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Neuroanatomy through Clinical Cases
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To Michelle
For your patience, encouragement, and love
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How to Use This Book

The goal of this book is to provide a treatment of neuroanatomy that is comprehensive, yet enables students to focus on the most important "take-home messages" for each topic. This goal is motivated by the recognition that, while access to detailed information is often useful in mastering neuroanatomy, certain selected pieces of information carry the most clinical relevance, or are most important for exam review.

General Outline

The first four chapters of the book contain introductory material that will be especially useful to students who have little previous clinical background. Chapter 1 is an introduction to the standard format commonly used for presenting clinical cases, including an outline of the material presented in this chapter. Chapter 2 is a brief overview of neuroanatomy which includes definitions and descriptions of basic structures that will be studied in greater detail in later chapters. Chapter 3 builds on this knowledge by describing the neurolologic examination. It includes a summary of the structures and pathways tested in each part of the exam, which is essential for localizing the lesions presented in the clinical cases throughout the remainder of the book. Much of the material in this chapter is also covered on the neuroexam.com website described below, which provides video demonstrations for each part of the exam. For readers who are unfamiliar with neuroimaging techniques, Chapter 4 contains a concise introduction to CT, MRI, and other imaging methods. This chapter also includes a Neuroradiological Atlas showing normal CT, MRI, and angiographic images of the brain. Chapters 5–19 cover the major neuroanatomical systems and present relevant clinical cases.

Chapters 5–19

Chapters 5–19 have a common structure. An "Anatomical and Clinical Review" at the beginning of the chapters presents relevant neuroanatomical structures and pathways, and generously sized, carefully labeled color illustrations are used to vividly depict spatial relationships. The first part of each chapter also includes numbered sections called "Key Clinical Concept," or "KCC," which cover common disorders of the system being discussed.
Clinical Cases. The second part of each chapter is a “Clinical Cases” section that describes patients seen by the author and colleagues, each presented in a numbered color box. Full-length cases include complete findings from the neurologic examination, while “Mini-cases” have a briefer format. Each case begins with a narrative of how the patient’s symptoms developed and what deficits were found on neurologic examination. For example, one patient in Chapter 10 suddenly developed weakness in the right hand and lost the ability to speak. Another, in Chapter 14, experienced double vision and lapsed into a coma. Important symptoms and signs are indicated in boldface type. The reader is then challenged through a series of questions to deduce the neuroanatomical location of the patient’s lesion and the eventual diagnosis.

A discussion follows each case, beginning with a summary of the key symptoms and signs. Answers to the questions are provided which refer to anatomical and clinical material presented in the first half of the chapter that is demonstrated by the case. Continual improvements in imaging technology have allowed us to make clear and detailed radiographs of the nervous system in vivo, and one of the most exciting features of the book is the inclusion of large-format, labeled CT, MRI, or other scans that show the lesion for each patient, and serve as a central tool for teaching neuroanatomy. These images reveal, with striking clarity, both the lesion’s location and the anatomy of the system being studied. In addition, these radiographs help the reader develop skill in interpreting the kinds of diagnostic images employed on the wards. The neuroimaging studies for each case are provided in special boxes at least one page turn away from the case questions, so the answers to the questions are not “given away” by the imaging (see below).

The clinical course is also provided for each patient, and includes a discussion of how the patient was managed, and what outcome followed. Thus, by the end of each case, students learn the relevant material by application and diagnostic sleuthing rather than by rote memorization.

Special Features for Focused Study and Review

Since one of the goals of this book is to enable students to either read the material in depth, or to distill it down to the most clinically relevant points or to material most directly covered on the national boards or other examinations, several special features have been included to expedite focused study and review:

- **Boldface type** is used rather differently than in most texts. In addition to identifying the text for all important topics and definitions, boldface is also used to facilitate rapid or focused reading.

- **Review Exercises** appear in the margins throughout the text, highlighting the most important anatomical concepts in each chapter, and providing practice exam questions.

- **Helpful mnemonics** are provided throughout the text, and these are flagged in the margins by a special icon (shown at left) showing a section of the hippocampus (a structure important in memory formation).

- A Brief Anatomical Study Guide appears at the end of each chapter, which summarizes the most important neuroanatomical material, and refers to the appropriate figures and tables needed for focused exam review.

- The Neuroanatomical Atlas in Chapter 4 also provides a useful review of neuroanatomical structures in three-dimensional space, and can be used for reference and comparison to lesions seen in clinical cases.

- The neuroexam.com website includes much of the text from Chapter 3 describing the neurologic exam and its anatomical interpretation, and also features video demonstrations of each part of the exam that are cited in the text (e.g., “see neuroexam.com Video 37”). Selected video frames are also shown in the book margins, as shown at right, to illustrate relevant portions of the neurologic exam. Students or instructors who prefer to view a full-length VHS tape of the neurologic exam can obtain The NeuroExam Video from Sinauer Associates (www.sinauer.com).

- The Key Clinical Concept (KCC) sections provide a comprehensive introduction to clinical topics in neurology and neurosurgery, and enable an efficient review of these topics.

- Finally, the Clinical Cases can be used by themselves for study and review, since they consist of anatomical puzzles that reinforce the subject matter for each chapter in the most clinically relevant context. As noted above, the neuroimaging studies for each case are deliberately placed at least one page turn away from the case questions; the location of the images for each case are indicated by page numbers located within black arrows, as shown at right.

- The Additional Cases section at the end of each chapter, and the Case Index at the end of the book provide further cases relevant to the topics in each chapter.

Suggested Course Use

Neuroanatomy through Clinical Cases is intended primarily for first- or second-year medical students enrolled in a course in neuroanatomy or neuroscience, but it is a versatile text that could be used in many settings. The topics covered in the book include all neuroanatomical material required for the medical school board examinations. Although fundamental concepts are emphasized, some advanced subject matter is also provided. Because the book includes chapters on peripheral nerves, students will also find this book useful in their general gross anatomy course in which peripheral nerves are usually covered. The Key Clinical Concept sections in this book also cover the major neurologic and neurosurgical disorders at a level appropriate for medical school pathophysiology courses, clinical rotations, and residents early in their training.

Students of other health professions, especially physical therapy, occupational therapy, nursing, dentistry, speech therapy, and neuropsychology will find this textbook useful as well, and it may also be of interest to graduate students of neuroscience. In addition to those learning neuroanatomy, it is hoped that the cases in this book will serve as a resource for advanced medical students in their clinical rotations, and residents in neurology, neurosurgery, and neuroanatomy looking examples of “typical” cases of neurologic disorders. Because each case is a real patient, the clinical cases in this book are, in effect, a collection of case reports that can serve as a useful resource, especially for teaching purposes and board review. It should be noted, however, that the cases presented here are highly selected for their teaching value and do not constitute an unbiased sampling of the kinds of cases found in clinical practice.
Here are some suggestions for using Neuroanatomy through Clinical Cases in various courses and curricula:

- For a comprehensive course in medical school neuroanatomy, students should read Chapters 2 and 5-18, with selected topics from Chapters 1, 3, 4 and 19. Reading assignments and large class lectures could focus on the Anatomical and Clinical Review sections at the beginning of each chapter. The clinical cases are most effectively discussed in small groups of students, where instructors can help students puzzle through the anatomical localization and diagnosis, and then discuss the neuroradiology and clinical outcome.

- For medical school courses covering both neuroanatomy and other topics in neuroscience, additional readings from neuroscience texts such as Neuroscience by Purves et al. (2001, Sinauer Associates) or Principles of Neural Science by Kandel et al. (2000, McGraw-Hill) should be provided.

