a particular direction, for example, parallel to white matter tracts, is referred to as anisotropy (i.e., nonisotropic movement). Many abnormal processes can produce anisotropy as well. In acute ischemic stroke, failure of the sodium-potassium ATPase pump leads to cellular swelling and reduced intercellular space, thus limiting the free movement of water and producing hyperintensity on DWI. This imaging technique reveals the abnormalities of ischemic stroke earlier than standard T1- or T2-weighted MRI, or CT. Pus-filled abscesses and hypercellular tumors can also show DWI hyperintensity, reflecting the limitation of free diffusion of water in these lesions.

True restricted diffusion, appearing hyperintense on the DWI sequence in acute infarction, is *hypointense* on a related sequence termed apparent diffusion coefficient (ADC). If the hyperintense DWI signal is also *hyperintense* on ADC, then diffusion is termed facilitated rather than restricted. This phenomenon is seen when the free movement of water within a tissue becomes increasingly isotropic, as with vasogenic edema. Therefore, the interpretation of DWI signal hyperintensity must be gauged in the context of the ADC signal in the same region.

The administration of gadolinium, a paramagnetic agent that accelerates the process of proton relaxation during the T1 sequence of MRI, permits even sharper definition and highlights regions surrounding many types of lesions where the blood–brain barrier has been disrupted in the brain, spinal cord, or nerve roots.

Limitations and Safety of MRI

The degree of cooperation in holding still that is required to perform MRI limits its use in young children and in the cognitively impaired. Some form of sedation may be required in these individuals and most hospitals have services to safely accomplish conscious sedation for this purpose. Studying a patient who requires a ventilator is also difficult but manageable by using either manual ventilation or nonferromagnetic ventilators.

The main dangers in the use of MRI are torque, dislodgement or heating of metal clips on blood vessels, of dental devices and other ferromagnetic objects, and of small metal fragments in the orbit, the last of these often acquired unnoticed by operators of machine tools. For this reason it is wise, in appropriate patients, to obtain plain radiographs of the orbits so as to detect metal in these regions. Corneal metal fragments can be removed by an ophthalmic surgeon if an MRI is necessary. The presence of a cardiac pacemaker, defibrillator, or implanted stimulator in the brain or spinal cord is an absolute contraindication to the use of MRI as the magnetic field induces unwanted currents in the device and the wires exiting from it. However, many new implantable medical devices have been developed that are unaffected by and do not distort the magnetic field. Most of the newer, weakly ferromagnetic prosthetic heart valves, joint prostheses, some cochleae implants, intravascular access ports, aneurysm clips, and ventricular shunts and adjustable valves do not represent an untoward risk for magnetic imaging although shunt valves may require resetting after MRI. An extensive list of devices that have been tested for their ferromagnetic susceptibility and their safety in the MRI machine can be found at www.mrisafety.com. MRI entails some risk in these situations unless there is direct knowledge of the type of material contained in the device. It should be noted that devices or materials that are deemed safe for 1.0 or 1.5 Tesla scanners may not be compatible with higher magnetic field strength scanners.

Because of the development of cataracts in the fetuses of animals exposed to MRI, there has been hesitation in performing MRI in pregnant patients, especially in the first trimester. However, current data indicate that imaging may be performed provided that the study is medically indicated. In a study of 1,000 pregnant MRI technicians who entered the magnetic field frequently (the magnet remains on between procedures), no adverse effects on the fetus could be discerned (Kanal et al).

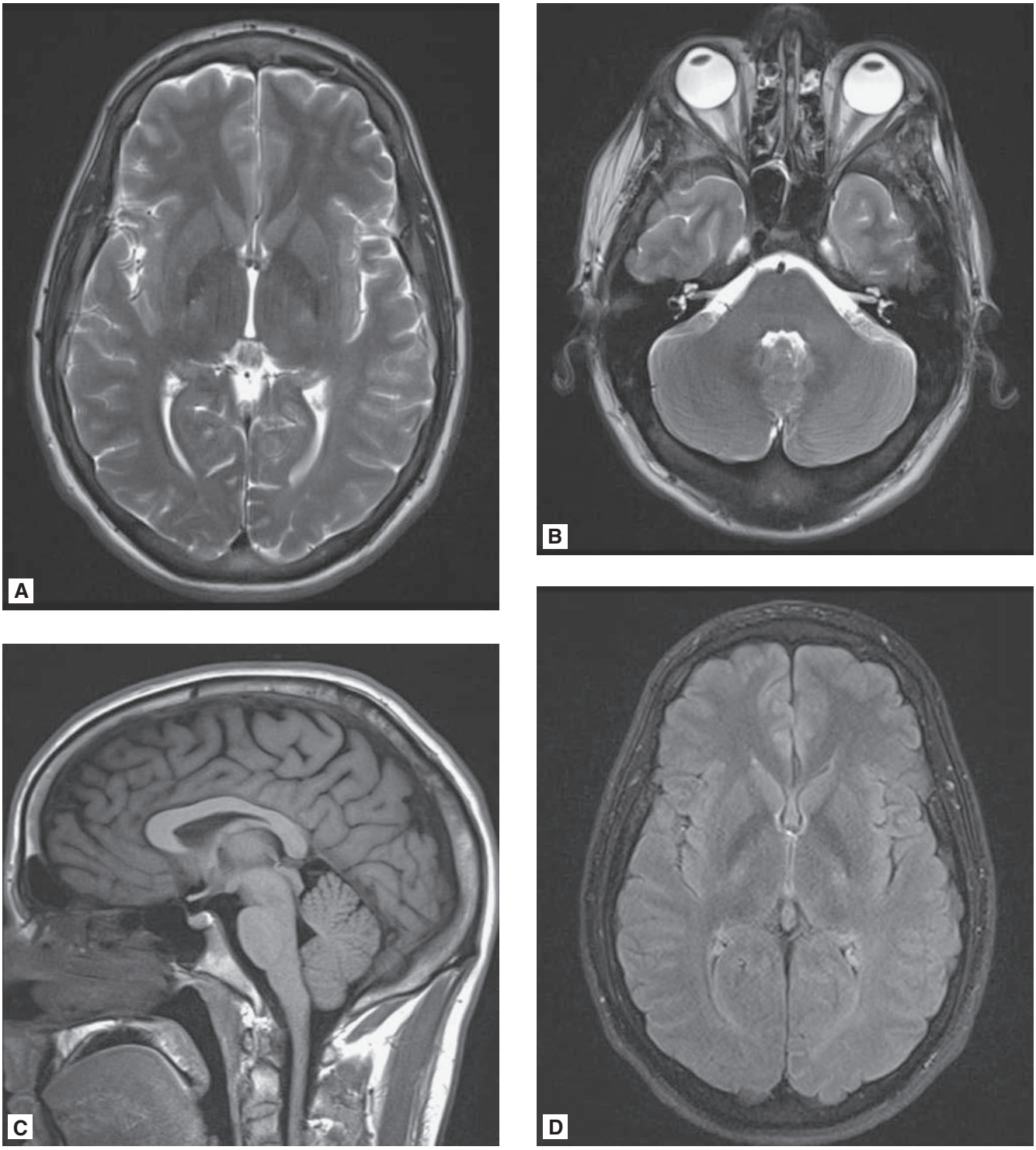

Figure 2-3. Normal brain MRI. *A*. Axial T2-weighted MRI at the level of the lenticular nuclei. Gray matter appears brighter than white matter. CSF within the ventricles and cortical sulci is very bright. The caudate nuclei, putamen, and thalamus appear brighter than the internal capsule. *B*. Axial T2-weighted MRI at the level of the pons. Subcutaneous fat and calvarial marrow appear relatively bright. CSF within the fourth ventricle and prepontine cistern, endolymph within the cochlea and semicircular canals, and ocular vitreous fluid appears very bright. Signal is absent (i.e., a "flow void") within the basilar artery. *C*. Midline sagittal T1-weighted MRI of the brain. Note that white matter appears brighter than gray matter and the corpus callosum is well defined. The pons, medulla, and cervicomedullary junction are well delineated, and the pituitary gland is demonstrated with a normal posterior pituitary bright spot. The cerebral aqueduct is seen between the ventral midbrain and the tectum. The clivus and upper cervical vertebrae are noted as well. *D*. Axial T2-weighted fluid-attenuated inversion recovery (FLAIR) MRI of the brain at the same level as in *A*. Note that the hyperintense fluid signal from CSF is now suppressed, and the differentiation between brighter gray matter and darker white matter is accentuated.

An additional risk of the administration of gadolinium is nephrogenic systemic fibrosis, a severe cutaneous sclerosing disease. Most instances occur in patients with preexisting renal failure, for which reason it has become common to obtain BUN and creatinine measurements before administering gadolinium. The problem had not been appreciated initially in part because of its rarity (the frequency has not been well established) and because of a delay in the appearance of sclerosis in the kidney and skin, of several days to months.

Many types of MRI image artifacts are known, most having to do with technical aspects of the electronic characteristics of the magnetic field or of the mechanics involved in the imaging procedure (for details, see Morelli et al). Among the most common and problematic are CSF flow artifacts in the thoracic spinal cord, giving the impression of an intradural mass; distortions of the appearance of structures at the base of the brain from ferromagnetic dental appliances; and lines across the entire image induced by vascular pulsations and patient movement.

The increasing use of MRI and the sensitivity of current machines have had the unintended effect of revealing a large number of unimportant findings that create undue worry and often trigger neurologic consultation. Moreover, many lesions are not referable to the clinical problem at hand. A surprising number of incidental brain lesions are exposed by indiscriminate use of imaging. For example, a large survey of asymptomatic adults who were being followed in the "Rotterdam Study" is in accord with several prior studies in which cerebral aneurysms were found in approximately 2 percent, meningiomas in 1 percent, and a smaller but not insignificant number of vestibular schwannomas and pituitary tumors; the meningiomas, but not the aneurysms, increased in frequency with age. One percent had the Chiari type I malformation, and a similar number had arachnoid cysts. In addition, 7 percent of adults older than age 45 years had occult strokes, mostly lacunar. Because this survey was performed without gadolinium infusion, it might be expected that even more small asymptomatic lesions could be revealed (Vernooij et al).

Magnetic Resonance and Computed Tomographic Angiography

These are noninvasive techniques for visualizing the intracranial and cervical arteries. They can reliably detect intracranial vascular lesions and extracranial arterial stenosis and are supplanting conventional angiography. They approach the radiographic resolution of catheter-based angiography, but do not engender the risk of selective arterial catheterization (Fig. 2-4). Visualization of the cerebral veins is also possible by CT (Fig. 2-4*D*) and MRI.

CT angiography requires contrast administration. In comparison, MR angiography can be performed without contrast, using the "time-of-flight" technique. This data can be reconstructed into an image that reflects flow-related enhancement. The signal obtained from time-of-flight MRA represents flow through the lumen of a vessel, rather than the configuration as obtained by contrast opacification. The use of these and other methods for the investigation of carotid artery disease is discussed further below and in Chap. 35, on cerebral vascular disease.

Catheter Angiography

This technique is a valuable method for the diagnosis and treatment of aneurysms, vascular malformations, narrowed or occluded arteries and veins, arterial dissections, and angiitis. To a large extent, CT and MRI angiographic techniques have supplanted the diagnostic role of catheter angiography, but the latter remains necessary for a variety of conditions, particularly small vascular malformations. It is also possible to introduce thrombolytic substances and mechanical devices through catheters for the treatment of cerebrovascular disease.

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 agent is 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 and the vasculature in and surrounding the spinal cord. This allows the visualization of the cerebral and spinal cord vessels to less than 1 mm in lumen diameter. With refinements in technique it is possible to produce images of the major cervical and intracranial arteries with relatively limited amounts of contrast medium introduced through small catheters.

Angiography is not altogether without risk. Overall morbidity from the procedure is approximately 2.5 percent, mainly in the form of worsening of a preexistent vascular lesion or from complications at the site of artery puncture. Occasionally, cerebral or systemic ischemic lesions are produced, the result of either particulate atheromatous material dislodged by the catheter, thrombus formation at or near the catheter tip, vasospasm, or more often by dissection of the artery by the catheter. A cervical myelopathy is a rare but disastrous complication of vertebral artery contrast injection; the problem is heralded by pain in the back of the neck immediately after injection. Progressive cord ischemia from an ill-defined vascular process ensues over the following hours. For these reasons, the procedure should not be undertaken unless it is deemed necessary to obtain a clear diagnosis or in anticipation of surgery that requires a definition of the location of the vessels.

Special Imaging Techniques

Perfusion Imaging

This imaging modality is a contrast-based technique that can be performed with both CT and MRI. Images are rapidly and serially acquired as the contrast transits through the vasculature and parenchyma. A time-intensity curve is produced, from which measurements of cerebral blood flow, cerebral blood volume, and transit time can be derived. Perfusion imaging has provided a means of

