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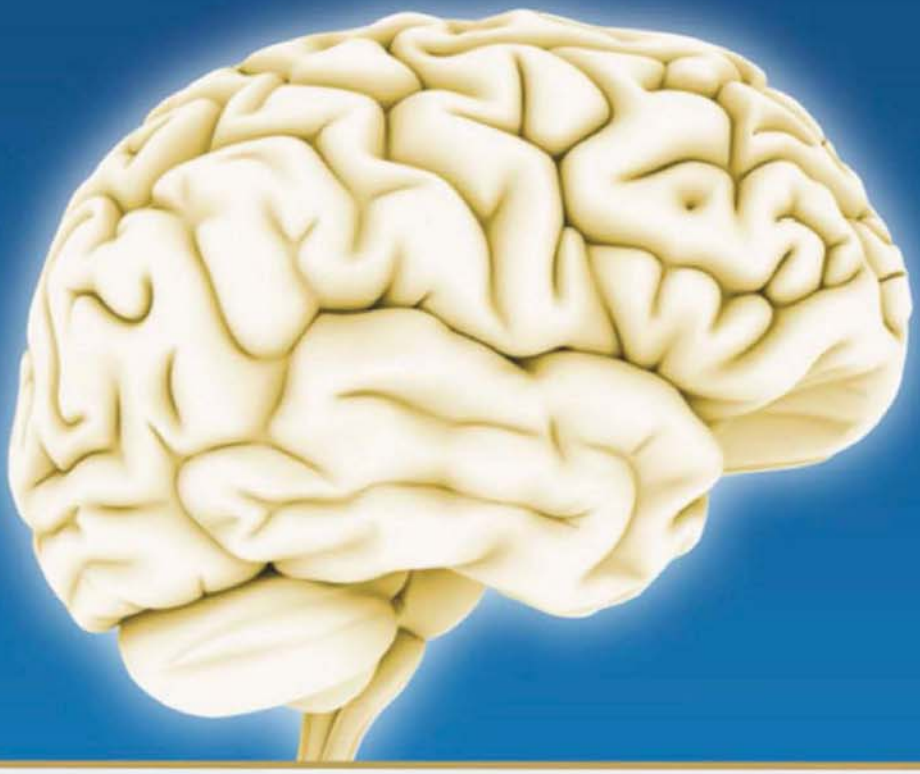

Adams and Victor's

Principles of Neurology

TENTH EDITION

Allan H. Ropper

Martin A. Samuels

Joshua P. Klein

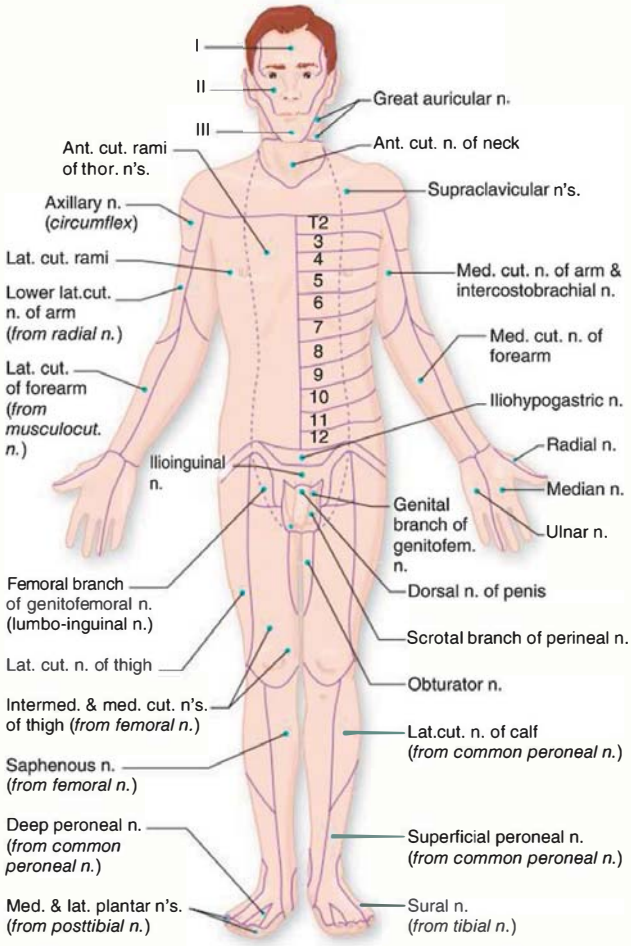

Figure 9-1. The cutaneous fields of peripheral nerves. (Reproduced by permission from Haymaker W, Woodhall B: *Peripheral Nerve Injuries*, 2nd ed. Philadelphia, Saunders, 1953.)

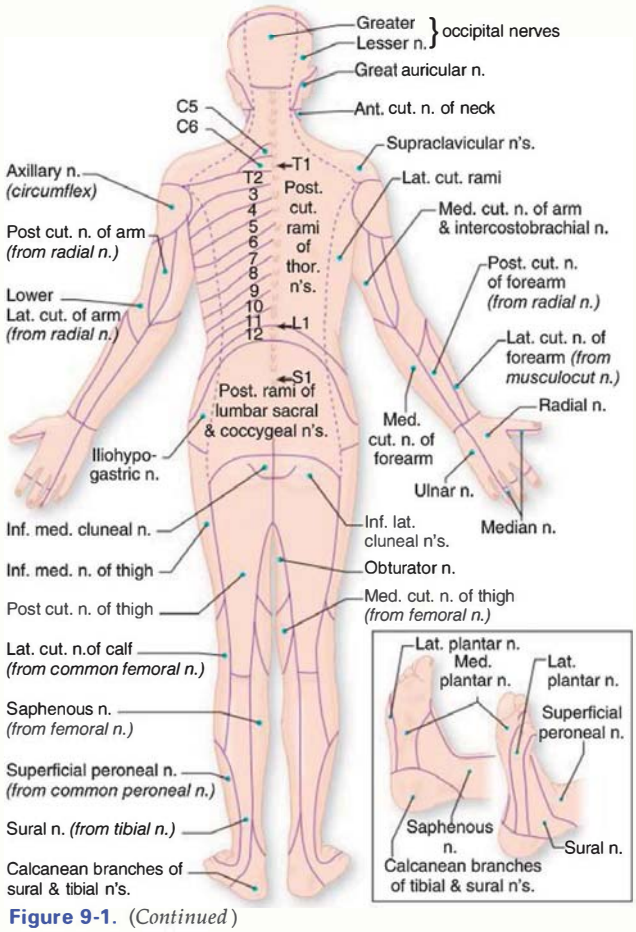

Figure 9-1. (*Continued*)