- For a comprehensive course in clinical disorders of the nervous system, students should read Chapters 3 and 4, and the Key Clinical Concept sections in Chapters 5-19. The NeuroExam Video should be viewed in class, and students referred to neuroexam.com for review. Clinical cases could then be presented in small groups, as described above.

- For a course focusing on neuropsychological disorders and anatomical correlations, students should read Chapters 2, 10, 18 and 19 and selected parts of Chapters 14 and 16.

- Finally, for a more basic course in clinical neuroanatomy, readings could be confined to selected topics in Chapters 2, 5-7, 10-16, and 18.
Case presentations provide the framework for all communications about patient care. They lay down the basic information needed to formulate hypotheses about the location and nature of patients' problems. This information is then used to decide on further diagnostic tests or treatment measures. To diagnose and treat patients such as those described in this book, we must first learn how clinicians generally present a patient's medical history and findings from their physical examination. In addition, we must learn how to formulate ideas about neurologic diagnosis, and how the neurologic evaluation fits into the general context of patient assessment.
Introduction

Neuropathology is one of the more clinically relevant courses taught in the first years of medical school. Principles learned in neuropathology are directly applicable to patient care, not just for the neurologist or neurosurgeon, but also for health care professionals in virtually every other field. However, medical students in their first years and other students of neuropathology are often unfamiliar with the basic principles of clinical case presentations used on the wards. Therefore, the first section of this chapter has been provided for the non-neurologist or the not-yet-neurologist as a basic orientation. Others may prefer to skip this section. The second section of this chapter discusses the neuropathologic differential diagnosis, a process through which several possible diagnoses are considered based on the available information. We will use this method when attempting to arrive at diagnoses in the cases throughout the remainder of the book.

Abbreviations will be avoided in the case presentations in this book whenever possible, although they are used quite often in the wards. Therefore, some commonly used abbreviations will be introduced in this chapter.

The neurologic exam is only one part of the general physical exam. Nevertheless, the patient should always be treated as a whole and, in addition, much can be learned about neurologic illness from other parts of the physical exam. Therefore, in the final section of this chapter we will discuss the dynamic relationship between the general physical exam and the neurologic exam.

The General History and Physical Exam

While there are variations in personal style, clinicians adhere to a fairly standardized format when presenting cases so that all of the essential information can be succinctly communicated. Since this may be your first exposure to this format, we will first discuss the general structure of the history and physical examination that is used in all fields of medicine. Although the basic structure is always the same, the emphasis varies depending on the specialty. Therefore, in Chapter 3 we discuss the neurologic part of the physical exam in more detail. Note that case presentations in this book focus on the neurologic history and physical exam, although it is crucial to treat the patient as a whole and to never neglect symptoms and signs arising from other body systems. In addition, as described in the discussion that follows, certain features of the general physical exam often provide important information about neurologic illness.

One of the most daunting tasks confronting medical students as they first enter the wards is to master the art of case presentations. When a new patient is admitted to the hospital, it is the responsibility of the medical student and resident on call to obtain a good history and physical exam (H&P) and then to communicate this knowledge to the other members of the medical team. These skills are continually refined throughout a clinician’s career as they see more patients.

The level of detail used in obtaining an H&P depends on both the setting and the patient. For example, the appropriate H&P when caring for an unfamiliar patient with multiple active medical problems is much more detailed than the H&P for a familiar patient who is generally healthy and comes to the outpatient office with an injured finger. As clinical skills develop, the H&P becomes a highly focused tool used both to investigate clinical problems of immediate concern, and to screen for other potential problems that may be suspected on the basis of the overall clinical picture.

Remember that the whole point of the H&P is to communicate. The goal is to present the important points of the case to one’s colleagues in the form of an interesting “story.” They can then contribute to the patient’s care through discussion of the case, and by taking care of the patient in the middle of the night when the people who originally admitted the patient may be sound asleep at home. As one learns more clinical medicine, one gradually comes to know the difference between critical details not to be overlooked and irrelevant side issues that put listeners to sleep. This distinction is often surprisingly subtle, but it makes all the difference in effective case presentation.

The general format most commonly used for an H&P contains the following elements, which we will discuss in more detail in the sections that follow:

- Chief complaint
- History of the present illness
- Past medical history
- Review of systems
- Family history
- Social and environmental history
- Medications and allergies
- Physical exam
- Laboratory data
- Assessment and plan

Chief Complaint (CC)

This is a succinct statement that includes the patient’s age, sex, and presenting problem. It may also include one or two very brief pieces of pertinent historical data.

**Example:** “The patient is a 53-year-old man with a history of hypertension now presenting with crushing substernal chest pain of 1 hour’s duration.”

History of the Present Illness (HPI)

This is the complete history of the current medical problem that brought the patient to medical attention. It should include possible risk factors or other causes of the current illness, as well as a detailed chronological description of all symptoms and prior care obtained for this problem. Related medical problems can be mentioned as well; however, those that are not of direct relevance to the present illness are usually covered instead in the section on past medical history (to be discussed next).

**Example:** “The patient has cardiac risk factors consisting of hypertension for 15 years, and a family history of coronary artery disease. He does not smoke, nor does he have diabetes or elevated cholesterol. He has not had previous myocardial infarction. For the past 5 years he has had a stable pattern of chest pain on exertion, brought on by walking up two or more flights of stairs, lasting less than 5 minutes, not accompanied by other symptoms. The pain is relieved by rest and sublingual nitroglycerin. He has refused to undergo further cardiology workup, such as exercise stress testing, in the past. His hypertension is being treated with a beta-blocker. He denies symptoms of congestive heart failure and has no history of peripheral vascular or cerebrovascular disease. Today while sitting at his desk at work, he developed sudden ‘crushing’ substernal chest pain and pressure radiating to his neck, accompanied by tingling of the left arm, shortness of breath.”
sweating, and nausea without vomiting. The pain was not relieved by three
sublingual nitroglycerin tablets, and his coworkers called an ambulance to
bring him to the emergency room, where he was admitted with pulse 101, BP
140/90, and respiratory rate 20, and had an EKG with ST elevations, sug-
gesting anterior myocardial ischemia. His pain was initially relieved by
IV nitroglycerin and 2 mg of morphine, but then returned again, lasting
about 20 minutes with continued ST elevations, so he was started on the tis-
sue plasminogen activator protocol for thrombolysis. He is now being
admitted to the cardiac intensive care unit for further care, currently pain
free."

Past Medical History (PMH)
Prior medical and surgical problems not directly related to the HPI are de-
scribed here.

Example: "The patient has a history of a mildly enlarged prostate gland. He
had a right inguinal hernia repair in 1978."

Review of Systems (ROS)
A brief head-to-toe review of all medical systems—including head, eyes,
ears, nose and throat, pulmonary, cardiac, gastrointestinal, genitourinary,
OB/GYN, dermatologic, neurologic, psychiatric, musculoskeletal, hematol-
ogical, oncologic, rheumatologic, endocrine, infectious diseases, and so
on—should be pursued with each patient to pick up problems or complaints
missed in earlier parts of the history. If something comes up that is rele-
vant to the HPI, it should be inserted in that section, not buried in the ROS.

Example: "The patient has had mild upper respiratory symptoms for the
past 4 days, with nasal congestion, but no cough, temperature, or sore
throat."

Family History (FHx)
This section should list all immediate relatives and note familial illnesses
such as diabetes, hypertension, asthma, heart disease, cancer, depression,
and so on, especially those relating to the HPI. Family tree format is often a
succinct and clear way to present this data.

Example: "Patient’s mother died at 66 of myocardial infarction, had hyper-
ension. Father had myocardial infarction at 55, had diabetes, died at 75 of
stroke, brother, 47 years old, healthy. Two children, healthy."