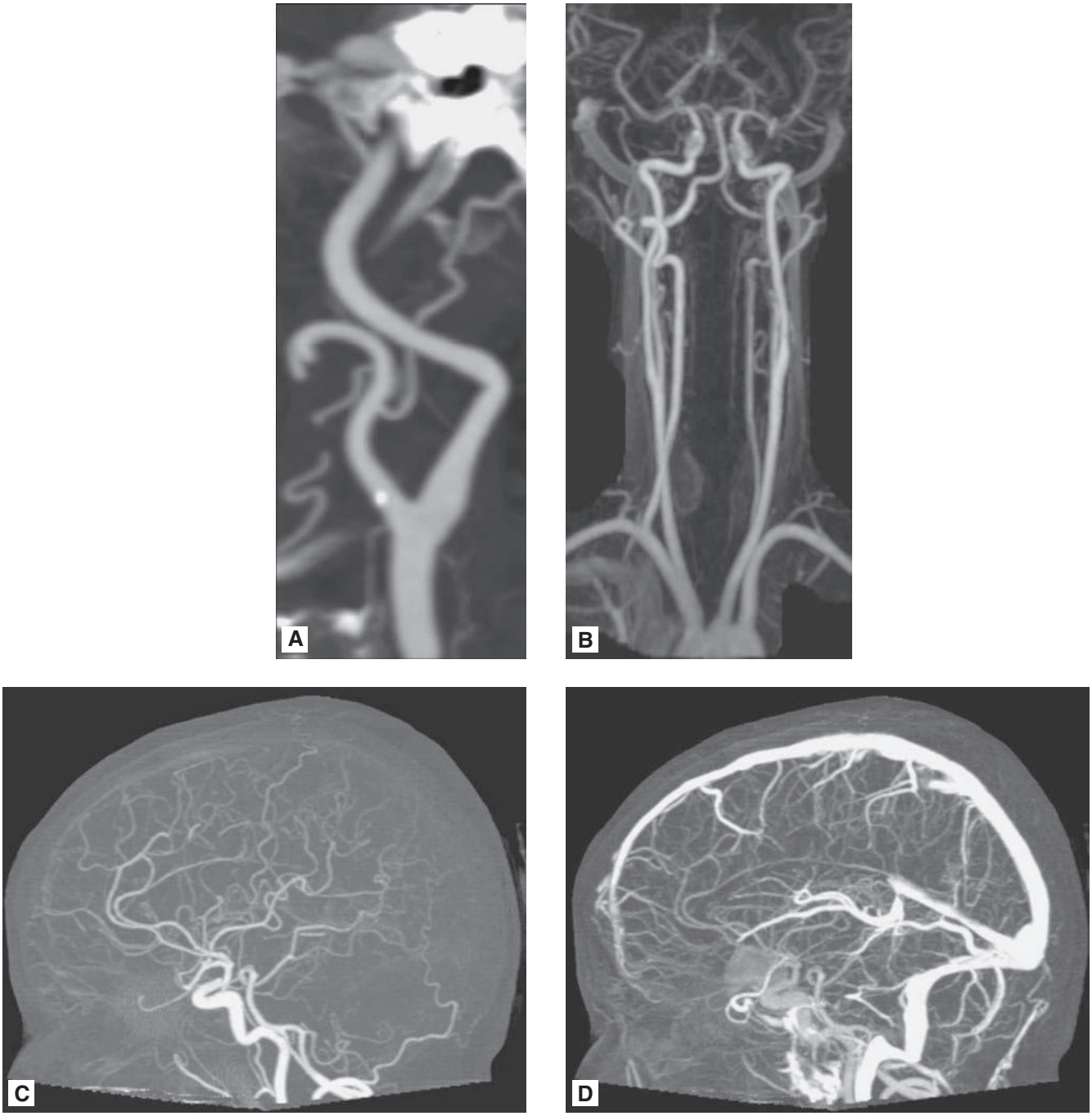

Figure 2-4. Intracranial and cervical angiography. *A*. Oblique CT angiogram of the neck showing the carotid bifurcation and the cervical segments of the internal and external carotid arteries. Note the slightly dilated carotid bulb at the initial segment of the internal carotid artery. A small focus of calcified atherosclerosis is noted near the origin of the external carotid artery. Note that the external carotid artery has multiple branches within the neck. *B*. Coronal MR angiogram of the neck showing the aortic arch, the origins and cervical courses of the carotid and vertebral arteries, and the vertebrobasilar junction. The sigmoid sinuses and internal jugular veins are faintly visible. *C–D*. Sagittal dynamic CT angiography of the head. Bony and soft tissue structures as well as brain parenchyma have been digitally subtracted. The image *C* was acquired during the arterial phase; the carotid and basilar termini and the anterior cerebral arteries are enhanced. Venous phase imaging (*D*) shows enhancement of the superior and inferior sagittal sinuses, straight sinus, vein of Galen, internal cerebral veins, basal veins of Rosenthal, and the transverse and sigmoid sinuses.

detecting regions of ischemic tissue, and to monitor the elevated blood volume in certain brain tumors.

Magnetic Resonance Spectroscopy

The tissue concentrations of a variety of cellular metabolites can be determined with the technique of magnetic resonance spectroscopy (MRS). Among these substances, *N*-acetyl aspartate (NAA) is a marker of neuronal integrity and is decreased in both destructive lesions and in circumstances in which there is a reduction in the density of neurons (e.g., edema or glioma that increases the distance between neurons). Choline (Cho), a marker of membrane turnover, is elevated in some rapidly dividing tumors. Therefore, compared to normal white matter, the spectrogram of a glioma characteristically shows decreased NAA and increased Cho. It is possible to measure a number of other metabolites such as myoinositol, creatine, and lactate that find occasional clinical utility.

Diffusion Tractography

A technique based on DWI, termed diffusion tensor imaging (DTI), integrates measurements of the amount of anisotropy with its directionality to model axonal tracts in the brain. This modality detects damage to, or displacement of white matter tracts because of trauma, vascular injury, or tumor. Tractography is also occasionally used in surgical planning to localize critical white matter tracts in order to avoid their transection during operations.

Functional Imaging

In the last decades, several techniques of functional imaging have been introduced to study the activation of regions of cerebral cortex during mental and physical actions or experiences. The MRI-based functional imaging technique (functional MRI, or fMRI) shows changes in local cerebral blood oxygenation, a surrogate for local neuronal metabolic activity. These changes are quantified as the blood oxygen level-dependent (BOLD) signal, and evolve over the 10 to 15 s following a change in neuronal activity (Fig. 2-5). In addition to its research application in cognitive neuroscience, this technique also has clinical utility, including presurgical planning in tumor and epilepsy surgery.

Positron emission tomography (PET) produces images that reflect the regional concentration of systemically administered radioactive compounds. Positron-emitting isotopes (mainly ^{11}C, ^{18}F, and ^{15}O) are produced in a cyclotron or linear accelerator, injected into the patient, and incorporated into biologically active compounds in the body. The concentration of these tracers in various parts of the brain is determined by an array of radiation detectors 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 also be measured by PET, and the procedure has proved to be of value in both detecting and grading brain tumors, distinguishing tumor tissue from radiation necrosis, localizing epileptic foci, and, in differentiating types of degenerative diseases. The technique has been applied to specially labeled ligands of beta-amyloid, producing images of the deposition of this protein in Alzheimer disease. This approach may become increasingly important in the study of degenerative diseases and their response to treatment. The ability of the technique to quantitate neurotransmitters and their receptors also promises to be of importance in the study of Parkinson disease and other degenerative conditions. However, this technology is costly and does not always add to the certainty of diagnosis. A representative PET of the brain is shown in Fig. 2-6.

Single-photon emission computed tomography (SPECT), a similar technique, uses isotopes that do not require a cyclotron for their production. Radioligands (usually containing iodine) are incorporated into biologically active compounds, which, as they decay, emit a single photon. This procedure allows the study of regional cerebral blood flow under conditions of cerebral ischemia and in degenerative diseases of the cortex, or during increased tissue metabolism (e.g., seizures and actively growing tumors). 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, for example, to inject the isotope at the time of a seizure, while the patient is undergoing video and electroencephalographic monitoring, and to scan the patient soon after. The limited anatomic resolution provided by SPECT limits its clinical usefulness, but it is more easily available than other functional imaging techniques. PET and SPECT

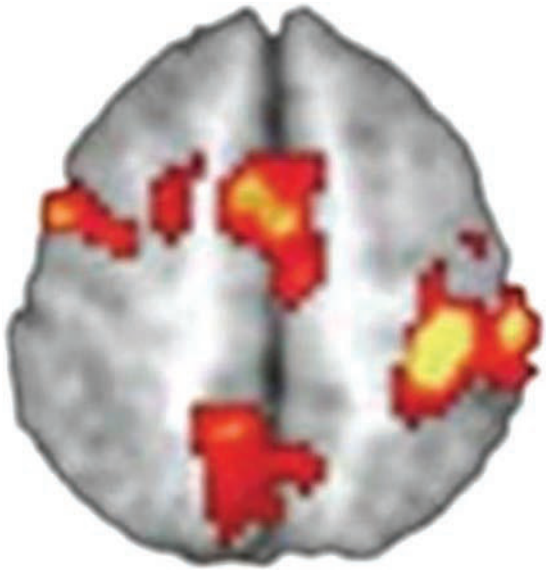

Figure 2-5. Blood oxygen level-dependent (BOLD) functional MRI. The image shown is from a subject performing repetitive motor functions (tapping a button) with his right finger. Superimposed upon the grayscale structural MRI image are areas of altered BOLD signal, in color, associated with the task. The most prominent signal (yellow) is in the left lateral cerebral cortex, corresponding to the right hand area of the precentral and postcentral gyri. Other sites of lesser signal (red, orange) include the supplementary motor area, which is near the midline anteriorly. (Image courtesy of Dr. Michael D. Fox. From Fox MD, Snyder AZ, Zacks JM, Raichle ME: Coherent spontaneous activity accounts for trial-to-trial variability in human evoked brain responses. *Nat Neurosci* 9:23, 2006. Reproduced with permission.)

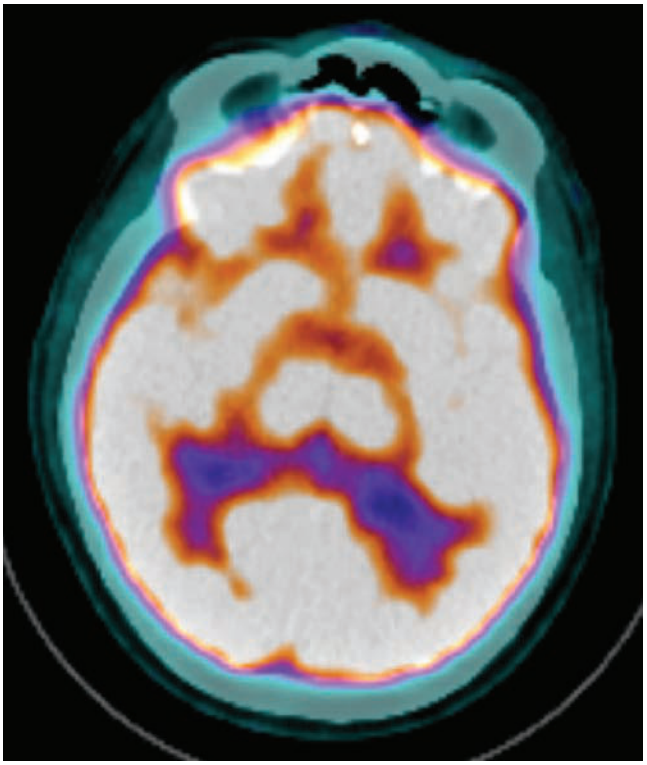

Figure 2-6. Axial ^{18}FDG-PET of a normal brain. The PET data is colorized and overlaid on a CT image. Brain areas with higher metabolic activity such as cortex and deep gray nuclei appear bright, and areas with lower metabolic activity such as white matter appear purple.

techniques that use I^{123} labeled dopamine, have been introduced and offer the possibility of imaging striatal dopamine and assisting in the diagnosis of parkinsonian disorders (see Chap. 38).

Ultrasonography

An ultrasound technique may be used to insonate 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 an acoustic 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 so as to make the insonated image and flow map easier to view and interpret.

This ultrasound technique using different sound frequencies and intensities, has also become a principal methodology for clinical study of the fetal and neonatal brain. Different tissues have specific acoustic impedances 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 in the neonate of choroid plexus, ventricles, and central nuclear masses. Usually several coronal and parasagittal views are obtained by placing the transducer over open fontanelles or the child's thin calvarium. 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 in adults ("transcranial Doppler"). The transcranial Doppler uses a 2-MHz pulsed signal that is able to pass through the calvarial bone 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.

Ultrasound has several advantages, notably that it is noninvasive, harmless (hence can be used repeatedly but caution is required in applying it to the globe), convenient because of the portability of the instrument, and inexpensive. More specific applications of this technique are discussed in Chap. 37, on developmental diseases of the nervous system, and in Chap. 33, on stroke. The related technique of echocardiography has also assumed a central role in the evaluation of stroke, as indicated in Chap. 33.

ELECTROENCEPHALOGRAPHY

The electroencephalographic examination, for many years a standard laboratory procedure in the study of all forms of cerebral disease, has been supplanted by CT and MRI for the purposes of localization of structural lesions. It continues to be an essential part of the assessment of patients with seizures and those suspected of having seizures, as well as in brain death, and for the study of sleep (polysomnography) as described in the American Electroencephalographic Society Guideliness. It is also used in evaluating the encephalopathy of many systemic metabolic diseases and in the operating room to monitor cerebral activity in anesthetized patients. For a few diseases, such as Creutzfeldt-Jakob (prion) disease, it is a useful confirmatory laboratory test. The technique is described here in some detail, as its general use in neurology cannot suitably be assigned to any other single chapter.

The electroencephalograph records spontaneous electrical activity generated in the cerebral cortex. This activity reflects the electrical currents that flow in the extracellular spaces of the brain that are the summated effects of innumerable excitatory and inhibitory synaptic potentials upon cortical neurons. This spontaneous activity of cortical neurons is highly influenced and synchronized by subcortical structures, particularly the thalamus and high brainstem reticular formation. Efferent impulses from these deep structures are probably responsible for entraining cortical neurons to produce characteristic rhythmic brain-wave patterns, such as alpha rhythm and sleep spindles (see further on).

Electrodes, which are typically silver or silver-silver chloride discs 0.5 cm in diameter, are placed on the

scalp using a conductive medium. The electroencephalograph has 8 to 32 or more amplifying units capable of recording from many areas of the scalp at the same time. The amplified brain rhythms are seen as waveforms of brain activity in the frequency range of 0.5 to 30 Hz (cycles per second) on a standard display that runs at 3 cm/s. In the past, the amplified signals were recorded on paper by a bank of pens but now, a digital format of the rhythms can be displayed on a computer screen and stored electronically.

The favored configuration of electrode pairs, or montage, is the "International 10-20" system, which uses 10 electrodes on each side of the cranium and emphasizes contiguous regions of the brain for ease of visual inspection of the record (Fig. 2-7*A*).

The resulting electroencephalogram (EEG), essentially a voltage-versus-time graph, consists of a number of simultaneous parallel wavy lines, or "channels" (Fig. 2-7*B*). Each channel represents the difference in electrical potential between two electrodes (a common or ground electrode may be used as one recording site, but the channel still represents a bipolar recording). A positive voltage potential deflects the signal downward, and a negative one, upward by convention. The channels are arranged for viewing into standard montages that generally allow comparison of the activity from one region of the cerebral cortex to others, and particularly to the corresponding region of the opposite side.

Patients are usually examined with their eyes closed and while relaxed. Consequently, the ordinary EEG represents the electrocerebral activity that is recorded under restricted circumstances, usually during the waking or sleeping state, from several parts of the cerebral convexities during an almost infinitesimal segment of the person's life.

In addition to the resting record, a number of activating procedures are usually employed. First, the patient is asked to breathe deeply 20 times a minute for 3 min. Hyperventilation, through a mechanism yet to be determined, may activate characteristic seizure patterns or other abnormalities. Second, a powerful strobe light is placed about 15 inches from the patient's eyes and flashed at frequencies of 1 to 20 per second with the patient's eyes open and closed. In a healthy subject, the occipital EEG leads show waves corresponding to each flash of light (photic driving, Fig. 2-7*C*).

The EEG is recorded while the patient is drowsy and after the patient is allowed to fall asleep naturally or following the administration of sedative drugs. The drowsy state and the transition to and from deeper stages of sleep can reveal abnormalities.