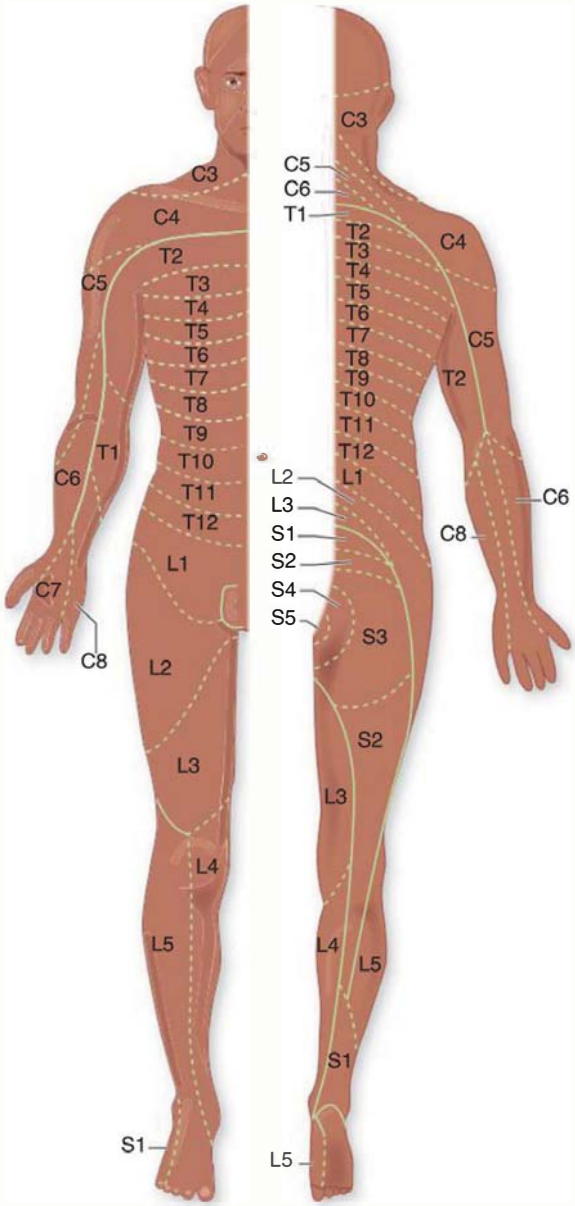

Figure 9-3. Distribution of the sensory spinal roots on the surface of the body (dermatomes). (Reproduced by permission from Sinclair.)

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Adams and Victor's

PRINCIPLES OF NEUROLOGY

TENTH EDITION

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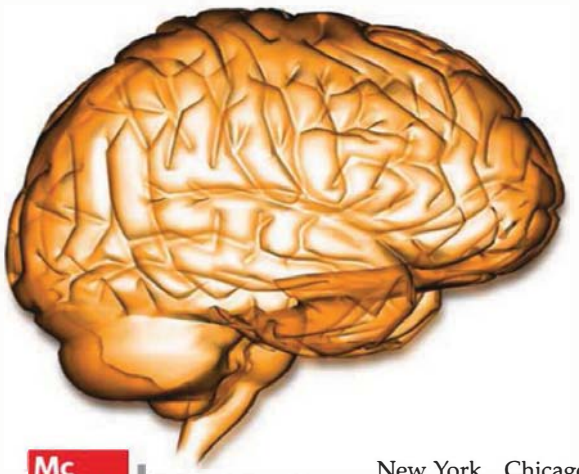

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Contents

Preface

As the rest of medicine changes, so does neurology. Neurologic diagnosis and treatment has been so vastly altered by modern neuroimaging, molecular biology, and genetics that the original authors of this book, Raymond D Adams and Maurice Victor, would barely recognize the practices of today. Secular interest in neurologic diseases is also expanding because of the large number of problems of the brain, spinal cord, nerves, and muscles that arise with aging and from the treatment and control of other, non-neurologic, diseases. Whereas cancer and heart disease had occupied foremost positions in the minds of individuals within developed societies, Alzheimer, Parkinson, and related diseases are central to the modern conversation about the quality of life. Moreover, the desire to understand the workings of the brain and to gain insights into human behavior has become a preoccupation of the public. At the same time, the manner in which information, both accurate and otherwise, is transmitted about the nervous system and neurologic diseases has changed. Access to information about diseases, accepted treatments, and clinical symptoms and signs, ubiquitously clutters the Internet. Physicians now less frequently seek a comprehensive understanding of a disease or class of diseases, "the whole story" if you will, but instead favor rapid access to single answers to a clinical problem.

For many reasons, particularly the last of these regarding the nature of medical information, writing a textbook on neurology has become a complex enterprise. We have even asked ourselves if there is a role for a textbook in the modern era, especially one written by only three authors. Yet, in identifying the characteristics of the capable clinician, one who is equipped to help patients and play a role in society to the fullest extent possible, we continuously return to the need for careful clinical analysis that is combined with a deep knowledge of disease. These are still the basis for high-quality practice and teaching. Even if the current goals of efficiency and economy in medicine are to be met, neurology is so complex that the confident implementation of a plan of diagnostic or therapeutic action quickly finds itself beyond algorithms, flow charts, and guidelines. The goal of our textbook therefore is to provide neurologic knowledge in an assembled way that transcends facts and information and to present this knowledge in a context that cannot be attained by disembodied details. While the biological bases of neurologic diseases are being discovered rapidly, the major contribution of the clinical neurologist remains, as it is for the whole of medicine: a synthesis of knowing how to listen to the patient, where to find the salient neurologic signs, and what to acquire from laboratory tests and imaging.