Social and Environmental History (SoEHx/EnvHx)
This section should include the patient’s occupation, family situation, travel
history, and habits.

Example: "Electrical engineer. Married with two children. No recent travel.
Denies ever smoking cigarettes or using drugs. Drinks 1-2 beers on
Sundays."

Medications and Allergies
This section should list all medications currently being taken by the patient,
as well as any known general or drug allergies.

Example: "Atenolol 50 mg PO daily. Sublingual nitroglycerin as needed.
No allergies. NKDA (no known drug allergies)."

Physical Exam
The examination generally proceeds from head to toe and includes the fol-
lowing sections:

- General appearance—for example, "A slightly obese man in no acute dis-
  tress."
- Vital signs—temperature (T), pulse (P), blood pressure (BP), respiratory
  rate (R)
- HEENT (head, eyes, ears, nose, and throat)
- Neck
- Back and spine
- Lymph nodes
- Breasts
- Lungs
- Heart
- Abdomen
- Extremities
- Pulses
- Neurologic (see Chapter 3)
- Rectal
- Pelvic and genitalia
- Dermatologic

Laboratory Data
This comprises all diagnostic tests, including blood work, urine tests, elec-
trocardiogram, and radiological tests (chest X-rays, CT scans, etc.).

Assessment and Plan
The assessment section usually begins with a one- or two-sentence sum-
mary, or formulation, that encapsulates the patient’s main clinical features
and most likely diagnosis. In more diagnostically uncertain cases, a brief
discussion is added to the assessment, including a differential diagnosis—that
is, a list of alternative possible diagnoses. With neurologic disorders, this
discussion is often broken down into two sections: (1) localization and (2)
differential diagnosis.

The plan section immediately follows the assessment and is usually bro-
ken down into a list of problems and proposed interventions and diagnostic
procedures.

Example: "This is a 53-year-old man with cardiac risk factors of hyperten-
sion and family history of coronary disease who presents with substernal
chest pain and EKG changes suggestive of anterolateral wall myocardial
infarction.

1. Coronary artery disease/hypertension: Will continue IV nitroglycerin
and IV heparin after completion of tissue plasminogen activator pro-
ocol. Will resume beta-blocker, as patient has no evidence of congestive
heart failure. Will check serial EKGs and cardiac enzymes to determine
whether or not the patient has had a myocardial infarction.

2. Further cardiac workup: To include echocardiogram and an exercise
stress test if cardiac enzymes are negative. If the patient develops further
chest pain, he may require emergency cardiac catheterization."
### Neurologic Differential Diagnosis

Reaching the correct diagnosis in patients with neurologic disorders sometimes presents a considerable challenge. As noted in the previous discussion, the assessment section of the H&P is, therefore, often broken down into several logical steps to facilitate this thought process. The first step is categorization based on neuroanatomical clues gleaned from the H&P. This integration of anatomical and clinical knowledge will be the focus of this book. However, we will also briefly discuss the next step, the neurologic differential diagnosis.

When the diagnosis is uncertain and multiple possibilities must be considered, it is often helpful to have a mnemonic device handy, especially while being questioned on rounds by a more senior clinician. Such a mnemonic, the Arrowhead of Neurologic Differential Diagnosis, is shown in Figure 1.1. Disorders that tend to be more acute and require more immediate attention appear along the top and left-hand leading edges of the arrowhead; disorders that are usually more chronic in nature appear on the inside. In visualizing and prioritizing one's clinical interventions, it can therefore be useful to move from the point on the left along the top row, and then along each subsequent row from left to right.

<table>
<thead>
<tr>
<th>Category</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trauma/Mechan</td>
<td>Traumatic disorders such as subdural hematoma; nontraumatic mechanical disorders such as herniated intervertebral disc</td>
</tr>
<tr>
<td>Vascular</td>
<td>Infarct, hemorrhage, migraine, vascular malformations</td>
</tr>
<tr>
<td>Epileptic</td>
<td>Partial or generalized seizures</td>
</tr>
<tr>
<td>Csf circulation</td>
<td>Hydrocephalus, pseudotumor cerebri, intracranial hypertension</td>
</tr>
<tr>
<td>Toxic/met</td>
<td>Toxic disorders such as poisons overdose; metabolic disorders such as hepatic encephalopathy (HEP)</td>
</tr>
<tr>
<td>Deemyo</td>
<td>Infec tious diseases (e.g., bacterial meningitis). inflammatory disorders. (e.g., multiple sclerosis)</td>
</tr>
<tr>
<td>Inf/Inf/CNS</td>
<td>Degenerative diseases (e.g., Alzheimer's disease). developmental disorders. (e.g., tuberous sclerosis)</td>
</tr>
<tr>
<td>DeMy/DeMy</td>
<td>Degenerative diseases (e.g., Alzheimer's disease). developmental disorders. (e.g., tuberous sclerosis)</td>
</tr>
<tr>
<td>Psych</td>
<td>Major depression, conversion disorder</td>
</tr>
<tr>
<td>Other</td>
<td>Loss of consciousness due to cardiac arrhythmia, impaired gait due to joint deformity</td>
</tr>
<tr>
<td>NONNEURO</td>
<td></td>
</tr>
</tbody>
</table>

### Relationship between the General Physical Exam and the Neurologic Exam

The neurologic exam is part of the general physical exam. Thus, although the neurologic exam is covered separately in Chapter 3, in reality the neurologic exam and the general physical exam should always be done and described as a single unit. The patient must be treated as a whole, with problems in different systems given priority depending on the situation. In addition, essential information about neurologic disease can be gleaned from all portions of the general physical exam. Some examples are given here (for explanations of unfamiliar terms see the Key Clinical Concepts throughout the rest of the book, or consult the Index):

- **General appearance.** How a person appears and behaves throughout the exam provides a wealth of information about his or her mental status and motor system.
- **Vital signs.** Hypertension, bradycardia, and other changes can be seen in elevated intracranial pressure. Exaggerated orthostatic changes (between reclining and upright positions) in heart rate and blood pressure can be seen in autonomic dysfunction and spinal cord injuries. Respiratory pattern provides important information about brainstem function. Elevated temperature suggests infection or inflammation, which may involve the nervous system.
- **HEENT.** Head shape can be a clue to congenital abnormalities, hydrocephalus, or tumors. Careful examination of the head, ears, and nose is essential in cranial trauma. Tongue abnormalities can suggest nutritional deficiencies, which many have neurologic manifestations. Oral thrush suggests immune dysfunction, which may predispose patients to a host of neurologic disorders. Palpation of the temporal and supraorbital arteries can give clues about vasculitis and collateral blood flow in cerebrovascular disease. A whooshing sound called a bruit can sometimes be heard with the stethoscope when intracranial vascular disease or arteriovenous malformations are present. Scalp tenderness may be present in migraine. The fundoscopic exam is so relevant to neurologic disease that it is often included as part of the neurologic exam itself.
- **Neck.** Neck stiffness can be a sign of meningial irritation. Cervical bruises can be heard with carotid artery disease. Thyroid abnormalities can cause mental status changes, eye movement disorders, and muscle weakness.
- **Back and spine.** Tenderness, misalignment, and curvature can give important information about possible fractures, metastases, osteoarthritis, and so on. Muscle stiffness and tenderness are diagnostically helpful in cases of back pain.
- **Lymph nodes.** Enlarged lymph nodes can be seen in neoplastic, infectious, and granulomatous disorders, which may involve the nervous system.
- **Breasts.** Breast cancer can metastasize to the nervous system or produce paraneoplastic disorders.
- **Lungs.** Unilateral decreased breath sounds with decreased movement of the diaphragm detected by percussion can be a sign of phrenic nerve dysfunction. An abnormal lung exam can also be associated with hypoxia and with infectious or neoplastic diseases, which may involve the nervous system.
- **Heart.** Clues to embolic sources can be provided by an irregular heartbeat with atrial fibrillation or by murmurs with valvular disease or endocarditis. Aortic stenosis can produce syncope, and severe heart failure results in cerebral hypoperfusion.
• Abdomen. Hepatomegaly may be palpated in Wilson's disease and other metabolic disorders that involve the nervous system. Abdominal aortic aneurysm, pancreatitis, and other abdominal pathologies can produce back pain, which can occasionally be mistaken for disease of the spine.