Many abnormalities associated with sleep are more evident with long-term, continuous EEG monitoring (hours to days) as described in Chap. 18. EEG activity can be synchronized with videographically recorded seizure activity in order to characterize the nature of a seizure. EEGs recorded by small digital devices or telemetry from freely moving ambulatory patients may be similarly useful in cases of suspected seizure disorders. Chapter 15 discusses these techniques in detail. Chapter 18 contains information on the use of EEG to analyze disorders of sleep (polysomnography).

Certain preparations are necessary if electroencephalography is to be most useful. The patient should not be sedated (except as noted above) and should not have been without food for a long time, for both sedative drugs and relative hypoglycemia may modify the normal EEG pattern and caffeine should be avoided if a sleep EEG study is planned. When dealing with patients who are suspected of having epilepsy and are already being treated for it, most physicians prefer to record the EEG while the patient continues to receive antiepileptic medications. During inpatient monitoring, these drugs are often withdrawn for a day or two in order to increase the likelihood of recording a seizure discharge but this requires careful clinical monitoring.

The interpretation of EEGs involves the recognition of several characteristic normal and abnormal patterns and background rhythms (in accordance with the age of the patient), the detection of asymmetries and periodic changes in rhythm, and, importantly, the differentiation of artifacts from genuine abnormalities (see Goldenshohn ES and Hughes JR).

Normal EEG Patterns

The normal record in adults shows slightly asymmetrical 8- to 12-per-second 50-mV sinusoidal *alpha waves* in both occipital and posterior parietal regions. These waves wax and wane in amplitude spontaneously and are attenuated or suppressed completely with eye opening or mental activity (see Fig. 2-7*B*). In contrast, the frequency of the alpha rhythm is almost invariant for an individual patient, although the rate slows with aging. Waves faster than 12 Hz and of lower amplitude (10 to 20 mV), called *beta waves*, are normally recorded from the frontal regions symmetrically. If benzodiazepines or other sedating drugs have been administered, an increase in the fast frequencies is typically observed. When the normal subject falls asleep, the alpha rhythm slows symmetrically and characteristic waveforms consisting of vertex sharp waves and sleep spindles appear (see Fig. 18-1). A small amount of theta (4- to 7-Hz) activity may normally be present over the temporal regions, somewhat more so in persons older than 60 years of age. Delta (1- to 3-Hz) activity is not present in the normal waking adult.

The presence of a photic driving response indicates that some of the visual pathways are preserved. Spread of the occipital response induced by photic stimulation, with the production of abnormal sharp or paroxysmal waves, provides evidence of abnormal cortical excitability (Fig. 2-7*D*). Seizure patterns may be produced during this type of EEG testing, accompanied by gross myoclonic jerks of the face, neck, and limbs (photomyoclonic response), by electrographic seizure activity that outlasts the photic stimulation (photoparoxysmal response), or by a convulsion (photoconvulsive response). Such effects occur often during periods of withdrawal from alcohol and other sedative drugs.

Children and adolescents are more sensitive than adults to all the activating procedures previously mentioned

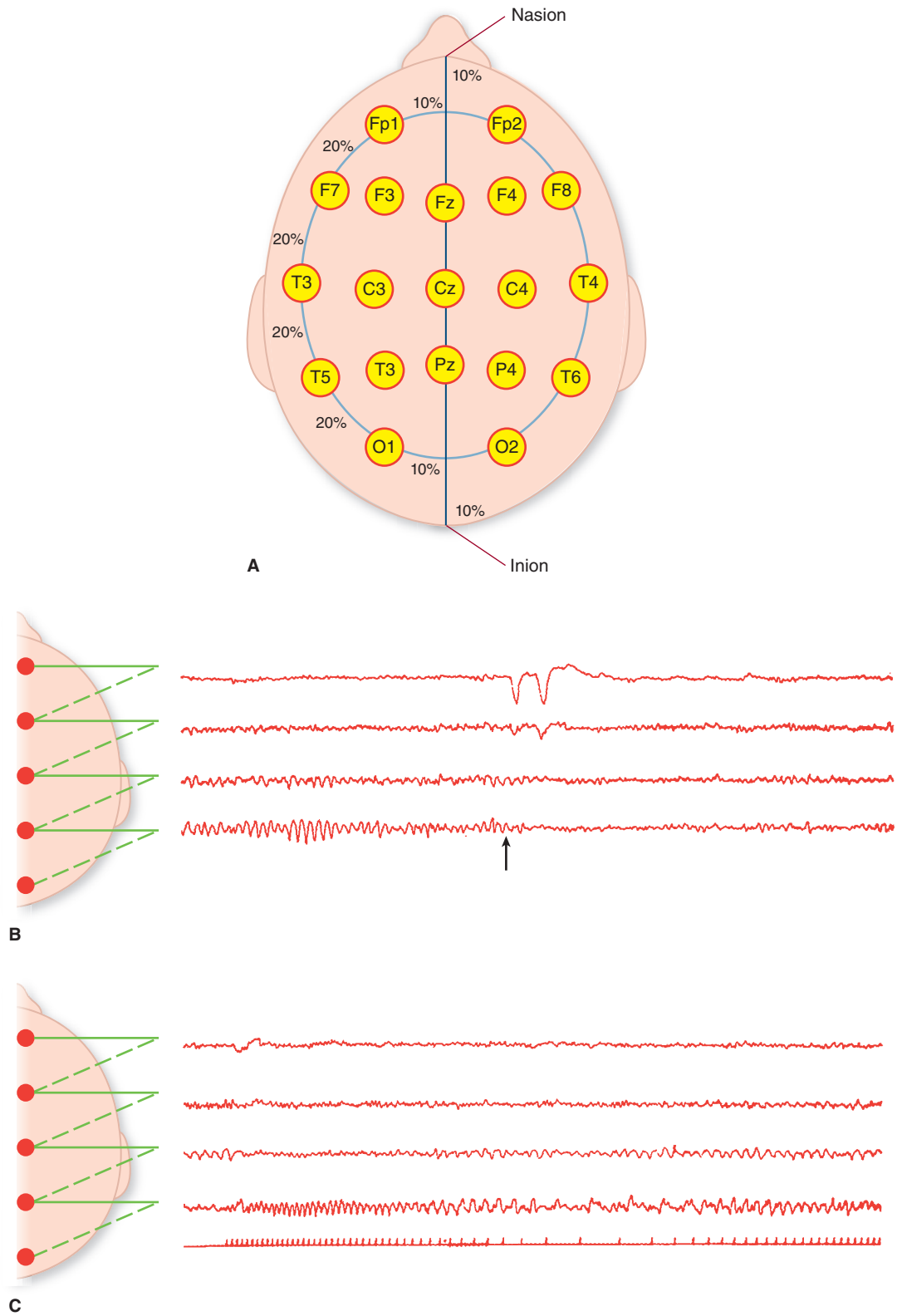

Figure 2-7 *A.* "10-20" is a measurement system designed to reliably reproduce electrode positions on different patients, regardless of head size. Electrodes are placed at intervals of either 10 or 20 percent of the hemi-circumference of the head. (Courtesy of Dr. Jay S. Pathmanathan.) *B.* Each channel represents the amplified recording of voltage changes over time between two electrodes. Normal alpha (8 to 12 per second) activity is present posteriorly (bottom channel). The top channel contains a large blink artifact. Note the striking reduction of the alpha rhythm with eye opening (arrow). *C.* Photic driving. During stroboscopic stimulation of a normal subject, a visually evoked response is seen posteriorly after each flash of light (signaled on the bottom channel). (*continued*)

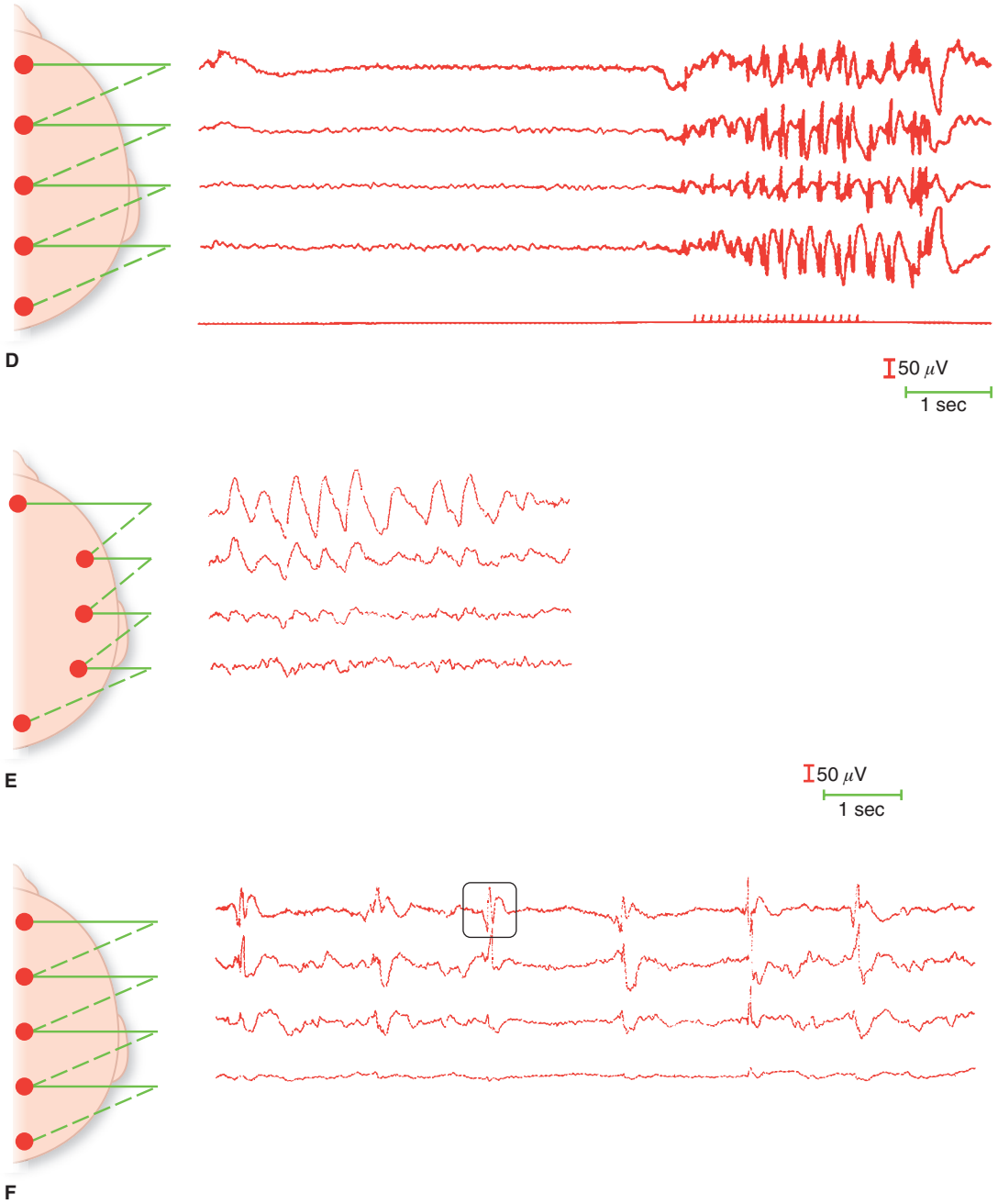

Figure 2-7 *(Continued) D.* Stroboscopic stimulation at 14 flashes per second (bottom channel) has produced a photoparoxysmal response in this epileptic patient, evidenced by the abnormal spike and slow-wave activity toward the end of the period of stimulation. *E.* Large, slow, irregular delta waves are seen in the right frontal region (channels 1 and 2). In this case a glioblastoma was found in the right cerebral hemisphere, but the EEG does not differ basically from that produced by a stroke, abscess, or contusion. *F.* An EEG showing focal spike-and-wave discharges over the right frontal region (channels 1 to 3). The box isolates a single spike–wave transient. (*continued*)

(see Blume and colleagues). It is customary for children to develop delta waves (3 to 4 Hz) during the middle and latter parts of a period of hyperventilation. This EEG activity, referred to as "breakdown," or "buildup," disappears soon after hyperventilation has stopped. The frequency of the dominant rhythms in infants is normally about 3 Hz, and they are very irregular. With maturation, there is a gradual increase in frequency and regularity of these occipital rhythms; an alpha rhythm appears by age 6 years and the adult frequency is reached by the age of 10 to 12 years (see Chap. 27 for further discussion of maturation of the brain as expressed in the EEG). The interpretation of records of infants and children require considerable experience because of the wide range of normal patterns at each age period (see Hahn and Tharp, Scher and Painter, and also Ebersole et al). Nevertheless, grossly asymmetrical records