There is always a risk of such a book being simply archival. But the dynamic nature of modern neurology requires more than ever a type of integration among knowledge of clinical neurosciences, traditional neurology, and the expanding scientific literature on disease mechanisms. Only a text that has been thoughtfully constructed for the educated neurologist can fulfill this need and we hope that we have done so in this edition. Furthermore, in appropriate conformity to the methods by which physicians obtain information, McGraw-Hill has made an investment in their Access Medicine website that will highlight our book as well as several other neurology texts. Combined with these books will be sophisticated search functions, teaching curricula for students and residents, and, hopefully in the future, a form of interaction with us, the authors. Another inception has been the addition of color figures and photographs to this edition in order to make the visual material more accessible and appropriate for the web version.

To these ends, we offer the current 10th edition of *Principles of Neurology* to meet the needs of the seasoned as well as the aspiring neurologist, neurosurgeon, internist, psychiatrist, pediatrician, emergency physician, physiatrist, and all clinicians who have need of a comprehensive discussion on neurologic problems. We begin with an explanation of the functioning of the nervous system as it pertains to neurologic disease in the first part of the book, followed by detailed descriptions of the clinical aspects of neurology in its great diversity. In all matters, we have put the patient and relief of suffering from neurologic disease in a central place. The book is meant to be practical without being prescriptive and readable without being too exhaustive. When there is a digression, it has been purposely structured to complete a picture of a particular disease. We have also retained historical aspects of many diseases that are central to the understanding of the specialty and its place in medicine.

By taking an inclusive and yet sensibly chosen clinical approach, we do not eschew or criticize the modern movement to homogenize medicine in order to attain uniformity of practice. We ourselves have witnessed over 35 years the unappealing aspects of idiosyncratic practices, which were based on limited basic information and on a superficial understanding of neurology. Nonetheless, the complexity of neurologic diseases, especially now, puts the practitioner in a position of choosing among many options for diagnosis and treatment that are equivalent, or for which the results are uncertain. Clinical trials abound in neurology and set a direction for clinical practice in large populations, but are difficult to apply to individual patients. The need for a coherent method of clinical work is one reason we have retained authorship rather than editorial management that characterizes many textbooks in other areas of medicine. Limited authorship permits a uniform style of writing and level of exposition across subject matter and chapter headings.

It also allows us to judiciously include our own experiences and opinions when we feel there is something more to say than is evident in published articles. Our comments should be taken as advisory and we have no doubt that our colleagues in practice will develop their own views based on the body of information provided in the book and what is available from many outside sources. To the extent that some of the views we express in the book may be perceived as having a "Boston-centric" outlook, we appeal to the reader's forbearance. We have neither a proprietary formula for success in neurology nor the answers to many of the big clinical questions. If there is a stylistic aspect that comes through in the book, we hope it is still that neurology must be taken one patient at a time.

We gratefully acknowledge on the following pages several experts in particular fields of neurology whose help was invaluable in revising this edition. We sought their guidance because of the high regard we have for their clinical skills and experience. If there are concerns regarding specific comments in the book, they are our responsibility.

With this edition, we introduce our colleague Joshua P. Klein, MD, PhD, the chief of the Division of Hospital Neurology in the Department of Neurology at Brigham and Women's Hospital. Dr. Klein is dually trained in neurology and neuroradiology. He brings a wealth of perspective on imaging and has been a powerful partner in moving the book toward a more modern idiom that recognizes the centrality of neuroimaging in practice. It is a privilege to have him join us to bring the book through the beginning of the current century.

Allan H. Ropper, MD
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Acknowledgments

The authors gratefully acknowledge the colleagues listed below who gave considerably of their time to assist us with sections of the book. Any oversights in the content of the book are our responsibility. Updating this 10th edition of *Principles of Neurology* would not have been possible without these expert physicians and we extend to them our sincere thanks.

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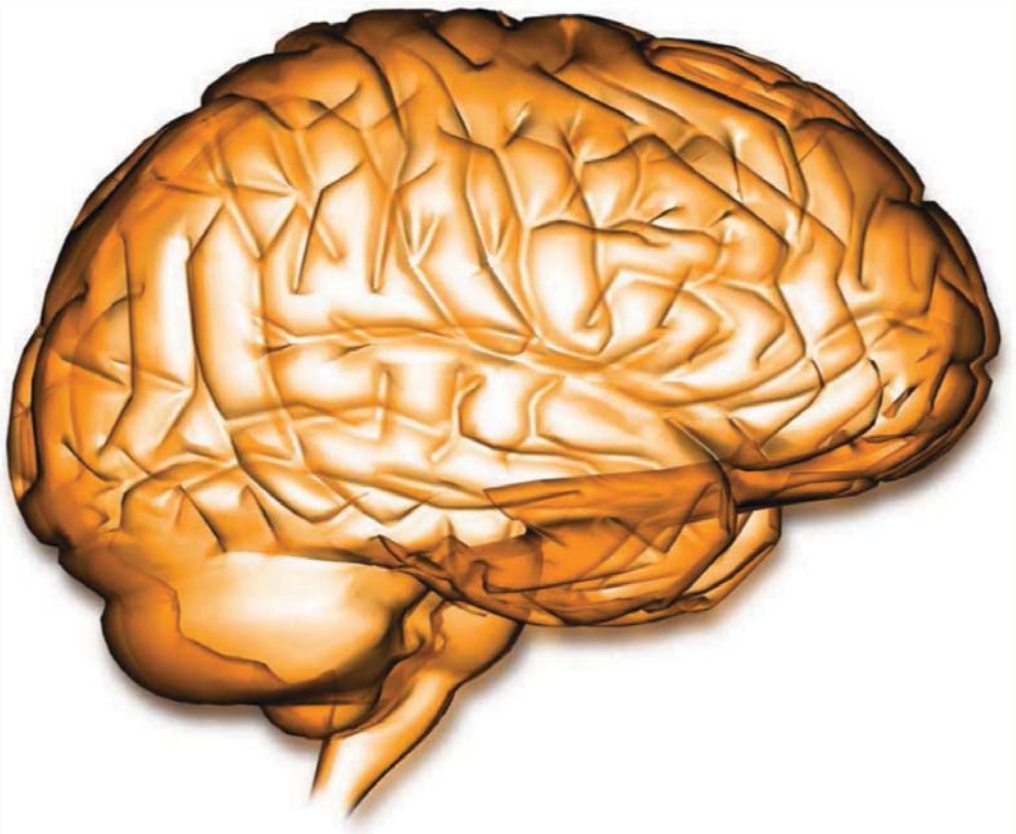
PART 1