• Extremities. Pain on straight-leg raising is a sign of nerve root compression. Kernig's sign (when examiner straightens the patient's knees with the hips flexed, patient has pain in the hamstring) and Brudzinski's sign (when examiner flexes the patient's neck, patient's legs at the hips) are signs of meningeal irritation. Arthritis can be seen in autoimmune disorders, which often involve the nervous system. Clubbing or cyanosis suggests systemic illness, which may involve the nervous system. Leg edema can be seen in deep venous thrombosis, which is a common complication of neurologic disease, occurring with increased incidence in patients who rarely rise from bed.

• Pulses. Peripheral vascular disease suggests atherosclerosis, which may also involve intracranial vessels. Peripheral vascular disease produces symptoms such as pain, tingling, numbness, and even weakness, which can masquerade as neurologic disease.

• Neurologic exam. See Chapter 3.

• Rectal. Decreased rectal sphincter tone can signify pathology of the spinal cord or sacral nerve roots.

• Pelvic and genitalia. Gynecologic malignancies can be associated with paraneoplastic disorders involving the nervous system and, sometimes, with metastases. Testicular abnormalities can be seen in some neurodevelopmental disorders.

• Dermatologic. Several so-called neurocutaneous disorders have important dermatologic manifestations that can signal neurologic disease. These include neurofibromatosis, tuberous sclerosis, Sturge-Weber syndrome, and other disorders. A characteristic skin eruption is also seen in dermato-myositis. Local changes in skin texture, temperature, and color can be signs of chronic neurologic injury to the affected area. Other dermatologic abnormalities can, once again, signify systemic illnesses that may involve the nervous system.

Many more examples could be mentioned, but this list should at least illustrate that the neurologic exam and the general physical exam are inextricably linked.

Conclusions

In this chapter we have introduced the general format of the history and physical exam used in most medical settings. In the case presentations throughout the rest of the book, the same format will be used, with a focus on aspects of the H&P that reveal neurologic abnormalities. We have seen that much can be learned about neurologic disease from the non-neurologic portions of the general physical exam. Nevertheless, the neurologic portion of the general physical exam ultimately provides much of the information that enables us to localize lesions within the nervous system. Before we explore the neurologic exam in more detail, we must first lay down some foundations of basic neuroanatomy. This we will do in the next chapter, and we will then return to the neurologic exam in Chapter 3.

References


CHAPTER 2

Neuroanatomy Overview and Basic Definitions

The nervous system is perhaps the most beautiful, elegant, and complex system in the body. Its interconnected networks perform processing that is simultaneously local and distributed, serial and parallel, hierarchical and global. Accordingly, structures of the nervous system can be described on multiple levels: in terms of macroscopic brain divisions; connecting pathways and cell groupings; individual brain cells; and, ultimately, receptors, neurotransmitters, and other signaling molecules. In this chapter, we will learn about the nervous system’s overall organization, and we will learn some basic terminology that will help us become oriented when we embark on a detailed study of the individual parts of the nervous system in subsequent chapters.
Basic Macroscopic Organization of the Nervous System

Deciding to study neuroanatomy is somewhat like agreeing to paint a large mural that you will spend the rest of your life carefully improving and refining. To begin painting this mural we must first agree on the orientation of our subject matter—choose an up and down, forward and backward. Then we will boldly sketch out the major features of the composition, paying particular attention to the relationships between different components and to how the composition works as a whole. The rough sketch provides a framework so that as we embark on painting various segments of the mural in ever finer detail we never lose sight of the big picture, and we are therefore able to pass seamlessly from one area of the mural to another.

This chapter is devoted to the rough sketch. It would be a vain undertaking to attempt to learn the neuroanatomy of one system or region without some concept of how it relates both spatially and functionally to the whole nervous system. This is especially true when one uses clinical cases to learn neuroanatomy. Thus, although each of the clinical cases in this book focuses on a particular neuroanatomical system, lesions almost invariably affect neighboring regions as well. These neighborhood effects are often critical in localizing neuroanatomical lesions. Therefore, in this chapter we will sketch out the main components of the nervous system and begin to describe some of the most important functions of each part.

After reading this chapter you should have some understanding of the nervous system as a whole. In addition, when you begin reading the clinical cases (Chapters 5–19), you should be able to localize lesions in certain general locations in the nervous system even though you have not yet studied those regions in detail. Finally, this chapter will provide the necessary background for understanding Chapter 3, in which we introduce the neurologic exam.

A caveat is in order before reading this chapter. This material is presented in the traditional style, without clinical cases. Therefore, do not become discouraged if you have trouble remembering all of the details. As you read the clinical cases in later chapters and refer back to this information to reach clinical diagnoses, the material will gradually be reinforced and solidified.

Main Parts of the Nervous System

The human nervous system can be divided into the central nervous system (CNS) and the peripheral nervous system (PNS). The CNS includes the brain and spinal cord; the PNS is everything else (Figure 2.1; Table 2.1). During embryological development the CNS arises from a sheet of ectodermal cells that folds over to form the neural tube. The neural tube forms several swellings and outpouchings in the head that eventually develop into the brain, while the part of the neural tube running down the back of the embryo forms the spinal cord (Figure 2.2A, B). The fluid-filled cavities within the neural tube develop into the brain ventricles, which contain cerebrospinal fluid (CSF).

The developing brain has three main divisions: the forebrain, or prosencephalon; the midbrain, or mesencephalon; and the hindbrain, or rhombencephalon (Figure 2.2). The forebrain is the largest part of the nervous system in humans, and it is further subdivided into the telencephalon and diencephalon. The telencephalon (meaning "ear brain" in Greek) is made up of the cerebral hemispheres, and includes structures discussed later in this chapter such as the cerebral cortex, white matter, and basal ganglia. The diencephalon is composed of the thalamus, hypothalamus, and associated structures. The midbrain is a relatively small and narrow region connecting the forebrain and hindbrain. The hindbrain is composed of the pons and cerebellum (metencephalon) together with the medulla (myelencephalon) (Figure 2.2).

The midbrain, pons, and medulla together form a connection between the forebrain and the spinal cord. Since the forebrain sits on top of the midbrain, pons, and medulla, almost like a cauliflower on its stalk (see Figure 2.2C), these structures are often referred to as the "brainstem." The brainstem is the most evolutionarily ancient part of the human brain and is the part that

Some authors formerly defined the brainstem to include the cerebellum and diencephalon. In common clinical usage today, however, the term "brainstem" refers to the midbrain, pons, and medulla.

Figure 2.2. Embryological Development of the Central Nervous System. (A) View of developing nervous system from the back. The neural tube has formed various vesicles that give rise to the different parts of the central nervous system (see table). (B) View of developing nervous system from the side. (C) Parts of adult central nervous system.
Figure 2.3: Orientation of the Central Nervous System in Reptiles
The same terms apply above and below the midbrain.

most closely resembles the brains of fish and reptiles. It contains many of the
most basic bodily functions necessary for survival, such as respiration, blood
pressure, and heart rate.

