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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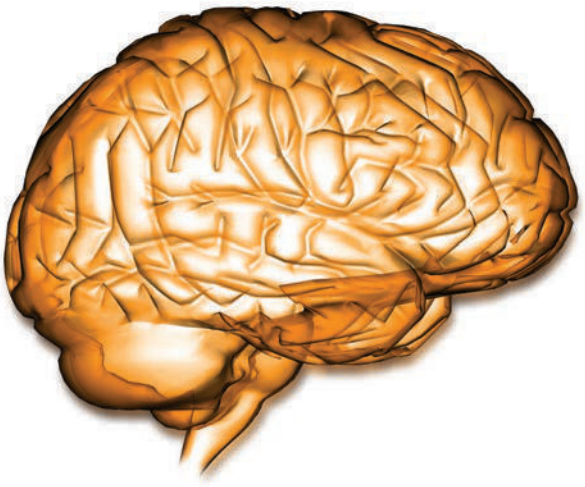

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Preface

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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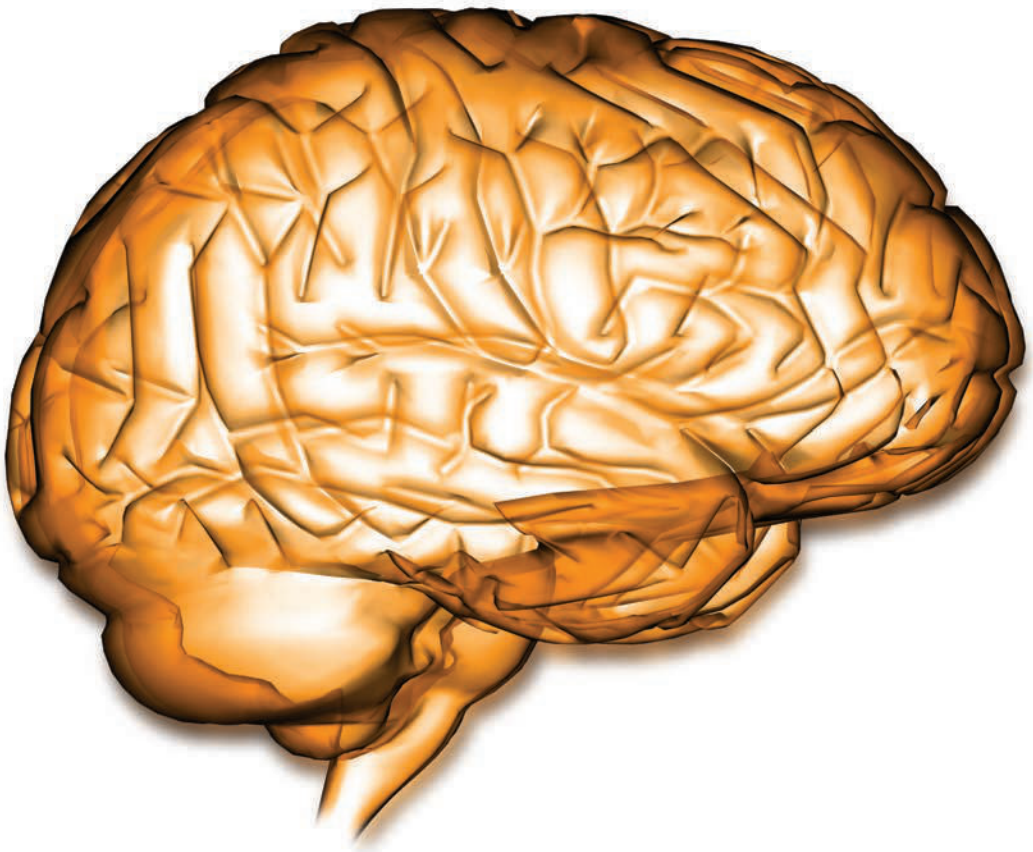
PART 1

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.

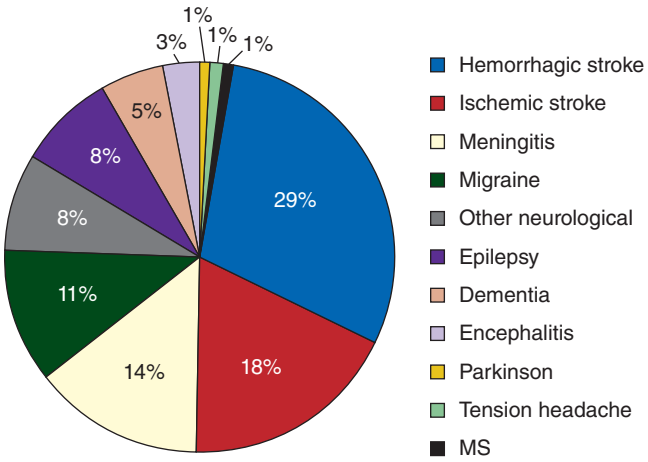

Figure 1-1. Contribution of neurologic conditions to the global burden of neurologic disease. The analysis, from WHO, includes communicable and noncommunicable diseases, but does not include traumatic brain injury or spine disease. (Modified from Chin and Vora.)