THE CLINICAL METHOD OF NEUROLOGY



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1

Approach to the Patient with Neurologic Disease

Neurology is regarded by many as one of the most difficult and exacting medical specialties. Students and residents who come to a neurology service for the first time may be intimidated by the complexity of the nervous system through their brief contact with neuroanatomy, neurophysiology, and neuropathology. The ritual they then witness of putting the patient through a series of maneuvers designed to evoke certain mysterious signs is hardly reassuring. In fact, the examination appears to conceal the intellectual processes by which neurologic diagnosis is made. Moreover, the students have had little or no experience with the many special tests used in neurologic diagnosis—such as lumbar puncture, EMG (electromyography), EEG (electroencephalography), CT (computed tomography), MRI (magnetic resonance imaging), and other imaging procedures—nor do they know how to interpret the results of such tests. Neurology textbooks only confirm their fears as they read the detailed accounts of the many unusual diseases of the nervous system.

The authors believe that many of the difficulties in comprehending neurology can be overcome by adhering to the basic principles of the clinical method. Even the experienced neurologist faced with a complex clinical problem depends on this basic approach.

The importance of the clinical method stands out more clearly in the study of neurologic disease than in certain other fields of medicine. In most cases, it 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(s) of function and the anatomic structure(s) that are implicated.
3. These analyses permit the physician to localize the disease process, i.e., to name the part or parts of the nervous system involved. This is the *anatomic*, or *topographic* diagnosis, which often allows the recognition of a characteristic clustering of symptoms and signs, constituting a syndrome. This step is called *syndromic diagnosis* and is sometimes conducted in parallel with anatomic diagnosis.
4. Expert diagnosticians often make successively more accurate estimates of the likely diagnosis, utilizing pieces of the history and findings on the examination to either further refine or exclude specific diseases. Flexibility of thought must be practiced so as to avoid the common pitfall of retaining an initially incorrect impression and selectively ignoring data that would bring it into question. It is perhaps not surprising that the method of successive estimations works well in that evidence from neuroscience reveals that this is the mechanism that the nervous system uses to process information.
5. From the anatomic or syndromic 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 laboratory findings—one deduces the *pathologic diagnosis* and, when the mechanism and causation of the disease can be determined, the *etiologic diagnosis*. This may include the rapidly increasing number of molecular and genetic etiologies if they have been determined for a particular disorder.
6. 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.

In recent decades, many of these steps have been eclipsed by imaging methods that allow precise localization of a lesion and furthermore often characterize the etiology of disease. Many of the elaborate parts of the examination that were intended to localize lesions are no longer necessary in daily clinical work. 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 scans. The loss of the personal impact by the physician that is created by listening to a story and observing responses to various maneuvers is regrettable. 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 prospect 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 more 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 a much wider choice in the order and manner by which information is collected and interpreted. In fact, in some cases, adherence to a formal scheme is not necessary at all. In relation to 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. If the signs point to disease of the peripheral nerves, it is usually not necessary to consider the causes of disease of the spinal cord. Some signs themselves are almost specific—e.g., opsoclonus for paraneoplastic cerebellar degeneration and Argyll Robertson pupils for neurosyphilitic or diabetic oculomotor neuropathy. 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. Many of these facts are well known and form the substance of later chapters. When confronted with a constellation of clinical features that do not lend themselves to a simple or sequential analysis, one resorts to considering the broad classical division of diseases in all branches of medicine, as summarized in Table 1-1.

Table 1-1

THE MAJOR CATEGORIES OF NEUROLOGIC DISEASE

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

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. Thus, if a complaint of dizziness is identified as vertigo instead of light-headedness or if partial continuous epilepsy is mistaken for a tremor or choreoathetosis, then the clinical method is derailed from the beginning. Repeated examinations may be necessary to establish the fundamental clinical findings beyond doubt. Hence the aphorism: A second examination is the most helpful diagnostic test in a difficult neurologic case.

PREVALENCE AND INCIDENCE OF NEUROLOGIC DISEASE

To offer the physician the broadest perspective on the relative frequency of neurologic diseases, estimates of their approximate prevalence in the United States, taken from several sources, including the NIH, are given in Table 1-2. Donaghy and colleagues have provided a similar but more extensive listing of the incidence of various neurologic diseases that are likely to be seen by a general physician practicing in the United Kingdom. They note stroke as far and away the most commonly

Table 1-2

RELATIVE 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

Table 1-3

APPROXIMATE ORDER OF INCIDENCE AND PREVALENCE OF NEUROLOGIC CONDITIONS IN A GENERAL PRACTICE IN THE UNITED KINGDOM

INCIDENCE IN GENERAL PRACTICE	PREVALENCE IN THE COMMUNITY
Stroke (all types)	Migraine
Carpal tunnel syndrome	Chronic tension headache
Epilepsy	Stroke
Bell's palsy	Alzheimer disease
Essential tremor	Epilepsy
Parkinson disease	Essential tremor
Brain tumor	Multiple sclerosis
Multiple sclerosis	Chronic fatigue syndrome
Giant cell arteritis	Parkinson disease
Migraine	Unexplained motor symptoms
Unexplained motor symptoms	Neurofibromatosis
Trigeminal neuralgia	Myasthenia gravis

Source: Adapted from Donaghy and colleagues: *Brain's Diseases of the Nervous System.*

encountered condition; those that follow in frequency are listed in Table 1-3. 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 guiding societal resources to the cure of various conditions, but they are somewhat less helpful in leading the physician to the correct diagnosis except insofar as they emphasize the oft-stated dictum that "common conditions occur commonly" and therefore should be considered a priori to be more likely diagnoses (see further discussion under "Shortcomings of the Clinical Method").