Cerebrospinal fluid is formed mainly by vascular tufts lying within
the ventricles called choroid plexus (see Figure 3.10). CSF circulates from the
lateral ventricles to the third ventricle, and then leaves the ventricular system
via foramina in the fourth ventricle, to percolate around the outside
surface of the brain and spinal cord. The central nervous system is covered
by three membranous protective layers called meninges (see Figure 5.1).
Listed from inside to outside, the meninges are the pia, arachnoid, and dura
(mnemonic = P.A.D). Once it leaves the ventricular system, CSF travels in
the space between the arachnoid and pia and is ultimately reabsorbed into
the venous system.

Orientation and Planes of Section
A variety of terms is used for different directions and planes of section in the
nervous system. These terms are relatively simple in animals, like fish and
reptiles, in which the nervous system is linear in orientation (Figure 2.3). In
these animals, ventral (from the Latin ventralis, meaning "belly") is always to
ward the earth, dorsal (Latin for "back," as in a shark’s fin) is toward the
sky, rostral (Latin for "beak"—think of a "rooster’s roost") is toward the
snout, and caudal (Latin for "tail") is toward the tail. However, since hu-
mans have an upright posture, the nervous system makes a bend of nearly
90° somewhere between the forebrain and the spinal cord (Figure 2.4). By
definition, this bend is said to occur in the region of the midbrain—dienceph-
al junction. Therefore, for structures above the midbrain, the orienta-
tion of the nervous system is the same with respect to the ground (as in re-
tiles). At the midbrain and below, however, there is a rotation of 90°, since in
the standing position the spinal cord is approximately perpendicular to the
ground in humans.

Figure 2.4 Orientation of the Central Nervous System
in Humans The meaning of some terms (dorsal, ventral, rostral, caudal) changes at the midbrain—diencephalic junction.

Another set of terms that is often used for orientation in the nervous sys-
tem remains constant with respect to the environment both above and below
the midbrain. These are anterior, posterior, superior, and inferior. By look-
ing at Figure 2.4 you should be able to confirm the definitions of the follow-
ing terms as they apply to humans:
- Above the midbrain:
  - Anterior = rostral
  - Superior = dorsal
- Below the midbrain:
  - Posterior = rostral
  - Inferior = caudal

Thus, for example, above the midbrain the anterior commissure is rostral,
the posterior commissure is caudal, the superior sagittal sinus is dorsal, and
the inferior sagittal sinus is ventral. Meanwhile, below the midbrain the ante-
rior horn of the spinal cord is ventral, the posterior horn is dorsal, the superior
cerebellar peduncle is rostral, and the inferior cerebellar peduncle is caudal.
In the midbrain itself, the same conventions as below the midbrain are gen-
erally used.

When the nervous system is studied pathologically or imaged radiologi-
cally, it is usually cut in one of three different orthogonal planes of section
(Figure 2.5). Horizontal sections are parallel to the floor. Equivalent terms for
horizontal sections in humans include axial or transverse sections, meaning
sections perpendicular to the long axis of the person’s body. The name coro-
nal comes from the sectioning plane approximating that of a toad-like crown.
Sagittal sections are in the direction of an arrow shot, and this plane of sec-
tion is best visualized by imagining the plane defined by a bow and arrow
held by an archer (as in the constellation Sagittarius). Sagittal sections pass-
ning through the midline are referred to as parasagittal sections.

Note that the sagittal plane is orthogonal to the left-right axis, the coro-
nal plane is orthogonal to the anterior-posterior axis, and the horizontal plane
is orthogonal to the superior-inferior axis. When a plane of section lies some-
where between the three principal planes, it is referred to as oblique. The
planes of section used for CT and MRI scans are approximately horizontal,
coronal, or sagittal, with some slight adjustments (especially in the horizon-
tal plane) often being necessary for technical reasons (see Chapter 4).

Basic Cellular and Neurochemical Organization
of the Nervous System
Microscopically, the nervous system is composed of nerve cells, or neurons,
and support cells called glial cells (or simply glia). Neurons are mainly re-
ponsible for signaling in the nervous system, although glial cells may con-
tribute as well. Neuronal signaling is a complex phenomenon, presented here
in a very simplified manner geared toward the clinical-anatomical discussions
in this book (see the references at the end of this chapter for a more detailed
Figure 2.5 Anatomical Planes of Section (A) Horizontal, axial, trans-
verse) plane. (B) Coronal plane. (C) Sagittal plane.

A typical neuron has a cell body containing the nucleus, relatively
short processes called dendrites, which receive most inputs to the cell, and
long processes called axons, which carry most outputs (Figure 2.6). Most
Mammalian neurons are multipolar, meaning that they have several dendrites, as well as several axons (Figure 2.6A). Often, a single axon arising from the cell body will travel for a distance, and then one or several axon collaterals branch off the main axon to reach different targets. Some neurons are bipolar, with a single dendrite and a single axon arising from the cell body. Bipolar cells are often sensory neurons, such as those involved in vision (see Figure 11.4) or olfaction (see Figure 18.5). Some bipolar neurons are called pseudounipolar, since their processes are initially fused, and then split to produce two long axons. An example is dorsal root ganglion sensory neurons (see Figure 2.21). Unipolar neurons, in which both axons and dendrites arise from a single process coming off the cell body, occur mainly in invertebrates.

Communication between neurons takes place mainly at specialized regions called synapses. Classically, synapses carry information from the axon terminals of one neuron to the dendrites of the next neuron. However, there are also axo-axonic and dendro-dendritic synapses, and some forms of communication can even occur in reverse, traveling from dendrites back to axons. At chemical synapses, chemical neurotransmitter molecules, stored mainly in synaptic vesicles, are released from presynaptic terminals of the neuron (see Figure 2.6C). They then bind to neurotransmitter receptors on the postsynaptic neuron, giving rise to either excitation or inhibition of the postsynaptic neuron. In some cases, communication also takes place at electrical synapses where direct electrical coupling of neurons occurs through specialized junctions.

Neurons are electrically and chemically active. When excitatory synaptic inputs combine with endogenous transmembrane currents to sufficiently excite a neuron, a transient voltage change called an action potential occurs, lasting about 1 millisecond. Action potentials can travel rapidly throughout the length of a neuron, propagating at rates of up to about 60 meters per second along the cell membrane. Classically, action potentials travel from the dendritic end of the neuron along its axon to reach presynaptic terminals, where communication can occur with the next neuron (see Figure 2.6). Action potentials trigger release of neurotransmitter molecules from synaptic vesicles, allowing chemical communication with the postsynaptic cell (see Figure 2.6C).

Axons are often insulated by specialized glial cells that form a lipid myelin sheath, thereby speeding the rate of action potential conduction (see Figure 2.6B). The myelin-forming glial cells in the CNS are oligodendrocytes; in the PNS they are Schwann cells. Voltage-gated ion channels are concentrated in short exposed segments of the axon called nodes of Ranvier (see Figure 2.6B). Conduction from node to node occurs rapidly by a process called saltatory conduction.

Chemical neurotransmitters have two general types of functions. One is to mediate rapid communication between neurons through fast excitatory or inhibitory electrical events known as excitatory postsynaptic potentials (EPSPs) and inhibitory postsynaptic potentials (IPSPs). Fast EPSPs and IPSPs occur on the time scale of tens of milliseconds, and rapidly move the membrane voltage of the postsynaptic neuron between states more or less likely to fire an action potential. The postsynaptic neuron summates EPSPs and IPSPs arising from many presynaptic inputs. The second function of chemical neurotransmitters is neuromodulation, generally occurring over slower time scales. Neuromodulation includes a broad range of cellular mechanisms involving signaling cascades that regulate synaptic transmission, neuronal growth, and other functions. Neuromodulation can either facilitate or inhibit the subsequent signaling properties of the neuron.