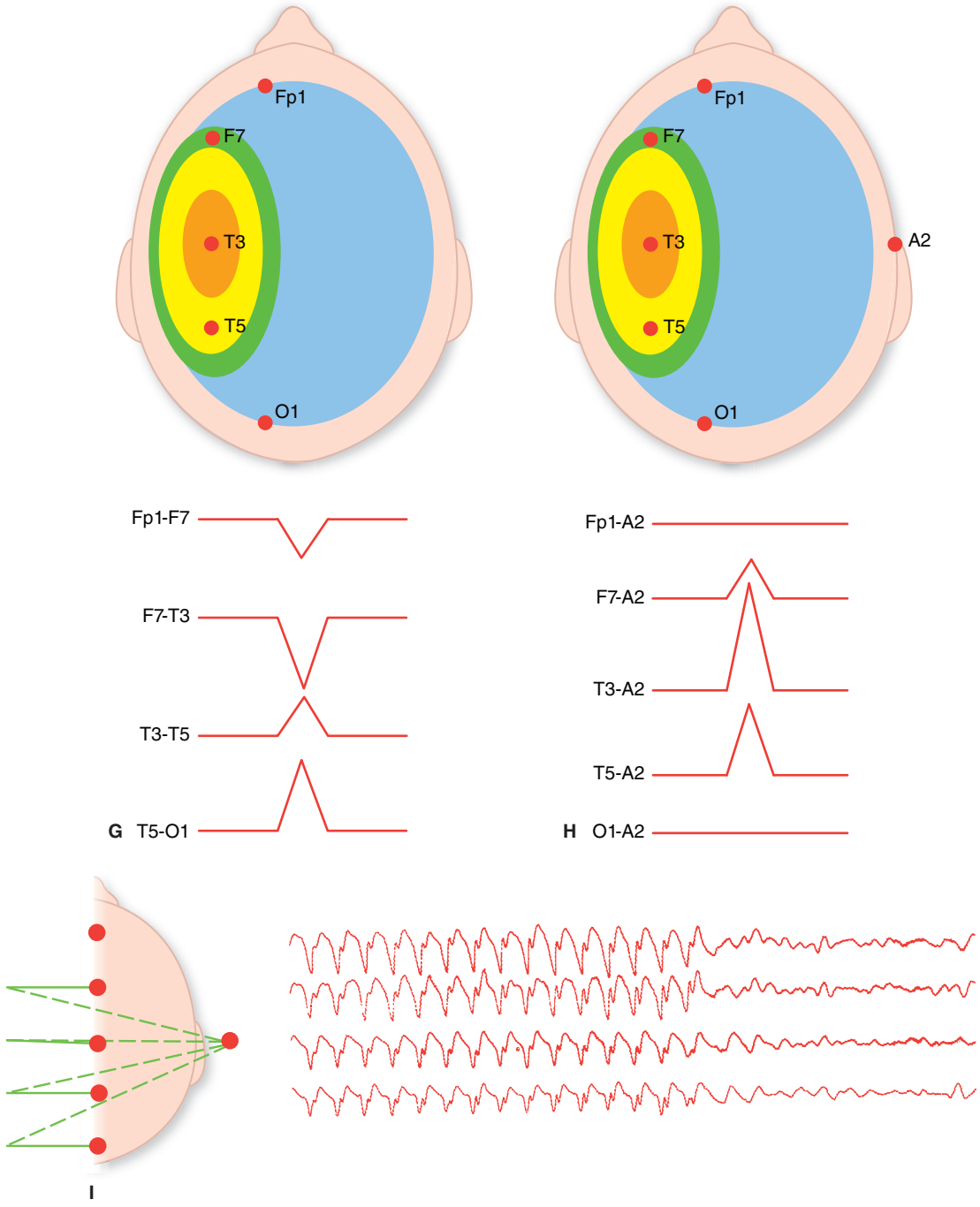

Figure 2-7 *(Continued) G.* Phase reversal is shown between electrode pairs, F7-T3 and T3-T5, implying that the site of the spike generator is under the T3 electrode. (Courtesy of Dr. Jay S. Pathmanathan.) *H.* Localization of a spike in a montage that utilizes the right ear (A2) as a reference electrode. The amplitude of the transient at T3 is greater than at other locations, implying that the source of the spike is closest to the T3 electrode. (Courtesy of Dr. Jay S. Pathmanathan.) *I.* Absence seizures, showing generalized 3-per-second spike-and-wave discharge. The abnormal activity ends abruptly and normal background activity appears. (*continued*)

or seizure patterns are clearly abnormal in children of any age. Normal patterns in the fetus, from the seventh month onward, have been established. Certain changes in these patterns, as described by Stockard-Pope et al and by deWeerd, are indicative of a developmental disorder or disease.

Types of Abnormal Recordings

Localized regions of greatly diminished or absent brain waves are seen overlying large area of cerebral infarction, traumatic necrosis, tumor, or extensive clot. These findings allow gross localization of the abnormality—but, of

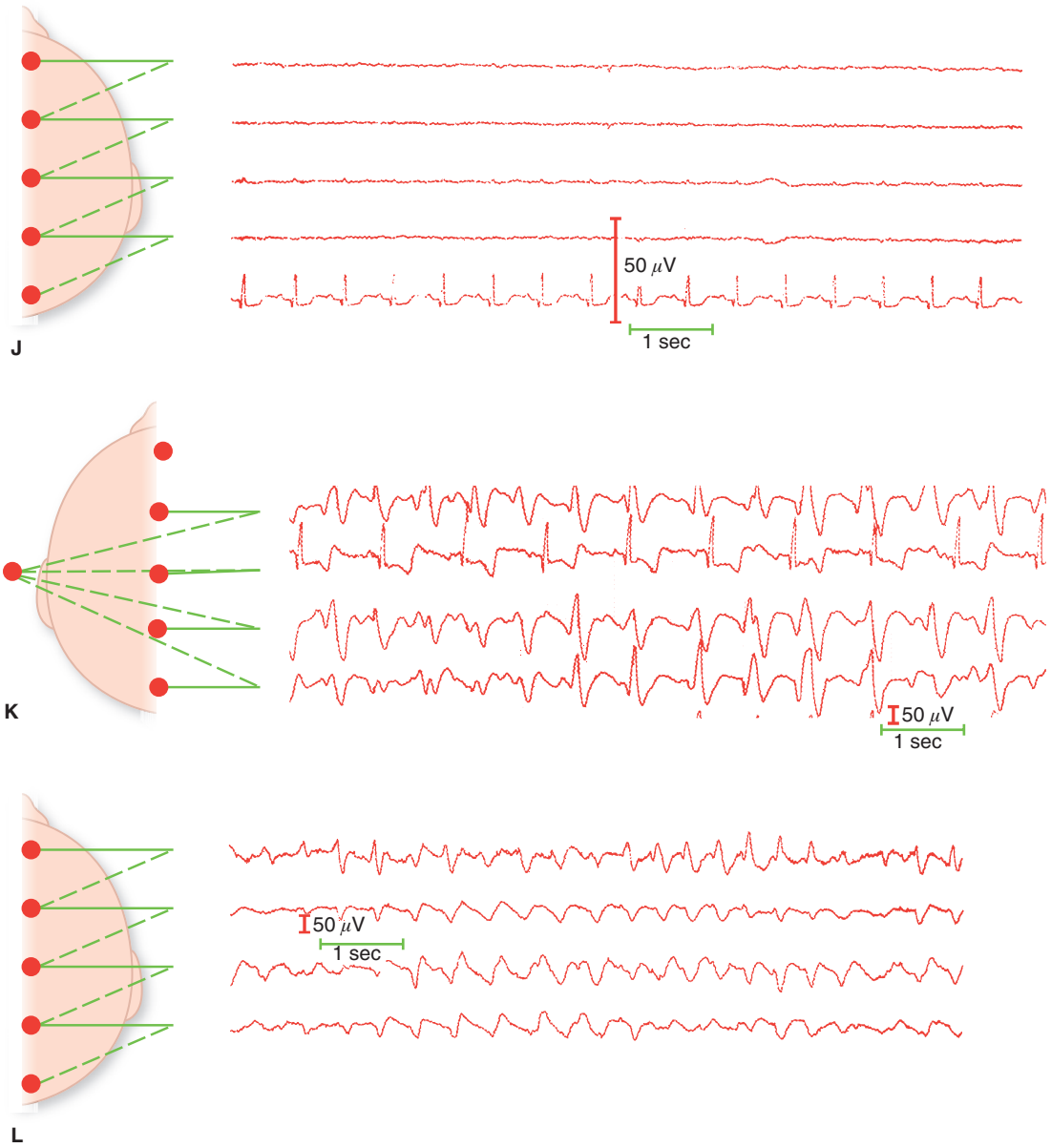

Figure 2-7 *(Continued) J.* Deep coma following cardiac arrest, showing electrocerebral silence. With the highest amplification, electrocardiogram (ECG) and other artifacts may be seen, so that the record is not truly "flat" or isoelectric. However, no cerebral rhythms are visible. Note the ECG (lower channel). *K.* Grossly disorganized background activity interrupted by repetitive "pseudoperiodic" discharges consisting of large, sharp waves from all leads about once per second. This pattern is characteristic of Creutzfeldt-Jakob disease. *L.* Advanced hepatic coma. Slow (about 2 per second) waves have replaced the normal activity in all leads. This record demonstrates the triphasic waves often seen in this disorder.

course, the nature of the lesion is not disclosed. Two types of abnormal waves, already mentioned, are of lower frequency and higher amplitude than normal. Waves below 4 Hz with amplitudes from 50 to 350 mV are called *delta waves* (Fig. 2-7*E*); those with a frequency of 4 to 7 Hz are called *theta waves*. Fast (beta) activity tends to be prominent frontally and usually reflects the effects of sedative drugs or, if focal, an immediately underlying skull defect called a "breach rhythm" (bone normally filters the abundant fast activity of the cortex).

Spikes are transient high-voltage waveforms that have a pointed peak at recording speeds and duration of 20 to 70 ms; a sharp waves is a similarly configured transient with a duration of 70 to 200 ms (Fig. 2-7*F*). Spikes or sharp waves that occur interictally are referred to as epileptiform discharges. At times, it is possible to infer localization from the reversal of the polarity of a sharp transient or spike in the EEG record. This "phase reversal" between two channels implies that the electrical activity originates near the site of the position of the common electrode (Fig. 2-7*G, H*).

The paroxysmal interruption of normal background EEG activity by a run of fast or slow waves is suggestive of seizures. When this paroxysmal discharge is composed

of spikes and sharp waves, it signifies a seizure with greater certainty. The electrical discharges associated with absence seizures have a more stereotyped pattern of 3-per-second spike-and-wave complexes that characteristically appear abruptly in all leads of the EEG simultaneously and disappear almost as suddenly at the end of the seizure (Fig. 2-7*I*).

The absence of EEG activity, or "electrocerebral silence," is a component of brain death but may be simulated by deep sedation with drugs or by profound hypothermia (Fig. 2-7*J*). Artifacts of various types should be apparent as the amplifier gains are increased; if not, there is a risk that the leads are not properly connected to the machine or of another technical fault. In the absence of nervous system depressants or extreme degrees of hypothermia, a record that is isoelectric (<2 uV except for artifacts) over all parts of the head is almost always a result of profound cerebral hypoxia, ischemia, massive cerebral hemorrhage or of trauma and raised intracranial pressure. Such a patient—without EEG activity, brainstem reflexes, and spontaneous respiratory or muscular activity of any kind—is said to be brain dead as discussed in Chap. 16.

Neurologic Conditions Causing Abnormal Electroencephalograms

Epilepsy

Epileptic seizures (see Chap. 15) are almost by definition associated with some abnormality in the EEG provided that it is being recorded at the time of the seizure. Rare exceptions are seizure states that originate in deep temporal, medial, or orbital frontal foci, from which the discharge fails to reach the scalp in sufficient amplitude to be seen against the normal background activity of the EEG. Most often, a completely normal EEG during a convulsion indicates a "pseudoseizure" (a psychogenic nonepileptic seizure, or "nonepileptic behavioral event").

Some of the different types of seizure patterns are shown in Fig. 2-7*F* and *I* are associated with particular clinical syndromes in Chap. 16. The absence, myoclonic, and grand mal EEG patterns correlate closely with the clinical seizure type and may be present in milder form in the EEG during periods between clinically evident seizures (interictally). Seizures appear as generalized discharges throughout the cerebrum, or as localized to one region.

Between seizures, a single EEG recording will show a normal pattern in as many as 30 percent of patients with absence seizures and 50 percent of those with generalized tonic-clonic (grand mal) epilepsy (this percentage is less with repeated recordings). Antepileptic therapy may mask interictal EEG abnormalities but the extent to which this occurs is not known. The records of 30 to 40 percent of those with epilepsy, although abnormal between seizures, are nonspecifically so; consequently, the diagnosis of epilepsy can be made only by the correct interpretation of clinical data in relation to the EEG abnormality.

Focal Brain Lesions (Brain Tumor, Abscess, Subdural Hematoma, Stroke, and Encephalitis)

In a high proportion of patients, intracranial mass lesions are associated with focal or localized slow-wave activity (usually delta, as in Fig. 2-*7E*) or, occasionally, seizure activity. EEG is of considerable value in the diagnosis of herpes simplex encephalitis in which periodic high-voltage sharp waves and slow-wave complexes at intervals of 1 to 3 per second in the temporal regions are characteristic. The other encephalitides are also often associated with sharp or spike activity, particularly if there have been seizures. The EEG is particularly helpful in the diagnosis of prion disease as also noted below. Figure 2-7*K* shows the characteristic pattern of almost periodic sharp waves seen in Creutzfeldt-Jakob disease.

The EEG is now little used in the differential diagnosis of stroke, except to distinguish a transient ischemic attack from a seizure. In the past, one practical value was in the ability to differentiate an acute ischemic lesion in the distribution of the middle cerebral artery, which produces a large area of slowing, from lacunar infarction deep in the cerebrum or brainstem, in which the surface EEG is usually normal despite prominent clinical abnormalities. After 3 to 6 months, in roughly 50 percent of patients with infarction in the territory of the middle cerebral artery, the focal EEG slowing becomes normal. Perhaps half of these patients will have had normal EEGs even in the week or two following the stroke. A persistent abnormality is generally associated with a poor prognosis for further recovery. Large lesions of the diencephalon or midbrain produce bilaterally synchronous slow waves, but those of the pons and medulla (i.e., below the mesencephalon) are usually associated with a normal or near-normal EEG pattern despite catastrophic clinical changes.

A brief episode of cerebral concussion in animals produces focal EEG slowing similar to those described for cerebral infarction. Sharp waves or spikes sometimes emerge as the focal slow-wave abnormality resolves and these seizure-like changes may precede posttraumatic epilepsy; serial EEGs may be of value in this regard. During syncope, the EEG is slowed and of reduced amplitude even to the point of becoming "flat." Upon recovery, a number of patterns have been described as discussed further in Chap. 17.

Diseases That Cause Coma and States of Impaired Consciousness

The EEG is abnormal in almost all conditions in which there is impairment of the level of consciousness. There is, for example, a fairly close correspondence between the severity of acute anoxic damage from cardiac arrest and the degree of EEG slowing. The mildest forms are associated with generalized theta activity, intermediate forms with widespread delta waves and the loss of normal background activity, and the most severe forms with "burst suppression," in which brief isoelectric periods are followed by high-voltage sharp and irregular delta activity. The latter pattern usually progresses to the electrocerebral silence of brain death, a condition discussed earlier.

The term *alpha coma* refers to a unique EEG pattern in which an apparent alpha activity in the 8- to 12-Hz range is distributed widely over the hemispheres rather than in its normal location posteriorly. When analyzed carefully, this background activity, unlike the normal monorhythmic alpha, is found to vary slightly in frequency. This is usually a transitional pattern after global anoxia; less often, alpha coma occurs with large acute pontine lesions. With severe hypothyroidism, the brain waves are normal in configuration but usually of decreased amplitude and frequency.

In altered states of alertness, the more profound the depression of consciousness, in general, the more abnormal and slower the EEG rhythms. In states of deep stupor or coma, the slow (delta) waves are bilateral and of high amplitude and tend to be more conspicuous over the frontal regions (Fig. 2-7*L*). This pertains in such differing conditions as acute meningitis or encephalitis and disorders that severely alter blood gases, glucose, electrolytes, and water balance; uremia; diabetic coma; and impairment of consciousness accompanying the large cerebral lesions discussed above. In hepatic coma, the degree of abnormality in the EEG corresponds roughly to the degree of confusion, stupor, or coma. Characteristics of hepatic coma are paroxysms of bilaterally synchronous large, sharp "triphasic waves" (Fig. 2-7*L*), although such waveforms may also be seen with less regularity in encephalopathies related to renal or pulmonary failure and with acute hydrocephalus (intermittent biphasic frontal slowing is more typical of hydrocephalus).