TAKING THE HISTORY

In neurology, perhaps more than any other specialty, the physician is dependent upon 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.

The practice of making notes at the bedside or in the office is recommended. Of course, no matter how reliable the history appears to be, verification of the patient's account by a knowledgeable and objective informant is always desirable.

The following points about taking the neurologic history deserve further comment:

1. Special care must be taken to avoid suggesting to the patient the symptoms that one seeks. Errors and inconsistencies in the recorded history are as often the fault of the physician as of the patient. 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 description of the symptom—being asked, for example, to choose a word that best describes his pain and to describe precisely what he means by a particular term such as dizziness, imbalance, or vertigo. The patient who is given to highly circumstantial and rambling accounts can be kept on the subject of his illness by directive questions that draw out essential points.
2. The setting in which the illness occurred, its mode of onset and evolution, and its course are of paramount importance. One must attempt to learn precisely how each symptom began and progressed. Often the nature of the disease process can be decided from these data alone, such as in 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. Asking the patient to give his own interpretation of the possible meaning of symptoms may sometimes expose unnatural concern, anxiety, suspiciousness, or even delusional thinking. Young physicians and students also have a natural tendency to "normalize" the patient, 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.

THE NEUROLOGIC EXAMINATION

The neurologic examination begins with observations of the patient while the history is being obtained. The manner in which the patient tells the story of his illness may betray confusion or incoherence in thinking, impairment of memory or judgment, or difficulty in comprehending or expressing ideas. 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. 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 words, and simple arithmetic are adequate screening procedures.

One then proceeds from an examination of the cranial nerves including the optic discs, neck, and trunk to the testing of motor, reflex, and sensory functions of the upper and lower limbs. This is followed by an assessment of the function of sphincters and the autonomic nervous system if appropriate and testing for meningeal irritation by examining the suppleness of the neck and spine. Gait and station (standing position) are observed before or after the rest of the examination.

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 (motor: Chaps. 3, 4, and 5; sensory: Chaps. 8 and 9; and cognitive and language disorders: Chaps. 22 and 23) 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 should establish a consistent pattern. Even when it is impractical to perform the examination in the customary way, as in patients who are unable to cooperate because of age or cognitive deficiency, it is good practice to record the findings in an accustomed and sequential fashion. If certain portions are not performed, this omission should be stated so that those reading the description at a later time are not left wondering whether an abnormality was not previously detected. Some aspects of the complete examination that were performed routinely by neurologists in former years are now infrequently included because they provide limited or duplicative information—among these are tests of olfaction and superficial reflexes but each finding may have a place in special circumstances or to corroborate another sign.

The thoroughness of the neurologic examination must also 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. 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.

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, are essential in a patient with stroke. Likewise, the skin can reveal a number of conditions that pertain to congenital, metabolic, and infectious causes of neurologic disease.

EXAMINING PATIENTS WHO PRESENT WITH NEUROLOGIC SYMPTOMS

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 several of the monographs on the subject, including those of Bickerstaff and Spillane, Campbell (DeJong's Neurological Examination), and of the staff members of the Mayo Clinic, each of which approaches the subject from a somewhat different point of view. An inordinately large number of tests of neurologic function have been devised, and it is not proposed to review all of them here. Some are described in subsequent chapters dealing with disorders of mentation, cranial nerves, and motor, sensory, and autonomic functions. Many tests are of doubtful value or are repetitions of simpler tests and thus should not be taught to students of neurology. Merely to perform all of them on one patient would require several hours and, in most instances, would not make the examiner any the wiser. 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.

Testing of Higher Cortical Functions

These functions are tested in detail if the patient's history or behavior has provided a reason to suspect some defect. 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.

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. There are many useful bedside tests of attention, concentration, memory, and clarity of thinking including 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. 20, 21, 22, and 23. 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.

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, and solving simple logical problems should be assessed.

The ability to carry out commanded tasks (praxis) has great salience in the evaluation of several aspects of cortical function. Bisecting a line, drawing a clock or the floor plan of one's home or a map of one's country, and copying figures are useful tests of visuospatial perception and are indicated in cases of suspected cerebral disease. The testing of language, cognition, and other aspects of higher cerebral function are considered in Chaps. 21, 22, and 23.

Testing of Cranial Nerves

The function of the cranial nerves must be investigated more fully in patients who have neurologic symptoms than in those who do not. If one suspects a lesion in the anterior cranial fossa, the sense of smell should be tested in each nostril; then it should be determined whether odors can be discriminated. Visual fields can be outlined by confrontation testing, ideally by testing each eye separately. If an abnormality is suspected, it should be checked on a perimeter and scotomas sought on the tangent screen or, more accurately, by computerized perimetry. 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. 12, 13, and 14.

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.

Facial movements should be observed as the patient speaks and smiles, for a slight weakness may be more evident in these circumstances than on movements to command.

The auditory meati and tympanic membranes should be inspected with an otoscope. A high-frequency (512 Hz) tuning fork held next to the ear and on the mastoid discloses hearing loss and distinguishes middle-ear (conductive) from neural deafness. Audiograms and other special tests of auditory and vestibular function are needed if there is any suspicion of disease of the vestibulocochlear nerve or of the cochlear and labyrinthine end organs (see Chap. 15). The vocal cords must be inspected with special instruments in cases of suspected medullary or vagus nerve disease, especially when there is hoarseness. Voluntary pharyngeal elevation and elicited reflexes are meaningful if there is 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 and the snout, buccal, and sucking reflexes should be sought, particularly if there is a question of dysphagia, dysarthria, or dysphonia.