Some of the more important and common neurotransmitters are summarized in Table 2.2. Note that neurotransmitters can be small molecules such as acetylcholine, amino acids like glutamate, or larger molecules such as peptides. Depending on the specific receptors present, neurotransmitters can mediate fast neurotransmission through EPSPs or IPSPs, or may have facilitatory or inhibitory neuromodulatory effects on neuronal signaling. Some neurotransmitters have different actions at different synapses or even at the same synapse when a mixture of receptor types is present. In addition, more than one type of neurotransmitter molecule is often released, even at a single synapse.
### TABLE 2.2 Some Important Neurotransmitters

<table>
<thead>
<tr>
<th>NAME</th>
<th>LOCATION OF CELL BODIES</th>
<th>MAIN PROJECTIONS</th>
<th>RECEPTOR SUBTYPES</th>
<th>MAIN ACTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glutamate</td>
<td>Entire CNS</td>
<td>Entire CNS</td>
<td>AMPA/kainate</td>
<td>Excitatory neurotransmission</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NMDA</td>
<td>Modulation of synaptic plasticity</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Metabotropic</td>
<td>Activation of second messenger systems</td>
</tr>
<tr>
<td>GABA</td>
<td>Entire CNS</td>
<td>Entire CNS</td>
<td>GABA&lt;sub&gt;A&lt;/sub&gt;, GABA&lt;sub&gt;B&lt;/sub&gt;</td>
<td>Inhibitory neurotransmission</td>
</tr>
<tr>
<td>Acetylcholine</td>
<td>Spinal cord, anterior horn, autonomic preganglionic nuclei</td>
<td>Retina, autonomic ganglia</td>
<td>Muscarinic, nicotinic</td>
<td>Muscle contraction, autonomic functions</td>
</tr>
<tr>
<td>Parasympathetic ganglia</td>
<td>Ganglion, smooth muscle, cardiac muscle</td>
<td>Cerebral cortex</td>
<td>Muscarinic and nicotinic subtypes</td>
<td>Parasympathetic functions</td>
</tr>
<tr>
<td>Basal forebrain, nucleus basalis, medial septal nucleus, nucleus of diagonal band</td>
<td>Cerebral cortex</td>
<td>Muscarinic and nicotinic subtypes</td>
<td>Neuremodulation</td>
<td></td>
</tr>
<tr>
<td>Pontomesencephalic region, pedunculopontine nucleus, laterodorsal tegmental nucleus</td>
<td>Thalamus, cerebellum, pons, and medulla</td>
<td>Muscarinic and nicotinic subtypes</td>
<td>Neuremodulation</td>
<td></td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>Sympathetic ganglia</td>
<td>Smooth muscle, cardiac muscle</td>
<td>α and β subtypes</td>
<td>Sympathetic functions</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Entire CNS</td>
<td>Neuremodulation</td>
</tr>
<tr>
<td>Dopamine</td>
<td>Midbrain: substantia nigra, pars compacta, ventral tegmental area</td>
<td>striatum, prefrontal cortex, limbic cortex, nucleus accumbens, amygdala</td>
<td>D&lt;sub&gt;1&lt;/sub&gt;-D&lt;sub&gt;3&lt;/sub&gt;</td>
<td>Neuremodulation</td>
</tr>
<tr>
<td>Serotonin</td>
<td>Midbrain and pontine raphe nuclei</td>
<td>Entorhinal cortex</td>
<td>5-HT&lt;sub&gt;1A&lt;/sub&gt;, 5-HT&lt;sub&gt;1B&lt;/sub&gt;, 5-HT&lt;sub&gt;2C&lt;/sub&gt;, 5-HT&lt;sub&gt;7&lt;/sub&gt;</td>
<td>Neuremodulation</td>
</tr>
<tr>
<td>Histamine</td>
<td>Hypothalamus: tuberoinfundibular nucleus; midbrain; reticular formation</td>
<td>Entorhinal cortex</td>
<td>H&lt;sub&gt;3&lt;/sub&gt;</td>
<td>Mainly excitatory neurotransmission</td>
</tr>
<tr>
<td>Glycine</td>
<td>Spinal cord, possibly also brainstem and retia</td>
<td>Spinal cord, brainstem, and retia</td>
<td>Glycine</td>
<td>Inhibitory neurotransmission</td>
</tr>
<tr>
<td>Peptides</td>
<td>Entire CNS</td>
<td>Entire CNS</td>
<td>Numerous</td>
<td>Neuremodulation</td>
</tr>
</tbody>
</table>

*Glycine also has a modulatory role by binding to the NMDA receptor and increasing its response to glutamate.

In the CNS, the most common excitatory neurotransmitter is **glutamate**; the most common inhibitory neurotransmitter is **GABA** (gamma-aminobutyric acid). In the PNS, **acetylcholine** is the main transmitter at neuromuscular junctions, and both acetylcholine and **norepinephrine** are important in the autonomic nervous system (which we will discuss a little later). Aside from those listed in Table 2.2, numerous other neurotransmitters and neuro-receptor mechanisms have been described, and many more are yet to be discovered. Additional details of the functions of particular neurotransmitters will be provided in Chapters 6, 14, and 16.

### CNS Gray Matter and White Matter; PNS Ganglia and Nerves

Areas of the CNS made up mainly of myelinated axons are called **white matter**. Areas made up mainly of cell bodies are called **gray matter**. Most of the local synaptic communication between neurons in the CNS occurs in the gray matter, while axons in the white matter transmit signals over greater distances. The surface of the cerebral hemispheres is covered by a unique mantle of gray matter called the **cerebral cortex**, which is far more developed in higher mammals than in other species. Beneath this lies the white matter, which conveys signals to and from the cortex (Figure 2.7A). Gray matter is also found in large clusters of cells called nuclei located deep within the cerebral hemispheres and brainstem. Examples include the **basal ganglia**, **thalamus**, and **cerebellum** (Figure 2.7A,B).

In the cerebral hemispheres the gray matter cortex is outside, while the white matter is inside. In the spinal cord the opposite is true: White matter pathways lie on the outside, while the gray matter is in the center (Figure 2.7C). In the brainstem, gray matter and white matter regions are found both on the inside and on the outside, although most of the outside surface is in white matter.

![Figure 2.7 Gray Matter and White Matter in the Central Nervous System](image)
Several different names with similar meaning are used for white matter pathways in the CNS, including tract, fascicle, lemniscus, and bundle. A white matter pathway that connects identical structures on the right and left sides of the CNS is called a commissure. Axons in the PNS form bundles called peripheral nerves, or simply nerves. Clusters of cell bodies in the PNS are referred to as ganglia.

In general, pathways carrying signals toward a structure are called afferent, while those carrying signals away from a structure are called efferent (afferents arrive, efferents exit). Thus, peripheral nerves convey afferent sensory information about the environment to the CNS and carry efferent signals for motor activity from the CNS to the periphery.

**Spinal Cord and Peripheral Nervous System**

The human nervous system develops in segments similar to those of simpler animals, such as segmented worms. As already described, the segments in the head expand and fuse together, forming the cerebral hemispheres and brainstem. Twelve pairs of cranial nerves (see Figure 2.1) exit these segments (these will be discussed further later in the chapter). The spinal nerves arise from the segments of the spinal cord. Each segment gives rise to both sensory and motor nerve roots on each side of the body (Figure 2.8B).