An EEG may also be of help in the diagnosis of coma that is due to ongoing seizures ("nonconvulsive status epilepticus") or, when the pertinent history is not available and there was an unobserved convulsion. It may also point to an otherwise unexpected cause of coma, such as hepatic encephalopathy, intoxication with barbiturates or other sedative-hypnotic drugs, the effects of diffuse anoxia–ischemia, catatonia, or hysteria (in which the EEG is normal).

Diffuse Degenerative Diseases

Alzheimer disease and other degenerative diseases that cause serious impairment of cerebrocortical function are accompanied by relatively slight degrees of diffuse slow-wave abnormality in the theta (4- to 7-Hz) range; many recordings are normal in the early and midstages of illness. More rapidly progressive disorders—such as subacute sclerosing panencephalitis (SSPE), Creutzfeldt-Jakob disease, and to a lesser extent the cerebral lipidoses—often have, in addition, very characteristic and almost pathognomonic EEG changes consisting of periodic bursts of high-amplitude sharp waves, usually bisynchronous and symmetrical (Fig. 2-7*K*). In a negative sense, a normal EEG in a patient who is profoundly apathetic is a point in favor of the diagnosis of hysteria, catatonia, or schizophrenia.

Other Diseases of the Cerebrum

Many disorders of the brain cause little or no alteration in the EEG. Multiple sclerosis and other demyelinating diseases are examples, although as many as 50 percent of patients with advanced disease will have an abnormal record of nonspecific type (mild focal or diffuse slowing). Delirium tremens and Wernicke-Korsakoff disease, despite the dramatic nature of the clinical picture, cause little or no change in the EEG. Interestingly, the psychoses (bipolar disorders or schizophrenia), intoxication with hallucinogenic drugs such as lysergic acid diethylamide (LSD), and the majority of cases of mental retardation are associated either with no modification of the normal record or with only minor nonspecific abnormalities unless seizures are present.

Clinical Significance of Minor Electroencephalogram 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. Lesser degrees of abnormality form a continuum between the undoubtedly abnormal and the completely normal and are of correspondingly less 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 normal variants or borderline abnormalities. 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 was discussed above.

As a general clinical principle, the results of the EEG, like those of the EMG and electrocardiogram, are meaningful only in relation to the illnesses under consideration and to 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. The use of computerized averaging methods, introduced by Dawson in 1954, has provided a means of overcoming these problems. Initially, emphasis was on the study of late waves (over 100 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, 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 remarkable properties of

Table 2-4

MAIN SENSORY EVOKED POTENTIAL LATENCIES FROM STIMULUS (MILLISECONDS)[a]

TYPE OF EVOKED POTENTIAL	MEAN	UPPER LIMIT (MEAN + 3 SD)
PSVER (*70-min check size*)		
P100 absolute latency	104	118
Intereye difference	2	8
BAER (*60 dBSL, 10/s monaural stimuli*)		
Interwave latency		
I–III	2.1	2.6
III–V	1.9	2.4
I–V	4.0	4.7
Interside difference for most latencies	0.1	0.4
SEP—median nerve (*wrist stimulation*)		
Absolute latency		
Erb's point	9.7	12.0
P/N 13 (cervicomedullary)	13.5	16.3
N 19/P 21 (cortical)	19.0	22.1
Interwave latency		
Erb's-P/N 13	3.8	5.2
P/N 13–N 19	5.5	6.8
Interside difference		
P/N 13–N 19	0.3	1.1
SEP—tibial nerve (*ankle stimulation;* Fz-*Cz recording; 165-cm height; absolute latencies are shorter for stimulation at the knee*)		
Absolute latency		
Lumbar point (cauda equina)	20	25
N/P 37 (cortex)	36	42.5
Interwave latency		
Lumbar–N/P 37	16.4	21.6
Interside difference		
Lumbar–N/P 37	0.7	1.9

BAER, brainstem auditory evoked response; PSVER, pattern shift visual evoked response; SSEP, somatosensory evoked response.
[a]Norms must be verified in each laboratory; in most instances they are sensitive to the technique and stimulus used and height of the patient in the cases of limb stimulation.

evoked potentials is their resistance to anesthesia, sedative drugs, and in states of reduced consciousness such as hypoxic-ischemic encephalopathy. This permits their use for monitoring the integrity of cerebral pathways in situations that limit the value of the EEG.

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 for latencies have been established, but it is 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 (Table 2-4). The amplitudes of the waves are less informative for clinical work.

Visual Evoked Potentials

For many years it had been known that a light stimulus flashing on the retina evokes 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. 2-7*C*). It is also appreciated that a visual evoked response is produced by the sudden change of a viewed checkerboard pattern. These responses, produced by rapidly reversing the pattern of black and white squares, are easier to detect and to measure than are flash responses and are more consistent in waveform from one individual to another. The pattern shift stimulus, applied first to one eye and then to the other, can demonstrate conduction delays in the visual pathways of patients who have had disease of the optic nerve—even when there are no residual signs of reduced visual acuity, visual field abnormalities, alterations of the optic nerve head, or changes in pupillary reflexes. Furthermore, the presence of a normal visual evoked response suggests that blindness is not due to a lesion in the anterior visual pathways and their projections to the occipital cortex, for example, in hysterical blindness. Figure 2-8 illustrates the normal pattern shift visual evoked response (PSVER) and two types of delayed responses. Reductions in the amplitude and duration of PSVER usually accompany prolonged latencies but are difficult to quantify. By presenting the pattern-shift stimulus to one hemifield, it is possible to isolate a lesion to an optic tract or radiation, or one occipital lobe, but with much less precision than that provided by the usual monocular testing.

The expected latency for the positive wave, by convention a downward deflection, is near 100 ms (thus the term P100 has also been used to designate the waveform); an absolute latency from the stimulus longer than 118 ms

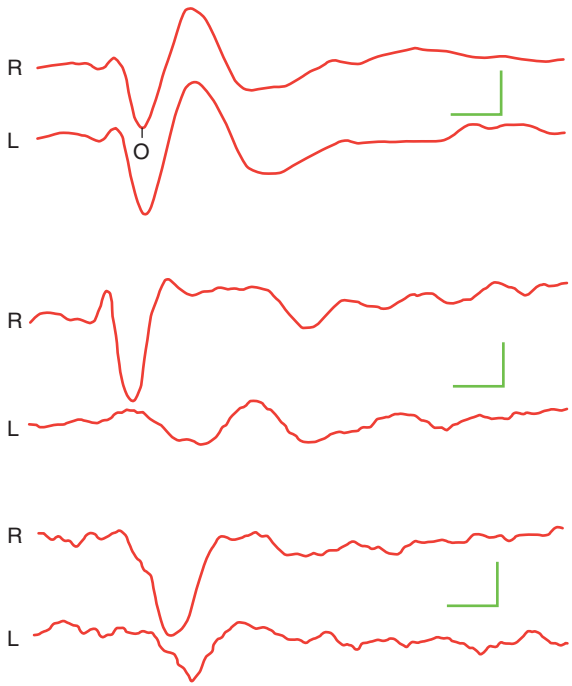

Figure 2-8. Pattern-shift visual evoked responses (PSVERs). Latency measured to first major positive peak (termed P100 because of its latency from the stimulus of approximate 100 ms) and marked by "o." Upper two tracings: These, from the right and left eyes, are normal. Middle tracings: PSVER from the 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 mV.

or a difference in latencies of greater than 9 ms between the two eyes signifies involvement of one optic nerve (see Table 2-4). Bilateral prolongation of latencies, demonstrated by separate stimulation of each eye, can be caused by lesions in both optic nerves, the optic chiasm, or the visual pathways posterior to the chiasm.

As indicated above, PSVER is especially valuable in proving the existence of active or residual disease of an optic nerve. Patients with previous optic neuritis almost invariably have prolonged latencies. Furthermore, prolongations of PSVER are found in about one-third of multiple sclerosis patients who have had 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 demyelinating lesion elsewhere in the CNS may usually be taken as evidence of multiple sclerosis, as discussed in Chap. 37.

A compressive lesion of an optic nerve will have the same effect as a primarily demyelinating 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 of the eye, if severe enough to affect the optic nerve, 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 some computerized testing for visual acuity).

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 1,000 and 2,000 clicks, delivered first to one ear and then to the other, are recorded through scalp electrodes and superimposed on each other by computer and thereby maximized. 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 disease, it has been established that each of the first five waves is generated by a specific brainstem structure, as indicated in Fig. 2-9. The generators of waves VI

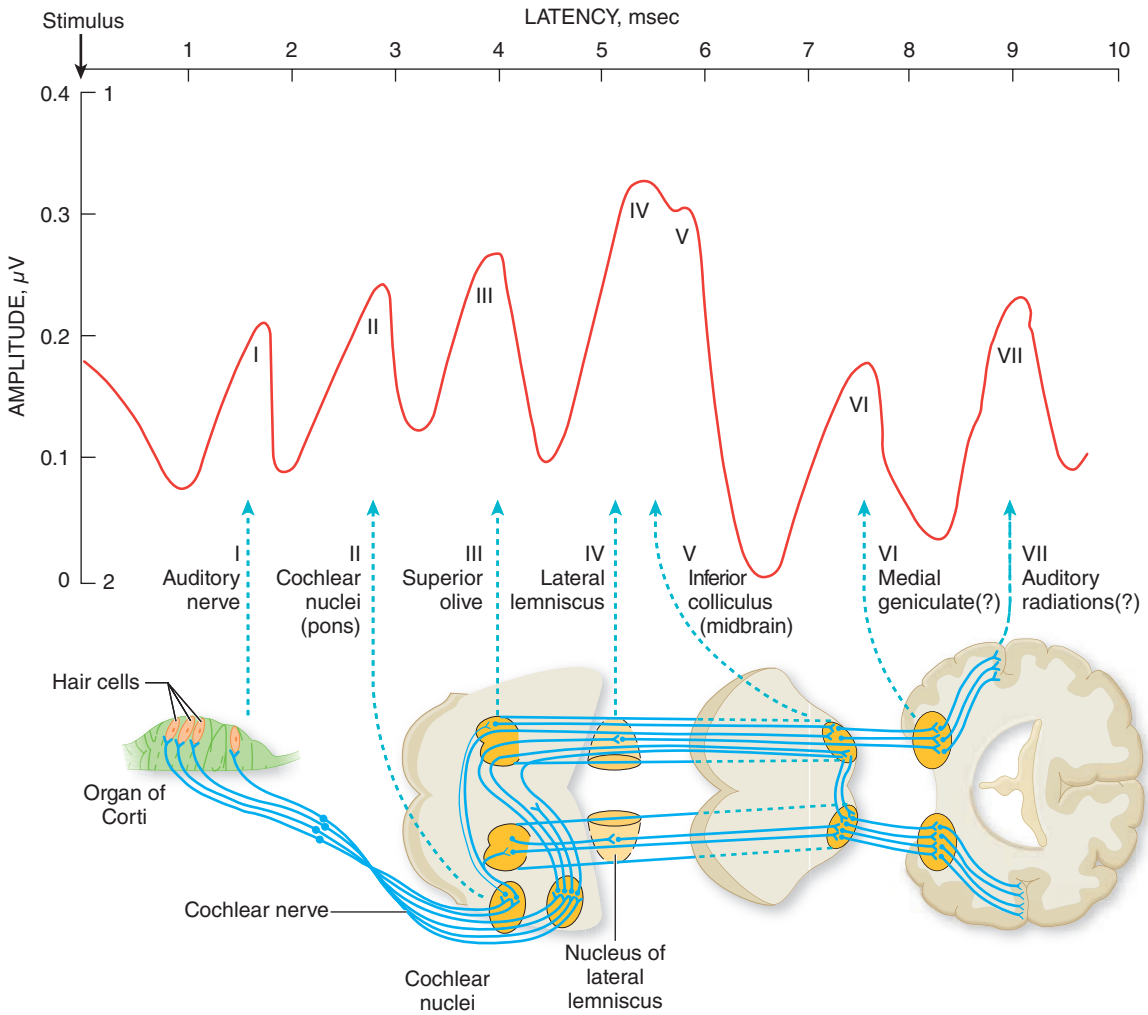

Figure 2-9. Short-latency brainstem auditory evoked responses (BAERs). Diagram of the proposed electrophysiologic-anatomic correlations in human subjects. Waves I through V are the ones measured in clinical practice.

and VII in particular are uncertain. The presence of wave I and its absolute latency test the integrity of the auditory nerve.

Clinical interpretations of BAERs are based mainly on latency measurements from the stimulus and interwave latencies. The most important are the interwave latencies between I and III, and III and V (see Table 2-4). A lesion that affects one of the auditory nuclear relay stations or its immediate connections manifests itself by a delay in the appearance or an absence of all subsequent waves; in other words, the nuclei behave as if they are connected in series. These effects are more pronounced on the side of the stimulated ear than contralaterally. This is difficult to understand, as a majority of the cochlear-superior olivary-lateral lemniscal-medial geniculate fibers cross to the opposite side. It is also surprising that a lesion of one relay station would allow impulses, even though delayed, to continue their ascent and be recordable in the cerebral cortex.

BAERs are a particularly sensitive means of detecting lesions of the eighth cranial nerve (vestibular schwannoma 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 BAERs, (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 BAERs 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 those with psychogenic or feigned deafness.

Somatosensory Evoked Potentials

The technique consists of applying 5-per-second painless transcutaneous electrical stimuli to the median, peroneal, or tibial nerves and recording the evoked potentials (for the upper limb) sequentially as they pass the brachial plexus over the Erb point above the clavicle, over the C2 vertebra, and over the opposite parietal cortex, and (for the lower limb) 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 corresponding peripheral nerves, spinal roots, and posterior columns to the cuneate and gracile nuclei 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 the Erb point or the lumbar spine indicates peripheral nerve disease; delay from the Erb 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. 2-10).

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., N11, N13, P13, P22, etc.). As shorthand for the polarity and approximate latency, the summated wave that is recorded at the cervicomedullary junction is termed N/P13, and the cortical potential from median nerve stimulation seen in two contiguous waves of opposite polarity is called N19–P22. The corresponding cortical wave after tibial or peroneal nerve stimulation is called N/P37. Each trace is the averaged response to 1,024 stimuli; the superimposed trace represents a repetition to demonstrate waveform consistency.

For purposes of clinical interpretation, the generators of the SEP waves are assumed to be linked in series, so that an interwave prolongation in latency indicates 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 ruptured lumbar and cervical discs, multiple sclerosis, and lumbar and cervical spondylosis when the clinical data are uncertain. The cerebral 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. For example, 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 on one side after stroke usually indicates such profound damage that only a limited clinical recovery is to be expected.