Testing of Motor Function

In the assessment of motor function, the most informative aspects are observations of the speed and strength of movements and of muscle bulk, tone, and coordination and these are considered in the context of the state of tendon reflexes. 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"). The strength of the legs can be similarly 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.

It is essential 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, 5, and 6). This is accomplished by watching the patient maintain the arms outstretched in the prone and supine positions; perform simple tasks, such as alternately touching his nose and the examiner's finger; make rapid alternating movements that necessitate sudden acceleration and deceleration and changes in direction, such as tapping one hand on the other while alternating pronation and supination of the forearm; rapidly touch the thumb to each fingertip; and accomplish simple tasks such as buttoning clothes, opening a safety pin, or handling common tools. Estimates of the strength of leg muscles with the patient in bed are often unreliable; there may seem to be little or no weakness even though the patient cannot arise from a chair or from a kneeling position without help. Running the heel down the front of the shin, alternately touching the examiner's finger with the toe and the opposite knee with the heel, and rhythmically tapping the heel on the shin are the only tests of coordination that need be carried out in bed.

Testing of Reflexes

Testing of the biceps, triceps, supinator-brachioradialis, patellar, Achilles, and cutaneous abdominal and plantar reflexes permits an adequate sampling of reflex activity of the spinal cord. Elicitation of muscle stretch (tendon) reflexes requires that the involved muscles be relaxed; underactive or barely elicitable reflexes can be facilitated by voluntary contraction of other muscles (Jendrassik maneuver).

The plantar response poses some difficulty because several different reactions besides the Babinski response can be evoked by stimulating the sole of the foot along its outer border from heel to toes. These are (1) the normal quick, high-level avoidance response that causes the foot and leg to withdraw; (2) the pathologic slower, spinal flexor nocifensive (protective) reflex (flexion of knee and hip and dorsiflexion of toes and foot, "triple flexion"). Dorsiflexion of the large toe and fanning of the other toes as part of the latter reflex is the well-known Babinski sign (see Chap. 3); (3) plantar grasp reflexes; and (4) support reactions in infants. Avoidance and withdrawal responses interfere with the interpretation of the Babinski sign and

can sometimes be overcome by utilizing one of several 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. An 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 patient cooperation. For the same reason, 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 for more than a few minutes. 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") calls attention to a disturbance of superficial sensation.

The sense of 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.

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. 8 and 9.

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 cases of cerebellar or frontal lobe disorder; and an impairment of posture and highly automatic adaptive movements in walking may provide the most definite diagnostic clues in the early stages of diseases such as Parkinson disease. Having the patient walk tandem or on the sides of the soles may bring out a lack of balance or 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. 7.

TESTING THE PATIENT WHO DOES NOT HAVE NEUROLOGIC SYMPTOMS (THE SCREENING NEUROLOGICAL EXAMINATION)

In this situation, 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 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 hand grip and dorsiflexion at the wrist; 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 few simple tests provides clues to the presence of disease of which the patient is not aware. For example,

Table 1-4

BRIEF NEUROLOGIC EXAMINATION IN THE GENERAL MEDICAL OR SURGICAL PATIENT (PERFORMED IN 5 MIN OR LESS)

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

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. 17.

THE PSYCHIATRIC PATIENT

One is compelled in the examination of psychiatric patients to rely less on the cooperation of the patient and to be unusually critical of their statements and opinions. 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 their age.

If the patient will speak and cooperate even to a slight degree, much may be learned about the functional integrity of different parts of the nervous system. 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. Ocular movements and visual fields can be tested with fair accuracy by observing the patient's response to a moving stimulus or threat in the visual fields. Cranial nerve, motor, and reflex functions are tested in the usual manner, but it must be remembered that the neurologic examination is never complete unless the patient will speak and cooperate in testing. On occasion, mute and resistive patients judged to be psychotic prove to have some widespread cerebral disease such as hypoxic or hypoglycemic encephalopathy, a brain tumor, a vascular lesion, or extensive demyelinative lesions.

INFANTS AND SMALL CHILDREN

The reader is referred to the special methods of examination described by Andrè-Thomas and colleagues, Volpe and the staff members of the Mayo Clinic, which are listed in the references and described in Chap. 28. Many of these volumes 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 explications of the child's neurologic examination.

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 incomplete without a search for hypertension, carotid bruits, heart murmurs, and irregular heart rhythm.

IMPORTANCE OF A WORKING KNOWLEDGE OF NEUROANATOMY, NEUROPHYSIOLOGY, MOLECULAR GENETICS, NEUROIMAGING AND NEUROPATHOLOGY

Once the technique of obtaining reliable clinical data is mastered, students and residents may find themselves handicapped in the interpretation of the findings by a lack of knowledge of the basic sciences of neurology. 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.

At a minimum, physicians should know 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 wide availability of imaging offers the possibility of localization and etiologic diagnosis with limited input from the traditional clinical method. At a minimum, the educated neurologist must therefore be very familiar with the optimal imaging technique to disclose each of the multitudes of clinical diseases encountered in practice, the imaging appearance of each, and the risk and pitfalls of imaging.

From a practical diagnostic and therapeutic point of view, we believe the neurologist is helped by a knowledge of pathologic anatomy—i.e., the neuropathologic changes that are produced by disease processes such as infarction, hemorrhage, demyelination, physical trauma, compression, 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 on 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 disease 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.

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 can expose a patient to unnecessary risk.

In the prevention of neurologic disease, however, the clinical method in itself is inadequate; thus, of necessity, 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. 45, 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.

SHORTCOMINGS OF THE CLINICAL METHOD

If one adheres to the clinical method, neurologic diagnosis is greatly simplified. In most cases one can reach an anatomic diagnosis. However, even after the most assiduous application of the clinical method and laboratory procedures, there are numerous patients whose diseases elude diagnosis. In such circumstances we have often been aided by the following perspectives:

As mentioned earlier, when 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. Focus the clinical analysis on the principal symptom and signs and avoid being distracted by minor signs and uncertain clinical data.