Throughout the nervous system, motor systems tend to be more ventral, or anterior, and sensory systems more dorsal, or posterior. The same holds true for the spinal cord. Thus, dorsal nerve roots convey mainly afferent sensory information into the dorsal spinal cord, while ventral nerve roots carry mainly efferent motor signals from the ventral spinal cord to the periphery. The segments and nerve roots of the spinal cord are named according to the level at which they exit the bony vertebral canal. Thus, there are cervical, thoracic, lumbar, and sacral nerve roots (see Figure 2.8A).

During development, the bony vertebral canal increases in length faster than the spinal cord. Therefore, the spinal cord ends at the level of the first or second lumbar vertebral bones (L1 or L2). Below this the spinal canal contains a collection of nerve roots known as the cauda equina ("horse's tail"), which continue down to their exit points. The sensory and motor nerve roots join together a short distance outside the spinal cord and form a mixed sensory and motor spinal nerve (see Figure 2.8B). Control of the arms and legs requires much more signal flow than does control of the chest and abdomen. Thus, the nerves controlling the extremities give rise to elaborate meshworks referred to as the brachial plexus for the arm and the lumbar plexus for the leg (Figure 2.8A). In addition, the spinal cord contains a relatively increased amount of gray matter in these segments, causing the overall thickness of the cord to be greater. These regions of the cord are called the cervical enlargement and the lumbar enlargement, respectively.

In addition to the sensory and motor pathways already described, the PNS includes some specialized nerves that are involved in controlling such automatic functions as heart rate, perspiration, sweating, and smooth muscle contraction in the walls of blood vessels, bronchi, sex organs, the pupils, and so on. These nerves are part of the autonomic nervous system. The autonomic nervous system has two major divisions (Figure 2.9): the sympathetic division and the parasympathetic division.

**Sympathetic division**

- **Cranial**
  - Sympathetic ganglia (prevertebral, paravertebral, adrenals)

**Parasympathetic division**

- **Cranial**
  - Vagus nerve (X)
  - Oculomotor (CN III)
  - Facial (CN VII)
  - Glossopharyngeal (CN IX)

- **Thoracic**
  - "Fight or Flight"
  - Dural dilation
  - Bronchodilation
  - Dilation of blood vessels

- **Lumbar**
  - Acetylcholine
  - Noradrenaline

- **Sacral**
  - "Rest or Digest"
  - Pupil constriction
  - Bronchoconstriction
  - Cardiac depression
  - Inhibition of digestion
  - Stimulation of blood vessels
  - Stimulation of respiration
  - Stimulation of oesophagus

**Figure 2.8** The Spinal Cord

(A) Cervical, thoracic, lumbar, and sacral spinal cord segments and nerves in relation to vertebral bones. (B) Dorsal sensory roots and ventral motor roots arise at each segment.
Cerebral Cortex: Basic Organization and Primary Sensory and Motor Areas

The cerebral cortex is not a smooth sheet, but rather has numerous indentations or crevices called sulci. The bumps or ridges of cortex that rise up between the sulci are called gyri. Some sulci and gyri have particular names and functions, as we will learn shortly. The cerebral hemispheres have four major lobes: the frontal, temporal, parietal, and occipital (Figure 2.10).

Lobes of the Cerebral Hemispheres

The frontal lobes are, appropriately, in the front of the brain and extend back to the central sulcus of Rolando. The frontal lobes are separated inferiorly and laterally from the temporal lobes by an especially deep sulcus called the Sylvian fissure, or lateral fissure. The term fissure is sometimes used to refer to deep sulci. The parietal lobes are bounded anteriorly by the central sulcus but have no sharp demarcation from the temporal lobes or the occipital lobes when viewed from the lateral side of the brain (see Figure 2.10A). When viewed from the medial aspect, the parieto-occipital sulcus can be seen more easily, separating the parietal from the occipital lobes (see Figure 2.10B).

In addition to these four major lobes, an additional region of cerebral cortex lies buried within the depths of the Sylvian fissure, called the insular cortex (see Figure 2.24B). The insula is covered by a lip of frontal cortex anteriorly and parietal cortex posteriorly, called the frontal operculum and parietal operculum, respectively (operculum means "covering" or "lid" in Latin) (see Figure 2.24B). The limbic cortex (see Figure 2.25) was formerly referred to as the "limbic lobe," but this terminology is no longer generally used.

The two cerebral hemispheres are separated in the midline by the interhemispheric fissure, also known as the longitudinal fissure (see Figure 2.11D). A large C-shaped band of white matter called the corpus callosum (meaning "broad body") connects homologous areas in the two hemispheres (see Figure 2.10).

Surface Anatomy of the Cerebral Hemispheres in Detail

Although there is some variability, the sulci and gyri of the cerebral hemispheres form certain fairly consistent patterns. We will now briefly review the names of the major sulci, gyri, and other structures of the cerebral hemispheres (Figure 2.11). Functions of these structures will be discussed in the next section and throughout the remainder of the book.

On the lateral surface (see Figure 2.11A), the frontal lobe is bounded posteriorly by the central sulcus, as already noted. The gyrus running in front of the central sulcus is called the precentral gyrus. The remainder of the lateral frontal surface is divided into the superior, middle, and inferior frontal gyri by the superior and inferior frontal sulci. Similarly, the lateral temporal lobe is divided into superior, middle, and inferior temporal gyri by the superior and middle temporal sulci. The most anterior portion of the parietal lobe is the postcentral gyrus, lying just behind the central sulcus. The intraparietal sulcus divides the superior parietal lobule from the inferior parietal lobule. The inferior parietal lobule consists of the supramarginal gyrus (surrounding the end of the Sylvian fissure) and the angular gyrus (surrounding the end of the superior temporal gyrus).

On the medial surface (see Figure 2.11B), the corpus callosum is clearly visible, consisting of the rostrum, genu, body, and splenium. The cingulate gyrus (cingulum means "girdle" or "belt") surrounds the corpus callosum, running from the parietal to the frontal gyri anteriorly to the insular posteriorly. It has a marginal branch, running up to the superior surface that forms an important landmark, since the sulcus immediately in front of it on the superior surface is the central sulcus. The central sulcus does not usually extend onto the medial surface, but the region surrounding it is called the paracentral lobule. The portion of the medial occipital lobe below the calcarine fissure is called the lingula (meaning "little tongue"), while the portion above the calcarine fissure is called the cuneus (meaning "wedge"). Just in front of the cuneus, the medial parietal lobe is called the precuneus.

On the inferior surface (see Figure 2.11C), the orbital frontal gyri can be seen, which lay on top of the orbital ridges of the eye. More medially, the olfactory sulcus (containing the olfactory bulb) separates the orbital frontal gyrus from the gyrus rectus (meaning "straight gyrus"). On the inferior surface of the temporal lobe, the inferior temporal sulcus separates the inferior temporal gyrus from the occipitotemporal, or fusiform, gyrus. More medially, the collateral sulcus, continuing anteriorly as the rhinal sulcus, separates the fusiform gyrus from the parahippocampal gyrus.