Evoked potential techniques have also been used in the experimental study of olfactory and trigeminal sensation (see Chap. 11).

Magnetic Stimulation of the Motor System

It is possible, by using single-pulse high-amplitude magnetic stimulation, to directly activate the motor cortex (transcranial magnetic stimulation) and cervical spine segments, and to detect delays or lack of conduction in descending motor pathways. This technique, introduced by Marsden and associates, painlessly stimulates only the largest motor neurons (presumably Betz cells) and the fastest-conducting axons. Cervical magnetic stimulation is believed to activate the anterior roots. The difference in time between the motor cortical and cervical activation of hand or forearm muscles reflects the conduction velocity of the cortical–cervical cord motor neurons. The technique has been used to understand the organization, function, and recovery of the motor cortex and the pathophysiology of stroke, multiple sclerosis, and amyotrophic lateral sclerosis. Although the degree of functional deficit does not precisely correlate with the degree of electrophysiologic change, one expects that refinements of this technique may be useful in evaluating the status of the

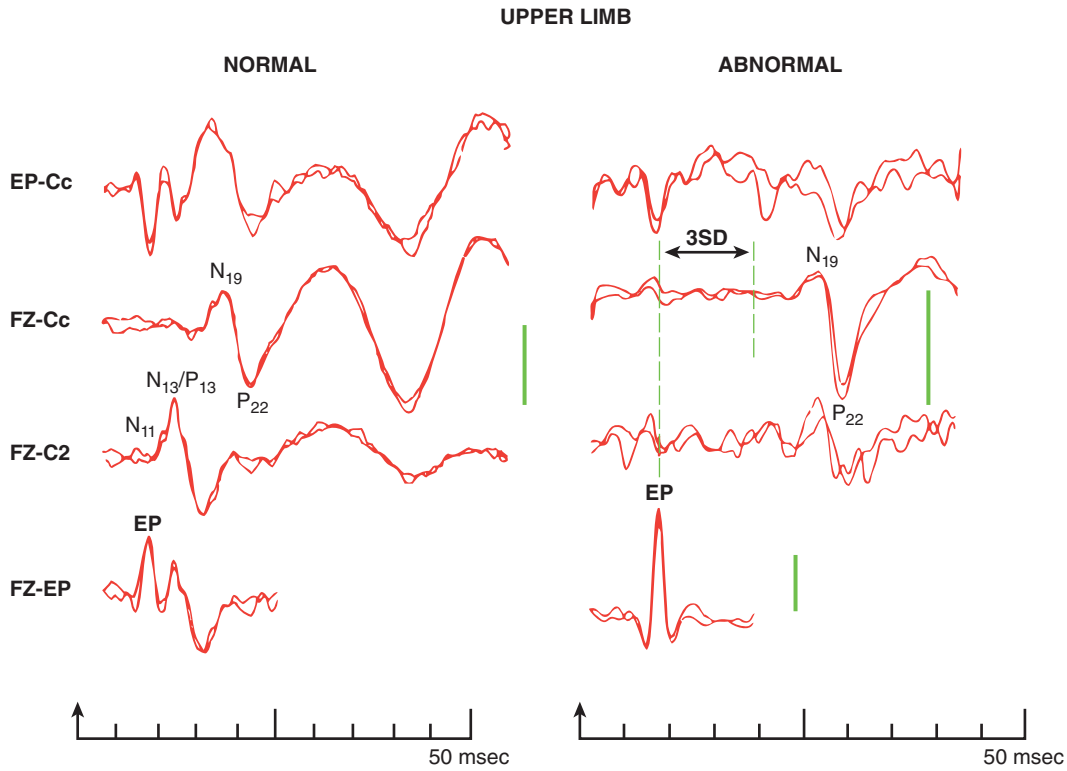

Figure 2-10. Short-latency SEPs produced by stimulation of the median nerve at the wrist. The set of responses shown at left is from a normal subject; the set at right is from a patient with multiple sclerosis who had no sensory symptoms or signs. In the patient tracing, note the preservation of the brachial-plexus component (EP), the absence of the cervical cord (N11) and lower-medullary components (N/P13), and the latency of the thalamocortical components (N19 and P22), prolonged above the normal mean +3 SD for the interval from the brachial plexus potential. Unilateral stimulation occurred at a frequency of 5 per second. Recording electrode locations are as follows: FZ, midfrontal; EP, the Erb 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. Relative negativity at the second electrode caused an upward trace deflection. Amplitude calibration marks denote 2 mV. (Reproduced by permission from Chiappa and Ropper.)

corticospinal motor system as well as other cortically based functions.

It is also possible to activate the motor (anterior) roots by magnetic stimulation and to measure the time required to elicit a muscle contraction (see review by Cros and Chiappa). These root stimulation tests can be quite uncomfortable for the patient as a result of the contraction of muscles surrounding the stimulation site. This technique finds its main use in diseases of the motor neuron, roots, and plexus.

Endogenous Event-Related Evoked Potentials

Among the very late brain electrical potentials (>100-ms latency) that can be extracted from background activity by computer methods, are a group that cannot be classified as sensory or motor but rather as psychophysical responses to environmental stimuli. These responses are of very low voltage, often fleeting and inconsistent, and of unknown anatomic origin. The most studied types occur approximately 300 ms (P300) after an attentive subject identifies an unexpected or novel stimulus that has been inserted into a regular train of stimuli. Almost any stimulus modality can be used and the potential occurs even when a stimulus has been omitted from a regular pattern. The amplitude of the response depends on the difficulty of the task and has an inverse relationship to the frequency of the unexpected or "odd" event; the latency depends on the task difficulty and other features of testing. There is therefore no single P300; instead, there are numerous types, depending on the experimental paradigm. Prolongation of the latency is found with aging and in dementia as well as with degenerative diseases such as Parkinson disease, progressive supranuclear palsy, and Huntington chorea. The amplitude is reduced in schizophrenia and depression. The potential has been interpreted by some as a reflection of the subject's orienting behavior or attention and by others, including Donchin, who discovered the phenomenon, as related to an updating of the brain's representation of the environment. The P300 remains a curiosity for the clinical neurologist because abnormalities are detected only when large groups are compared to normal individuals, and the technique is not as standardized as the conventional evoked potentials. A review of the subject can be found in sections by Altenmüller and Gerloff and by Polich in the Niedermeyer and Lopes DaSilva text on electroencephalography.

NERVE CONDUCTION STUDIES AND ELECTROMYOGRAPHY

It was long ago discovered that muscle would contract when a pulse of electric current was applied to the skin, near the point of entrance of the muscular nerve (*the motor point*). The electrical pulse required is brief, less than a millisecond, and is most effectively induced by rapidly alternating (faradic) current. If there has been muscle *denervation*, an electrical pulse of several milliseconds induced by a constant electrical (galvanic) stimulus is required to produce the same response. For decades, this was the standard electrical method for evaluating denervation of muscle. Although still valid, it was replaced by nerve conduction studies and by the needle electrode examination. The latter test, based on the sherringtonian concept of the "motor unit" described in Chap. 3, is accomplished by the insertion into muscle of needle electrodes to measure spontaneous and voluntarily evoked muscle fiber activity. The terms *electromyography* and *electromyogram* were used originally to describe the needle electrode examination but are now a common shorthand designation for the entire electrodiagnostic evaluation, including the *nerve conduction studies*.

Nerve Conduction Studies

The main laboratory technique for the study of peripheral nerve function involves the transcutaneous stimulation of motor or sensory nerves and recording of the elicited action potentials in the muscle (CMAP) and the sensory nerve action potential (SNAP). The results of these *motor and sensory nerve conduction studies*, expressed as amplitudes, conduction velocities, and distal latencies, yield certain quantitative information and additional qualitative observations regarding the waveform of electrical neural and muscular impulses.

Hodes and coworkers, in 1948, were the first to describe nerve conduction studies in patients, and the techniques used currently are not much changed. An accessible nerve is stimulated through the skin by surface electrodes, using a stimulus that is large enough to recruit (cause a discharge in) all the available nerve fibers. The resulting action potential is recorded by electrodes on the skin (1) over the muscle distally in the case of motor fibers stimulated in a mixed or motor nerve (CMAP), (2) over the nerve more distally, using antidromic techniques for sensory nerve conduction studies (this has technical advantages over orthodromic techniques), and (3) over the nerve more proximally for mixed (sensory and motor) nerve conduction studies. These techniques are the ones used most often in clinical work. An alternative but much more demanding experimental technique uses "near-nerve" needle electrodes to record action potentials as they course through the nerve. The main characteristics of the conventional nerve conduction studies are described below.

Compound Muscle Action Potential Amplitude

The peak amplitude of the evoked muscle action potential to a maximal stimulus (CMAP) yields valuable information about peripheral nerve function. The amplitude, usually in the order millivolts, reflects the summated electrical potential generated by the depolarization of a muscle innervated by the motor nerve (Fig. 2-11). In instances of disease, the amplitude is a semiquantitative measure of the number of remaining normal nerve fibers and of the innervated volume of muscle. It is usually possible to obtain a reliable motor conduction study as long as some functioning nerve fibers remain intact, although the compound muscle potential recorded may be very low. The latency to the CMAP waveform is the basis for calculations of motor nerve conduction velocity. Reduction in motor amplitudes is a specific and sensitive indicator of axonal loss. Demyelinative lesions affecting the large, fast-conducting fibers also reduce the peak summated amplitude of the CMAP but are the result of differential arrival times of the electrical potentials from each axon at the muscle. Table 2-5 shows the range of normal amplitudes for the CMAPs that are elicited by stimulation of the main motor nerves.

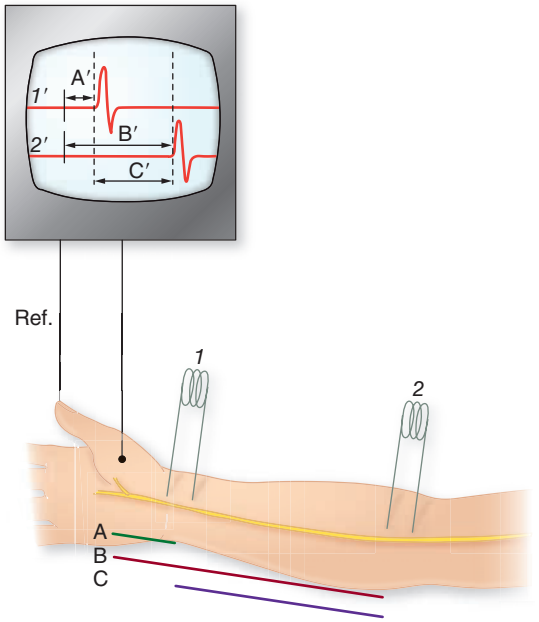

Figure 2-11. The median nerve is stimulated percutaneously (1) at the wrist and (2) in the antecubital fossa with the resultant compound muscle action potential recorded over the abductor pollicis brevis (*arrow*).The motor waveform is recorded as the voltage between the surface electrode and a reference electrode (*Ref.*) more distally. Sweep 1′ on the display depicts the stimulus artifact followed by the compound muscle action potential. The distal latency, A′, is the time from the stimulus artifact to the onset of the compound muscle action potential and corresponds to conduction over distance A. The same is true for sweep 2′, where stimulation is at site 2 and the time from the artifact to the response is B′. The maximum motor conduction velocity over segment C is calculated by dividing the distance between the two stimulating electrodes, C, by the time C′.

Motor Distal Latencies and Conduction Velocities

The conduction times that are utilized in clinical work are the latency from the stimulus artifact to the onset

Table 2-5

NORMAL VALUES FOR REPRESENTATIVE NERVE CONDUCTION VALUES AT VARIOUS SITES OF STIMULATION (MEAN VALUES ± 2 SD FOR ADULTS 16 TO 65 YEARS OF AGE)

MOTOR NERVE CONDUCTION STUDIES

NERVE	DISTAL STIMULATION SITE	OTHER STIMULATION SITES	RECORDING SITE	ONSET LATENCY (ms)	AMP (mV)	CV (m/s)	DISTANCE (cm)	F-WAVE LATENCY (ms)
Median	Wrist	Elbow	APB	<4.2	>4.4	>49	6–8	<31
Ulnar	Wrist	BG, AG	ADM	<3.4	>6.0	>49	5.5–7.5	<32
Radial	Forearm	Elbow, SG	EIP	<5.2	>4.0	>50	10	NA
Peroneal	Ankle	BFH, AFH	EDB	<5.8	>2.0	>42	6–11	<58
Peroneal	BFH	AFH	TA	<3.0	>5.0	>42	10	NA
Tibial	Ankle	PF	AH	<6.5	>3.0	>41	6–8	<59[a]

SENSORY NERVE CONDUCTION STUDIES[b]

NERVE	DISTAL STIMULATION SITES	RECORDING SITE	ONSET LATENCY (ms)	PEAK LATENCY (ms)	AMP (μV)	CV (m/s)	DISTANCE (cm)
Median	Wrist	Index finger	<2.5	<3.5	>20	>52	13
Ulnar	Wrist	Fifth finger	<2.1	<3.0	>15	>52	11
Radial	Forearm	Wrist	<1.9	<2.8	>20	>48	10
Sural	Calf	Ankle	<3.2	<4.4	>6	>42	14

LATE RESPONSE (F WAVE)

NERVE	DISTAL STIMULATION SITES	RECORDING SITE	UPPER LIMIT LATENCY (ms)
Median	Wrist	Abductor pollicis brevis	32
Ulnar	Wrist	Abductor digiti minimi	32
Peroneal	Fibular head	Extensor digitorum brevis	57
Tibial	Behind knee	Abductor hallucis	58

ADM, adductor digiti minimi; AFH, above fibular head; AG, above ulnar groove; AH, abductor hallucis; APB, abductor pollicis brevis; BFH, below fibular head; BG, below ulnar groove; EDB, extensor digitalis brevis; EIP, extensor indicis proprius; PF, popliteal fossa; SG, spiral groove; TA, anterior tibialis.

[a]Tibial H reflexes: latency <35 ms; side-to-side difference <1.4 ms.