As the lessons of cognitive psychology have been applied to error analysis in medical diagnosis, several heuristics (rules of thumb) have been identified as both necessary to the diagnostic process and as major pitfalls for the unwary clinician. The advantage of awareness of these heuristics is the opportunity to incorporate corrective strategies when shortcuts are employed. Investigators such as Redelmeier have given the following categories of cognitive mistakes that are common in arriving at a diagnosis:

- The framing effect reflects excessive weighting of specific initial data in the presentation of the problem.
- Anchoring heuristic, in which an initial impression cannot be subsequently adjusted to incorporate new data.
- Availability heuristic, in which experience with recent cases has an undue impact on the diagnosis of the case at hand.
- Representative heuristic refers to the lack of appreciation of the frequency of disease in the population under consideration, a restatement of Bayes theorem.
- 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. Common to all of these cognitive errors is the 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 anchoring effect). The first diagnostic formulation should be regarded as only a testable hypothesis, subject to modification when new items of information are secured (anchoring heuristic). Should the disease be in a stage of transition, time will allow the full picture to emerge and the diagnosis to be clarified.

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 (a paraphrasing of the representative heuristic).

It is advantageous to base diagnosis on clinical experience with the dominant symptoms and signs and not on statistical analyses of the frequency of clinical phenomena. Nonetheless, implicit in all diagnostic methods is an assessment of the likely causes of a sign or syndrome in the context of the patient's broad demographic characteristics including their sex, age, race, ethnicity, and the geographical circumstances. Moreover, as mentioned earlier, neurologists place a premium on finding treatable illnesses, even if the odds do not favor its presence.

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.

THERAPEUTICS IN NEUROLOGY

Among medical specialties, neurology has traditionally occupied a somewhat anomalous position, in the past being thought of by many as little more than an intellectual exercise concerned with making diagnoses of untreatable diseases. This view of our profession is fallacious, as we have pointed out in a recent review of 200 years of neurological progress (Ropper). There are a growing number of diseases, many medical and others surgical, for which specific therapy is now 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. 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. The neurologist must 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. 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 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 patient requires a skilled physician to make judgments based on partial or insufficient data. Even deciding actively to wait before committing to an intervention displays wisdom and adheres to the dictum, "first, do no harm". 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 throughout the world is appropriate. It is not just that conditions such as brain and spinal cord trauma, stroke, epilepsy, mental retardation, mental diseases, and dementia are ubiquitous and account for the majority of illness, second only in some parts of the world to infectious disease, but that these are highly disabling and often chronic in nature, altering in a fundamental way the lives of the affected individuals. Furthermore, more so than in other fields, 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.

References

Andrè-Thomas, Chesni Y, Dargassies St-Anne S: *The Neurological Examination of the Infant*. London, National Spastics Society, 1960.

Campbell WW: *DeJong's The Neurological Examination*, 6th ed. Philadelphia, Lippincott Williams & Wilkins, 2005.

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

DeMyer WE: *Technique of the Neurologic Examination: A Programmed Text*, 4th ed. New York, McGraw-Hill, 1994.

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

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

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

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

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

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

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

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

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

2

Imaging, Electrophysiologic, and Laboratory Techniques for Neurologic Diagnosis

The analysis and interpretation of data elicited by a careful history and examination may prove to be adequate for diagnosis. Special laboratory examinations then do no more than corroborate the clinical impression. However, it happens more often that the nature of the disease is not discerned by "case study" alone; the diagnostic possibilities may be reduced to two or three, but the correct one is uncertain. Under these circumstances, one resorts to ancillary examinations. The aim of the neurologist is to arrive at a final diagnosis by artful analysis of the clinical data aided by the least number of laboratory procedures.

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 electroencephalography. The physician's armamentarium has been expanded to include a multitude of neuroimaging modalities, biochemical, and genetic methods. Some of these new methods give the impression of such accuracy that there is a temptation to substitute them for a careful, detailed history and physical examination. Reflecting the limitations of laboratory diagnosis, in a carefully examined series of 86 consecutively hospitalized neurologic patients reported by Chimowitz and colleagues, laboratory findings (including MRI) clarified the clinical diagnosis in 40 patients but failed to do so in the remaining 46. Moreover, it is common in practice for ancillary 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 procedures that have application to a diversity of neurologic diseases. Procedures that are pertinent to a particular symptom complex or category of disease—e.g., audiography to study deafness; electronystagmography (ENG) in cases of vertigo; electromyography (EMG) and nerve conduction studies, as well as nerve and muscle biopsy, where there is neuromuscular disease—are presented in the chapters devoted to these disorders.

LUMBAR PUNCTURE AND EXAMINATION OF CEREBROSPINAL FLUID

The information yielded by examination of the cerebrospinal fluid (CSF) is crucial in the diagnosis of certain neurologic diseases, particularly infectious and inflammatory conditions, subarachnoid hemorrhage, and processes that alter intracranial pressure. Combinations of findings, or formulas, in the CSF generally denote particular classes of disease; these are summarized in Table 2-1.

Indications for Lumbar Puncture

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

Lumbar puncture (LP) carries 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 papilledema is the result of an intracranial mass, but it is much lower in patients with subarachnoid hemorrhage, in hydrocephalus with communication between all the ventricles, or with pseudotumor cerebri, conditions in which repeated LPs may at times be employed as a therapeutic measure. Asymmetric lesions, particularly those near the tentorium or foramen magnum carry a greater risk of herniation precipitated by lumbar puncture. In patients with purulent meningitis, there is also a small risk of herniation, but this is far outweighed by the need for a definitive diagnosis and the institution of appropriate treatment at the earliest moment. With this last exception, LP should generally be preceded by CT or MRI whenever an elevation of intracranial pressure is suspected. If radiologic procedures

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.

disclose a mass lesion that is causing displacement of brain tissue toward the tentorial opening or the foramen magnum (the presence of a mass alone is of less concern) and if 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—over 400 mm H_2O—one should obtain the smallest necessary sample of fluid and then, according to the suspected disease and patient's condition, administer mannitol or another hyperosmolar agent and ideally, to observe a fall in pressure on the manometer. Dexamethasone or an equivalent corticosteroid may generally 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, although safe in the hands of an expert, are too hazardous to entrust to those without experience and do not circumvent the problem of increased intracranial pressure. LP is preferred except in obvious instances of spinal block requiring a sample of cisternal fluid or for myelography above the lesion.