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.

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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

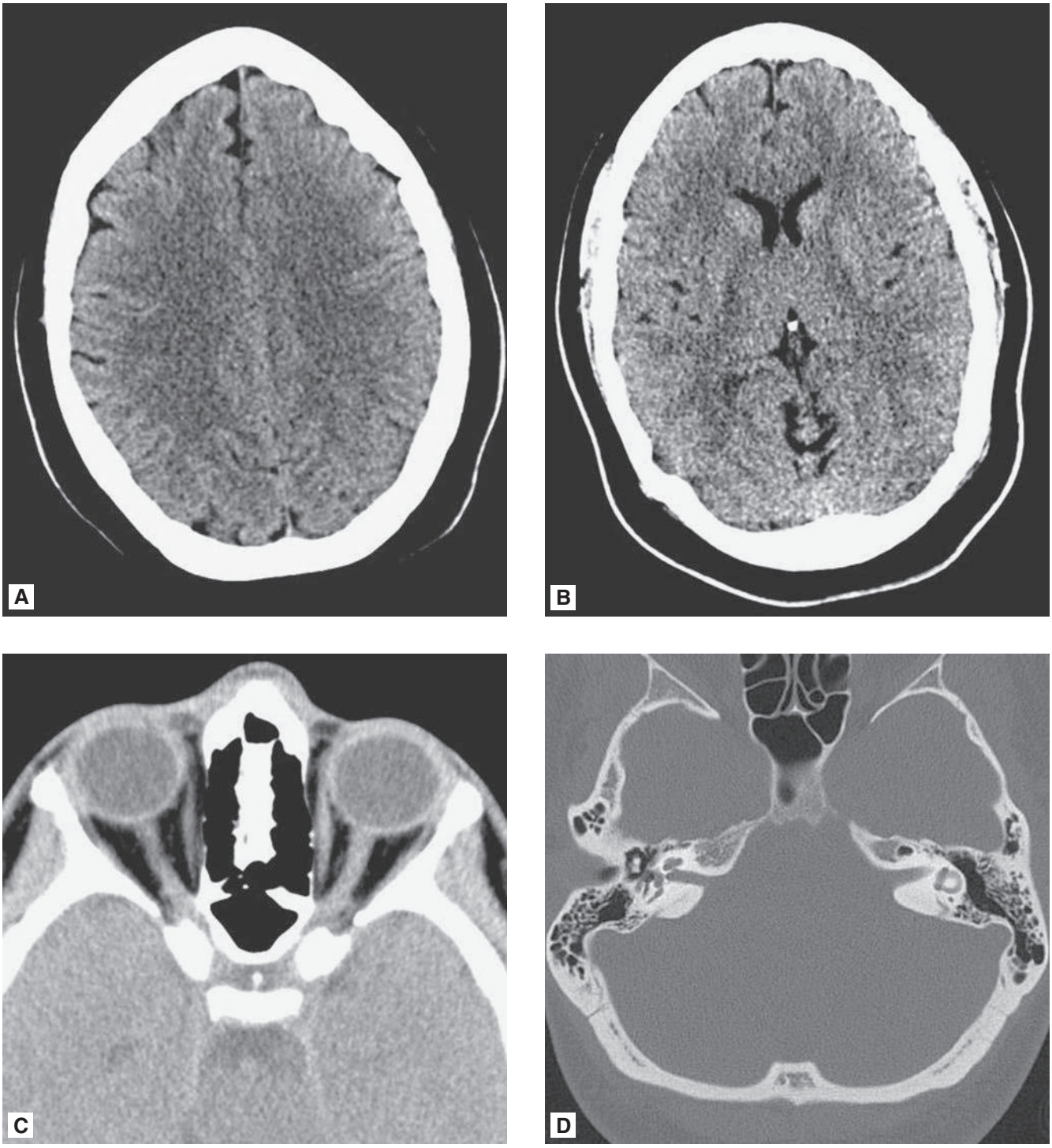

Figure 2-1. Normal CT in the axial plane of the brain, orbits, and skull base. *A*. Image through the cerebral hemispheres at the level of the corona radiata. The dense bone of the calvarium is white, and fat-containing subcutaneous tissue is dark. Gray matter appears denser than white matter due to 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.