[b]Sensory studies are performed antidromically; amplitudes are measured from baseline to negative peak of nerve potential.

of the compound muscle action potential (CMAP), the *distal* (or terminal) latency; and from the stimulus to the peak of the CMAP, *peak* motor latency (see Fig. 2-11). A stimulus is then applied to the nerve at a second site more proximally, and a conduction time can be measured over a longer segment of nerve. When the distance (in millimeters) between the two sites of stimulation is divided by the difference in the distal latencies (in milliseconds), one obtains a *conduction velocity* (in meters per second). This method isolates the conduction time across a segment of a peripheral nerve by eliminating the transmission time across the neuromuscular junction and the duration of muscle depolarization. Motor nerve conduction velocity represents the maximal velocity of propagation of the action potentials in the largest-diameter and fastest-conducting nerve fibers. These velocities in normal subjects vary from a minimum of 40 or 45 m/s to a maximum of 65 to 75 m/s, depending upon which nerve is studied (e.g., slower in the legs than in the arms; see Table 2-5). Values are lower in infants, reaching the adult range by the age of 2 to 4 years, and declining again slightly with advancing age. Conduction velocity also is diminished with exposure to cold, a potentially important factor if these recordings are taken when the patient's skin is cool; consequently, measurement of skin temperature is routinely done prior to performing the nerve conduction tests.

Normal values have been established for distal latencies from the usual sites of stimulation on various mixed nerves to the appropriate muscles. Stimulating the median nerve at the wrist, for example (see electrode 1 and segment A in Fig. 2-11), has a latency for motor conduction through the carpal tunnel to the median-innervated thenar muscles of less than approximately 4.5 ms in healthy adults. Similar normal values have been compiled for orthodromic and antidromic sensory conduction velocities and for distal latencies in all the main peripheral nerves (see Table 2-5).

The main effect of disease processes that preferentially injure axons, as mentioned above, is a reduction in the CMAP amplitude (Fig. 2-12*B*). However, some processes affect the fastest-conducting, large-diameter fibers and also usually reduce the conduction velocity because the remaining thinner fibers conduct more

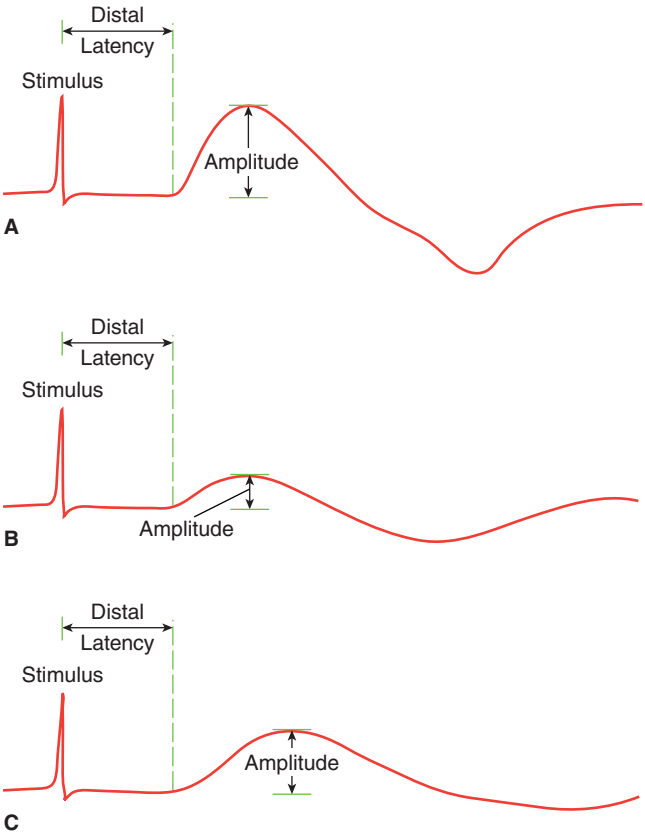

Figure 2-12. The principal pathologic alterations of CMAP. *A*. The normal CMAP, representing the summed discharges from a group of motor units activated by a supramaximal stimulus, measured over the muscle. *B*. With loss of motor axons, fewer motor units are activated and the CMAP has reduced amplitude. *C*. With demyelination of motor axons, the same number of motor units activate, but over a prolonged duration; thus the CMAP has reduced amplitude because there is temporal dispersion of the waveform.

slowly. In most neuropathies, all the axons are affected either by a fairly uniform "dying-back" phenomenon or by wallerian degeneration as described in Chap. 43, and nerve conduction velocities are then less affected. This is true, for example, in typical alcoholic-nutritional, carcinomatous, uremic, diabetic, and other metabolic neuropathies, in which conduction velocities range from the low-normal range to mildly slowed. By contrast, demyelinating neuropathies (see Chap. 46) show marked slowing of conduction and, in the case of the acquired demyelinating diseases, there is also dispersion of the motor action potential and a characteristic conduction block (Fig. 2-12*C*).

Sensory Nerve Action Potentials

The sensory nerve action potential (SNAP) is far lower in amplitude than the CMAP. It directly represents the action potentials in a group of sensory nerve axons. When one attempts to measure sensory nerve action potentials, the summation of electrical activity provided by many motor units discharging at the muscle is not available and electronic amplification is required. In contrast to motor conduction measurements, the nerve is typically stimulated at one site and recordings are performed at two distal sites (therefore antidromically for sensory conduction) in order to obtain both the amplitude (at the more proximal site) and conduction velocity by the subtraction method (Fig. 2-13). Sensory potentials, measured in microvolts, are sometimes very small or absent and sensory conduction measurements may then be difficult to determine. Table 2-5 gives the range of normal values for sensory nerve action potential amplitudes and velocities.

Conduction Block

By stimulating a motor nerve at multiple sites along its course, it is possible to demonstrate segments in which conduction is partially "blocked" or is differentially slowed. From such data one infers the presence of a multifocal demyelinative process in motor nerves. This contrasts with the findings in certain of the inherited and metabolic

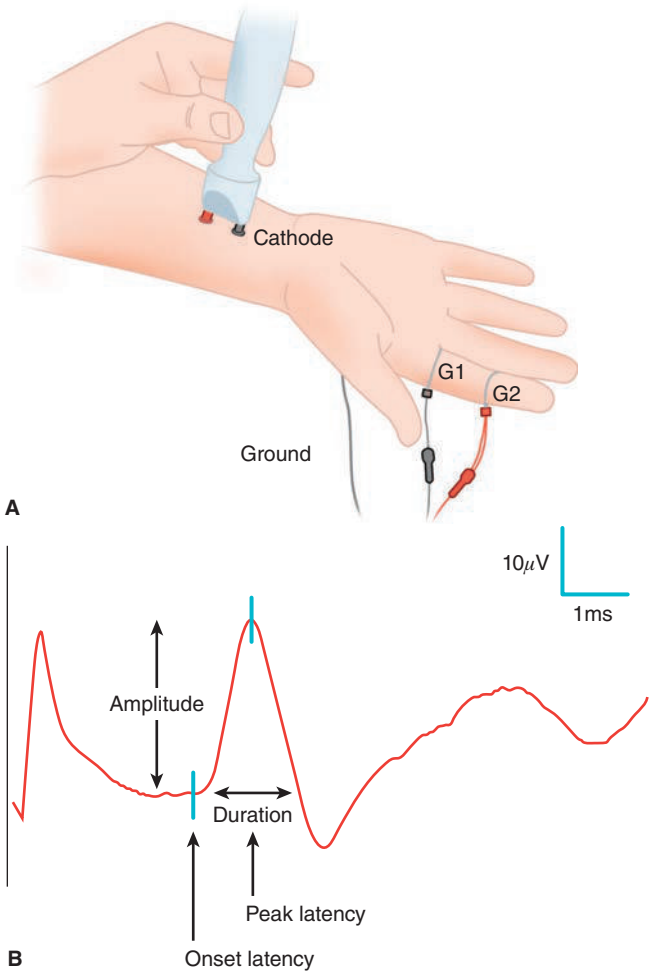

Figure 2-13. SNAP recording. *A*. Electrical stimulation of the median nerve at the wrist with recording of sensory action potentials at two sites in the second digit. The responses are generated by antidromic propagation of action potentials from the site of stimulation. *B*. A SNAP recorded from G1. Sensory nerve conduction velocity can be calculated by dividing the distance between G1 and G2 by the difference in onset latencies from these two sites.

demyelinating neuropathies, in which all parts of the nerve fiber are altered to more or less the same degree, that is, there is uniform slowing and reduction in amplitude and no conduction block.

As a technical matter, conduction block is demonstrated by a reduction in the amplitude of the CMAP elicited from the proximal site along the motor nerve, compared to stimulation at a distal site. Generally, a 40 percent reduction in amplitude over a short distance of nerve, or 50 percent over a longer distance, qualifies as a block, one possible exception being along the tibial nerve, in which there is some degree of physiologic dispersion; therefore, a slight drop in amplitude over the length of the nerve is normally expected. It is important to be sure that any reduction in amplitude along the course of the nerve is not solely a result of dispersion of the waveform as mentioned previously. The presence of a conduction block can also be inferred from the finding of poor recruitment of muscle action potentials and the concurrent absence of active denervation (see further on). The finding of conduction block is a main feature of a number of acquired immune demyelinating neuropathies, including Guillain-Barré syndrome, chronic inflammatory demyelinating neuropathy, and multifocal conduction block associated with the G_{M1} antibody, which are discussed in Chap. 46.

Focal conduction block may be caused simply by nerve compression at certain common sites (fibular head, across the elbow, flexor retinaculum at the wrist, etc.) rather than to an intrinsic disease of the peripheral nerves. *Focal compression of nerve*, as occurs in these entrapment syndromes, produces localized slowing or blocks in conduction, perhaps because of segmental demyelination at the site of compression. The demonstration of such localized changes of conduction affords ready confirmation of nerve entrapment; for example, if the distal latency of the median nerve (Fig. 2-11*A*) exceeds 4.5 ms while that of the ulnar nerve remains normal, compression of the median nerve in the carpal tunnel is likely. Similar focal slowing or partial block of conduction may be recorded from the ulnar nerve at the elbow and from the peroneal nerve at the fibular head.

The examiner should also be aware of a normal variant, the Martin-Gruber anastomosis that exists in close to 20 percent of individuals; in this configuration, axons from the median nerve cross into the ulnar nerve in the midforearm to innervate normally ulnar associated muscles in the hand. Distal stimulation of the ulnar nerve then gives higher amplitude ulnar CMAP than proximal stimulation, simulating conduction block, but without weakness or atrophy. The anastomosis can be demonstrated by obtaining a normal CMAP when stimulating the proximal median nerve and recording over ulnar innervated muscles.

Late Responses

Information about the conduction of impulses through the proximal segments of a nerve, including the spinal roots, is provided by the study of the H reflex and the F wave (Fig. 2-14).

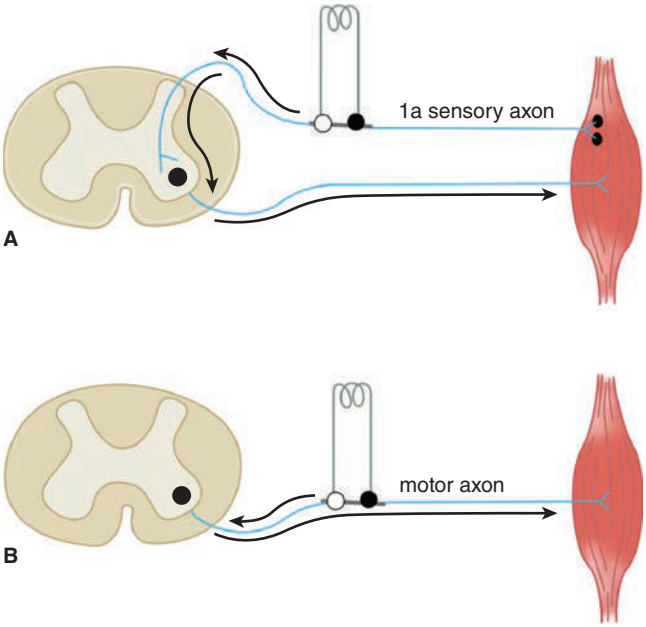

Figure 2-14. Late responses. *A*. The H reflex is elicited by stimulating a sensory nerve. The action potentials travel in an orthodromic fashion through the dorsal root into the spinal cord, where synapses occur with motor neurons. The motor axons innervate a muscle (the gastrocnemius) from which the late CMAP response is recorded. *B*. The F response is elicited by stimulating a motor nerve. Some of the action potentials that have traveled in an antidromic fashion though the anterior horn are volleyed back in an orthodromic fashion along the same motor neurons. The late CMAP response is recorded from the muscle innervated by these axons.

H reflex In 1918, Hoffmann, after whom the H reflex was named, showed that submaximal stimulation of mixed motor–sensory nerves induces a muscle contraction (H wave, Fig. 2-14*A*) after a latency that is far longer than that of the direct motor response. This reflex, the electrical representation of the ankle jerk, is based on the activation of afferent fibers from muscle spindles (the same axons that conduct the afferent volley of the tendon reflex). Thus the long delay, typically 28 to 35 ms after the stimulus (adjusted for height and age), reflects the cumulative time required for the impulses to reach the spinal cord via the sensory fibers, synapse with anterior horn cells, and to be transmitted along motor fibers to the muscle (see Fig. 3-1). The H reflex is a useful measure because the impulse traverses both the posterior and anterior spinal roots. The H reflex is particularly helpful in the diagnosis of S1 radiculopathy and of polyradiculopathies. It is difficult to obtain an H reflex from nerves other than the tibial. Stimuli of increasing frequency but low intensity cause a progressive depression and finally obliteration of H waves. In parallel with the Achilles tendon reflex, the H-reflex is transiently obliterated in spinal shock (see Chap. 42).

F response (wave) The F response, so named because it was initially elicited in the feet, was first described by Magladery and McDougal in 1950. It is evoked by a supramaximal stimulus of a mixed motor–sensory or pure motor nerve (Fig. 2-14*B*). After a latency substantially longer than for the CMAP, a second small muscle action potential

is normally recorded at 28 to 32 ms in arms and 40 to 58 ms in legs. This F wave is the result of impulses that travel antidromically in motor fibers to the anterior horn cells, a small number of which are activated and produce an orthodromic response that is recorded in a distal muscle. The F response is representative of proximal motor nerve and root conduction in that it traverses only the ventral root and can be elicited from a number of muscles.

Both responses are lost or delayed in some severe and generalized polyneuropathies (see Chap. 43). The combination of a normal F response and an absent H reflex is found in diseases of sensory nerves and roots. As with the H reflex, the F wave may be absent in the state of spinal shock or destructive diseases of the spinal cord (see Chap. 42). Both of these "late responses" find their main use as corroborative tests that are interpreted in the context of the entire nerve conduction examination.