Technique of Lumbar Puncture

Experience teaches the importance of meticulous technique and proper positioning of the patient. LP should be done under locally sterile conditions. Xylocaine is injected in and beneath the skin, which should render the procedure almost painless. Warming of the analgesic by rolling the vial between the palms seems to diminish the burning sensation that accompanies cutaneous infiltration. The patient is positioned on his side, preferably on the left side for right-handed physicians, with hips and knees flexed, 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, and a pillow placed under the ear. 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. Experienced anesthesiologists have suggested that the smallest possible needle be used and that the bevel be oriented in the longitudinal plane of the dural fibers (see below regarding atraumatic needles). It is usually possible to appreciate a palpable "give" as the needle approaches the dura, followed by a subtle "pop" on puncturing the arachnoid membrane. 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 patient's head can be elevated slowly. Occasionally, one resorts to gentle aspiration with a small-bore syringe to overcome the resistance of proteinaceous and viscous CSF. Failure to enter the lumbar subarachnoid space after two or three trials 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. Prolonged or severe post-lumbar puncture headache is usually seen in patients with a history of migraine. The pain 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 as the patient assumes the erect posture. Although neither recumbency nor oral fluid administration after LP has been shown to prevent headache, they are 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. Patients who are prone to frequent headaches before LP reportedly have higher rates of headache afterwards, which accords with our experience. Severe headache can be associated with vomiting and mild neck stiffness. Unilateral or bilateral sixth nerve or other cranial nerve palsies occur rarely after lumbar puncture, even at times without headache and rare cases of hearing loss or facial palsy have been reported. The syndrome of low CSF pressure, its treatment by "blood patch," and other complications of lumbar puncture are considered further in Chap. 30.

Bleeding into the spinal meningeal or epidural spaces after lumbar puncture can occur in patients who are taking anticoagulants (generally with an international normalized ratio [INR] >1.4), have low platelet counts (<50,000/mm^3), or impaired platelet function (alcoholism, uremia). Treatment is by reversal of the coagulopathy and, in some cases, surgical evacuation of the clot. Purulent meningitis and disc space infections rarely complicate LP as the result of imperfect sterile technique, and the introduction of particulate matter (e.g., talc) or irritant carriers of injected drugs can produce a sterile meningitis.

Examination Procedures For CSF

Once the subarachnoid space has been entered, the pressure and fluctuations with respiration of the CSF are determined, (see below) 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 (1) number and type of cells and presence of microorganisms by direct observation; (2) protein and glucose content; (3) tumor cells (cytology); (4) presence of oligoclonal bands or content of gamma globulin and other protein fractions, and serologic tests; (5) pigments, lactate, LDH, and substances elaborated by some tumors (e.g., β_2 microglobulin); and (6) bacteria and fungi (by culture), cryptococcal antigen, mycobacteria, the DNA of herpesvirus, cytomegalovirus and other organisms (by polymerase chain reaction), markers or 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 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. 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 within a few seconds 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. (A microhematocrit tube is too narrow for this purpose.) 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 to indicate a preexistent subarachnoid hemorrhage. To distinguish between these two types of "bloody taps," two or three serial samples of fluid should be taken at the time of the LP. 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 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 more than 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 one or two WBCs per 1,000 RBCs assuming that the hematocrit is normal, but in reality this ratio varies widely. 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. 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 diffuse 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, more or less in proportion to the albumin-bound fraction of bilirubin. 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 enter 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 may contain a small number of mononuclear cells. 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 to bacteria or other 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 and a Wright stain of the sediment or the use of a Millipore filter, cell fixation, and staining. One can then recognize and count differentially neutrophilic and eosinophilic leukocytes (the latter being prominent in Hodgkin disease, some parasitic infections, neurosyphilis, and cholesterol emboli), lymphocytes, plasma cells, mononuclear cells, arachnoid lining cells, macrophages, and tumor cells. Bacteria, fungi, and fragments of echinococci and cysticerci can also be seen in cell-stained or Gram-stained preparations. An India ink preparation is useful in distinguishing between lymphocytes and cryptococci or *Candida*. Acid-fast bacilli will be found in appropriately stained samples. The monographs of den Hartog-Jager and the article of Bigner are older but still excellent references on CSF cytology. Special cell separation and immunostaining techniques permit the recognition of leukemia and lymphoma cell markers, glial fibrillary acidic protein, and other special cellular elements and antigens. These and other specific 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. This gradient may reflect the fact that CSF proteins leak from the blood plasma through capillary tight junctions, which form the blood–brain and blood–CSF barrier. The spinal fluid is an ultrafiltrate of blood made by the choroid plexus in the lateral and the fourth ventricles in a manner that is 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 it 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 per 1,000 RBCs provided that the same tube of CSF is used in determining the cell count and protein content. (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, in which choroidal and meningeal perfusion are increased, often reaches 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. Paraventricular tumors, by reducing the blood–CSF barrier, often raise the total protein to over 100 mg/dL. Protein values as high as 500 mg/dL are found in exceptional cases of the Guillain-Barré syndrome and chronic inflammatory demyelinating polyneuropathy. Values in the lumbar CSF of 1,000 mg/dL or more usually indicate a block to CSF flow; the fluid is then deeply yellow and clots readily because of the presence of fibrinogen; a combination 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 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. 30).

The quantitative partition of CSF proteins by electrophoretic and immunochemical methods demonstrate 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.

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 also 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. 39. 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.

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

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/100 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.