Blink responses This special nerve conduction test is not in frequent clinical use but it serves a purpose in the diagnosis of certain demyelinating neuropathies and in any process that affects the trigeminal or facial nerve. The supraorbital (or infraorbital) nerve is stimulated transcutaneously and the reflex closure of both orbicularis oculi muscles is recorded with surface electrodes. Two CMAP bursts generated by facial motor neurons are observed: the first (R1) appears ipsilaterally 10 ms after the stimulus and the second (R2), ipsilaterally at 30 ms and contralaterally up to 5 ms later. The amplitudes of the responses vary considerably and are not in themselves clinically important. The first response is not visible as a muscular contraction but may serve some preparatory function by shortening the blink reflex delay. R1 is mediated by an oligosynaptic pontine circuit consisting of one to three neurons located in the vicinity of the principal sensory nucleus of the trigeminal nerve; R2 uses a broader and less-well-defined reflex pathway in the pons and medulla.

The pattern of abnormalities of the R1 and R2 responses assist in localizing a lesion to the afferent trigeminal nerve, the efferent facial nerve, or the interneurons in the pons. In Bell palsy there is a delay or absence of R1 and R2 responses only on the affected side. Large acoustic neuromas (vestibular schwannomas) also may interfere with the efferent portion of the response. The test may be helpful in identifying a demyelinating neuropathy when the facial and oropharyngeal muscles are affected. Diseases of the brainstem have yielded inconsistent responses. It is noteworthy that the test is normal in patients with trigeminal neuralgia.

Repetitive Motor Nerve Stimulation (See Also Chap. 46)

This test of the neuromuscular junction is based on Jolly's observation in 1895 that in myasthenia gravis the strength of muscular contractions progressively declines in response to a train of stimuli. By adjusting the amplitude of a stimulus over a nerve to the supramaximal range, a maximal CMAP may be obtained for each stimulus. With repeated stimuli, each response will have the same waveform and amplitude. In a healthy individual, a muscular response follows each stimulus with rates of stimulation up to 25 per second for periods of 60 s or more before a decrement of the CMAP appears. A decrement of 10 percent or more denotes a failure of a proportion of the neuromuscular junctions.

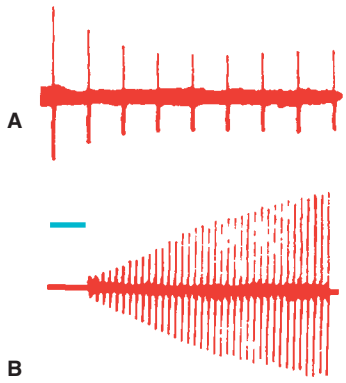

Figure 2-15. Repetitive stimulation of the hypothenar muscles. *A*. Patient with myasthenia gravis—typical pattern of decrement in first four responses followed by slight increment. At this rate of stimulation (3 per second), the decrement in response does not continue to zero. *B*. Patient with Lambert-Eaton syndrome and oat cell carcinoma—marked increase from low toward normal amplitude with rapid repetitive stimulation (20 per second). Horizontal calibration: 250 ms.

In certain disorders, notably myasthenia gravis, a train of 4 to 10 stimuli at rates optimally 2 to 3 per second, the amplitude of the motor potentials decreases (Fig. 2-15*A*). A progressive reduction in amplitude is most likely to be found in proximal muscles, but these are not easily stimulated for which reason the locations most commonly used for clinical testing are the accessory nerve in the posterior triangle of the neck (trapezius), the ulnar nerve (hypothenar muscle), the median nerve at the wrist (thenar muscle), and the facial nerve (orbicularis oculi muscle).

The sensitivity of the procedure is improved by first exercising the tested muscle for 30 to 60 s; a form of posttetanic potentiation. The full procedure consists of testing the muscle with a train of stimuli before and immediately after exercise (or maximal voluntary contraction) and at 30-s intervals for several minutes. The posttetanic potentiation at first partially compensates for the depletion of ACh during slow rates of stimulation; this is followed by an exaggerated decrease in the transmission through the neuromuscular junction during the approximately 2 to 4 min after exercise. The induced failure of neuromuscular transmission in myasthenia is similar to the one produced by curare and other nondepolarizing neuromuscular blocking agents, and the electrical features of both can be partially corrected with anticholinesterase drugs such as neostigmine and edrophonium. Similar but lesser decremental responses may occur in poliomyelitis, ALS, and certain other diseases of the motor unit or motor nerve, particularly those resulting in the growth of reinnervating nerve twigs.

The Lambert-Eaton myasthenic syndrome, sometimes associated with oat cell carcinoma of the lung, as discussed

in Chap. 46, is characterized by a presynaptic blockage of acetylcholine release and, with rapid rates of stimulation, produces the opposite effect on neuromuscular transmission to the one recorded in myasthenia gravis. There is instead an increment in the amplitude of the CMAP with continued stimulation. During very rapid repetitive stimulation (20- to 50-per-second), the muscle action potentials, which are small or practically absent with the first stimulus, increase in voltage with each successive response until a more nearly normal amplitude is attained (see Fig. 2-15*B*). Exercising the muscle for 10 s before stimulation will cause a posttetanic facilitation in patients with the Lambert-Eaton syndrome (200-fold increases are not uncommon). A less important decremental response to slow stimulation may occur, but it is difficult to discern because of the greatly diminished amplitude of the initial responses. The effects of botulinum toxin and of aminoglycoside antibiotics are similar, that is, being active at the presynaptic membrane, they produce an incremental response at high rates of stimulation.

The single-fiber EMG, discussed in a later section, is an even more sensitive method of detecting failure of the neuromuscular junction.

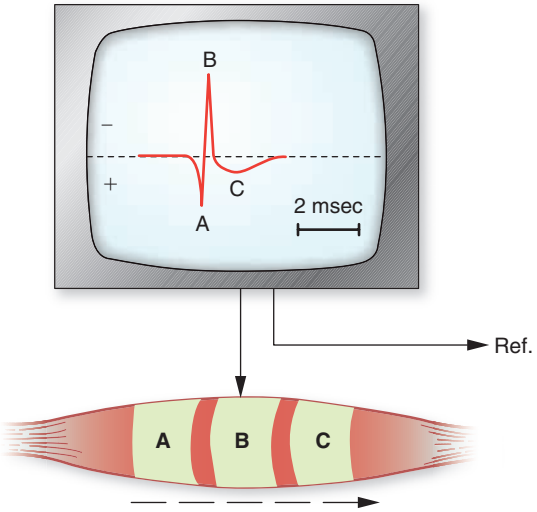

Figure 2-16. The shaded areas on the muscle (*A*, *B*, and *C*) represent zones of the propagating action potential depicted by the dashed arrow. The correspondingly lettered portions of the triphasic muscle action potential displayed on the screen reflect the potential difference between the active (*vertical arrow*) and reference (*Ref.*) electrodes. Polarity in this and subsequent figures is negative upward as depicted.

Needle Examination of Muscle (Electromyography)

In the usual EMG examination, a plan for the study is made based on detailed knowledge of muscular innervation and focusing on the regions affected by weakness. In some patients, as in those with motor neuron diseases or polymyositis, a wider sampling of muscles is required to detect changes in asymptomatic regions. This technique requires the use of monopolar or concentric bipolar needle electrodes, which are inserted into the body of the muscle to record the electrical activity generated by contraction. With concentric electrodes, the tip of the wire that runs in the hollow of the needle is in proximity to many muscle fibers belonging to several different overlapping motor units; this is the active recording electrode. The shaft of the needle, in contact over most of its length with intercellular fluid and many other muscle fibers, serves as the reference electrode. Monopolar electrodes use the uninsulated needle tip as the active electrode, while the reference electrode may be another monopolar needle electrode placed elsewhere in subcutaneous tissue or a surface electrode on the skin overlying the muscle. Patients almost invariably find this portion of the test uncomfortable and should be prepared by a description of the procedure. Rapid and brief needle insertion by the skilled examiner makes the test more tolerable.

As the electrical impulse travels along the surface of the muscle toward the recording electrode, a positive potential is recorded on the oscilloscope, that is, the recorded signal is deflected downward by convention (at A in Fig. 2-16). When the depolarized zone moves under the recording electrode, it becomes relatively negative and the recorded signal is deflected upward (at B). As the depolarized zone continues to move along the sarcolemma, away from the recording electrode, the current begins to flow outward through the membrane toward the distant depolarized region, and the recording electrode becomes relatively positive again (at C). There is then a return to the resting isopotential position. The net result is a triphasic action potential, as in Fig. 2-16. This configuration is typical of the firing of a single fiber.

The electrical activity of various muscles is recorded both at rest and during active contraction by the patient. Muscle fibers do not normally discharge until activated together in motor unit activity. This involves the almost simultaneous contraction of all the muscle fibers innervated by a single anterior horn cell. Although the typical configuration of a motor unit potential (MUP) is triphasic, up to 10 percent of normal MUPs consist of four or more phases (*polyphasic potentials*); however, an excess of polyphasic potentials beyond this is pathologic.

Normal muscle in the resting state should be electrically silent; the small tension spoken of as muscle tone has no EMG equivalent. There are, however, two closely related types of normal spontaneous activities and another that is induced by the insertion of the needle itself. One is a low-amplitude, 10- to 20-μV monophasic (negative) potential of very brief (0.5 to 1 ms) duration. These represent single or synchronized miniature end plate potentials (MEPPs) because of the small number of ACh quanta that are being released all the time. They are normally sparse but are most evident when the recording needle electrode is placed near a motor endplate ("endplate noise"). Fortuitous placement of the needle electrode very close to or in contact with the endplate gives rise to a second type of normal spontaneous activity that is characterized by irregularly discharging high-frequency (50- to 100-Hz) biphasic spike discharges, 100 to 300 μV in amplitude (i.e.,

large enough to cause an isolated muscle action potential). These potentials have been termed *endplate spikes* and represent discharges of single muscle fibers excited by spontaneous activity in nerve terminals. They must be distinguished from fibrillation potentials (see later). Finally, insertion of the needle electrode into the muscle injures and mechanically stimulates a number of fibers, causing a burst of potentials of short duration (300 ms). This is referred to as normal *insertional activity*, but the extent of this activity is greatly raised in certain pathologic states as noted below.

When a muscle is voluntarily contracted, the depolarization potentials of motor units begin to appear. One can observe a pattern of force build up by watching the progressive recruitment of MUPs; the initial ones, representing smaller motor units, firing at rates of 5 to 10 per second. With increased force of contraction, there is an increased rate of firing (40 to 50 per second as well as a recruitment of larger, previously inactive motor units; Fig. 2-17*A*). Because individual MUPs can no longer be distinguished during maximal voluntary contraction, this activity is referred to as a *complete interference pattern* (Fig. 2-17*A*, *right*). This is seen not only as a summated signal pattern but is also heard as a mixed high-frequency clicking when the electrical activity is made audible. As muscles relax, an increasing number of units drop out. If a muscle is weakened by denervation or if electrical conduction is blocked, there will be fewer MUPs, but the remaining ones will still show a rapid firing rate (*reduced recruitment*; see Fig. 2-17*B*). In contrast, with poor voluntary effort and with upper motor neuron lesions, the MUPs fire in decreased numbers, at slower rates, and often in an irregular pattern (termed *poor activation*).

The Abnormal Electromyogram

Clinically important deviations from the normal EMG include (1) increased or decreased activity upon insertion of the needle; (2) the occurrence of abnormal "spontaneous" activity during the relaxed state (fibrillation potentials, positive sharp waves, fasciculation potentials, cramp potentials, myotonic discharges, myokymic potentials); (3) abnormalities in the amplitude, duration, and shape of single MUPs; (4) a decrease in the number of MUPs and changes in their firing pattern such as recruitment discussed above; (5) variation in amplitude and number of phases of MUPs during voluntary contraction; and (6) the demonstration of special phenomena such as in states of continuous muscle fiber activity or electrical silence during shortening of the muscle (physiologic contracture). The underlying physiology of these changes is discussed in Chap. 45, in relation to diseases of the muscle.

Insertional activity At the moment the needle is inserted into muscle, there is a normally brief burst of action potentials that ceases once the needle is stable, provided that it is not in a position to irritate a nerve terminal. Increased insertional activity, however, is an abnormal finding seen in most instances of denervation as well as in many forms of primary muscle disease and in disorders that dispose to muscle cramps. In cases of advanced denervation or advanced myopathy, in which muscle fibers have been largely replaced by connective tissue and fat, insertional activity may be decreased and there is a palpable increase in the mechanical resistance to the insertion of the needle.

Abnormal spontaneous activity With the muscle at rest, spontaneous activity of single muscle fibers and of motor units, known as *fibrillation* potentials and *fasciculation* potentials, is abnormal. The two phenomena may be confused. *Fibrillation* is the spontaneous contraction of a *single muscle fiber*. It occurs when the muscle fiber has lost its nerve supply and is ordinarily not visible through the skin (but may be visible in the tongue). *Fasciculation* represents the spontaneous firing of an entire motor unit, causing contraction of a group of muscle fibers, and may be visible through the skin. The irregular firing of a number of motor units, seen as a rippling of the skin, is called *myokymia*.

Fibrillation potentials Destruction of a motor neuron or interruption of its axon causes the distal part of the axon to degenerate, a process that takes several days or more. The muscle fibers formerly innervated by the branches of the dead axon—that is, the motor unit—are thereby disconnected from the nervous system. By mechanisms that are still obscure, the chemosensitive region of the sarcolemma at the motor endplate "spreads" after denervation to involve the entire surface of the muscle

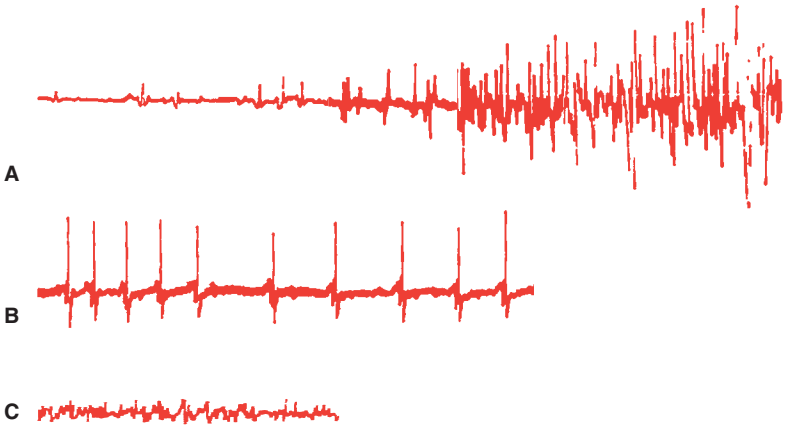

Figure 2-17. Patterns of motor unit recruitment. *A*. Normal. With each increment of voluntary effort, more and larger units are brought into play until, with full effort at the extreme right, a complete "interference pattern" is seen in which single units are no longer recognizable. *B*. After denervation, only a single motor unit is recorded despite maximal effort. It is seen to fire repetitively. *C*. With myopathic diseases, a normal number of units are recruited on minimal effort, though the amplitude of the pattern is reduced. Calibration: 50 ms (horizontal) and 1 mV (vertical).