Finally, on the superior surface (see Figure 2.11D), many of the same landmarks seen on the lateral surface are again visible.
Figure 2.11 Detailed Labeled Surface View of Cerebral Cortex. (A) Lateral view of left hemisphere. (B) Medial view of right hemisphere. (C) Interior view. (D) Superior view.
Primary Sensory and Motor Areas

The primary sensory and motor areas of the cortex are shown in Figure 2.12. The primary motor cortex lies in the precentral gyrus in the frontal lobe (see Figure 2.11A). This area controls movement of the opposite side of the body. The primary somatosensory cortex is in the postcentral gyrus in the parietal lobe and is involved in sensation for the opposite side of the body. Note that the precentral and postcentral gyri are separated by the central sulcus, and that (as in the spinal cord) motor areas lie anterior to somatosensory areas. The primary visual cortex is in the occipital lobes along the banks of a deep sulcus called the calcarine fissure (see Figures 2.11B, 2.12). The primary auditory cortex is composed of the transverse gyri of Heschl, which are two fingerlike gyri that lie inside the Sylvian fissure on the superior surface of each temporal lobe (see Figures 2.12, 2.24B). Higher-order sensory and motor information processing takes place in the association cortex, as will be discussed later in this chapter.

Sensory and motor pathways are usually topographically organized. This means that adjacent areas on the receptive (or motor) surface are mapped to adjacent fibers in white matter pathways and to adjacent regions of cortex. For example, in primary motor and primary somatosensory cortex, regions representing the hand are adjacent to regions representing the arm and so on (Figure 2.13). These somatotopic maps on the cortex are sometimes called the motor or sensory homunculus ("little man"). Similarly, adjacent retinal areas are mapped in a retinotopic fashion onto the primary visual cortex, and adjacent regions of the cochlea sensing different frequencies have a tonotopic representation on the primary auditory cortex.

Interestingly, the primary somatosensory cortex and primary motor cortex represent sensation and movement, respectively, for the opposite side of the body. This relationship was first noted by physicians in ancient Greece, including Hipocrates, who observed that patients with head injuries had deficits affecting the side of the body opposite to the side of the injury. Knowledge of the levels at which the somatosensory and motor pathways cross over in the nervous system can be helpful for clinical neuroanatomical localization, and will be discussed later in this chapter. The primary visual cortex represents visual inputs from the opposite visual field. Thus the left half of the visual field for each eye is mapped to the right primary visual cortex (see Figure 11.15). Information reaching the primary auditory cortex is less lateralized, and represents more of a mixture of inputs from both ears (the input from the opposite ear is slightly stronger, but this is usually not clinically detectable).

Cell Layers and Regional Classification of the Cerebral Cortex

The majority of the cerebral cortex is composed of neocortex, which has six cell layers, labeled I through VI, counting from the surface inward (Figure 2.14; Table 2.3). In a few regions associated with the limbic system, less than six layers are present. Neocortical circuitry is quite complex, and we will describe only a few of the major connections of each layer here. Layer I contains mainly dendrites of neurons from deeper layers and axons. Layers II and III contain neurons that project mainly to other areas of cortex. Layer IV receives the majority of inputs from the thalamus. Layer V projects mostly to subcortical structures other than the thalamus, such as the brainstem, spinal cord, and basal ganglia. Layer VI projects primarily to the thalamus. In addition to these connections, numerous other circuits exist between and within the cortical layers that are beyond the scope of this discussion. The cortical layers I to VI also have names that will not be used here but are included in Table 2.3 for reference.

The relative thickness of the cell layers varies according to the main function of that area of cortex. For example, the primary motor cortex has large
Different projections to the brainstem and spinal cord, which control movement. It receives relatively little direct sensory information from thalamic relay centers. Therefore, in the primary motor cortex, layer V is thick and has many more cell bodies than layer IV (see Figure 2.14B). The opposite holds for primary visual cortex, where layer IV contains many cell bodies and layer V is relatively cell poor (Figure 2.14C). Association cortex has a cellular structure that is intermediate between these types (Figure 2.14A).

A variety of classification schemes exist for different regions of the cerebral cortex based on microscopic appearance and function. The most widely known of these was published by Korbinian Brodmann in 1909. On the basis of microscopic studies, Brodmann parcelled the cortex into 52 cytoarchitectonic areas, each assigned a number corresponding to the order in which he prepared the slides (Figure 2.15; Table 2.4). It turns out that many of the areas identified by Brodmann correlate fairly well with various functional areas of the cortex, and therefore his nomenclature is still often used today.

### Table 2.3: Cell Layers of the Neocortex

<table>
<thead>
<tr>
<th>LAYER</th>
<th>NAME</th>
<th>ALTERNATIVE NAME</th>
<th>MAIN CONNECTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Molecular layer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>Small pyramidal layer</td>
<td></td>
<td>Dendrites and axons from other layers, Cortical-cortical connections</td>
</tr>
<tr>
<td>III</td>
<td>Medium pyramidal layer</td>
<td></td>
<td>Dendrites and axons from other layers, Cortical-cortical connections</td>
</tr>
<tr>
<td>IV</td>
<td>Granular layer</td>
<td></td>
<td>Dendrites and axons from other layers, Cortical-cortical connections</td>
</tr>
<tr>
<td>V</td>
<td>Large pyramidal layer</td>
<td></td>
<td>Dendrites and axons from other layers, Cortical-cortical connections</td>
</tr>
<tr>
<td>VI</td>
<td>Polymorphic layer</td>
<td></td>
<td>Dendrites and axons from other layers, Cortical-cortical connections</td>
</tr>
</tbody>
</table>

### Table 2.4: Brodmann's Cytoarchitectonic Areas

<table>
<thead>
<tr>
<th>BRODMANN'S AREA</th>
<th>FUNCTIONAL AREA</th>
<th>LOCATION</th>
<th>FUNCTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>1, 2, 3</td>
<td>Primary somatosensory cortex</td>
<td>Parietal sulcus</td>
<td>Parietal gyrus</td>
</tr>
<tr>
<td>4</td>
<td>Primary motor cortex</td>
<td>Parietal sulcus</td>
<td>Superior parietal lobe</td>
</tr>
<tr>
<td>5</td>
<td>Tertiary somatosensory cortex; posterior parietal association area</td>
<td>Parietal sulcus</td>
<td>Superior parietal lobe</td>
</tr>
<tr>
<td>6</td>
<td>Supplementary motor cortex; supplementary eye field; premotor cortex; frontal eye fields</td>
<td>Parietal sulcus</td>
<td>Precentral gyrus and rostral adjacent cortex</td>
</tr>
<tr>
<td>7</td>
<td>Posterior parietal association area</td>
<td>Parietal sulcus</td>
<td>Superior parietal lobe</td>
</tr>
<tr>
<td>8</td>
<td>Frontal eye fields</td>
<td>Parietal sulcus</td>
<td>Superior, middle frontal gyr, medial frontal lobe</td>
</tr>
<tr>
<td>9, 10, 11, 12</td>
<td>Prefrontal association cortex; frontal eye fields</td>
<td>Parietal sulcus</td>
<td>Superior, middle frontal gyr, medial frontal lobe</td>
</tr>
<tr>
<td>17</td>
<td>Primary visual cortex</td>
<td>Rolandic area</td>
<td>Banks of calcarine fissure</td>
</tr>
<tr>
<td>18</td>
<td>Secondary visual cortex</td>
<td>Rolandic area</td>
<td>Medial and lateral occipital gyr</td>
</tr>
<tr>
<td>19</td>
<td>Tertiary visual cortex, middle temporal visual area</td>
<td>Rolandic area</td>
<td>Medial and lateral occipital gyr</td>
</tr>
<tr>
<td>20</td>
<td>Visual infratemporal area</td>
<td>Rolandic area</td>
<td>Inferior temporal gyrus</td>
</tr>
<tr>
<td>21</td>
<td>Visual infratemporal area</td>
<td>Rolandic area</td>
<td>Inferior temporal gyrus</td>
</tr>
<tr>
<td>22</td>
<td>Higher-order auditory cortex</td>
<td>Rolandic area</td>
<td>Superior temporal gyrus</td>
</tr>
<tr>
<td>23</td>
<td>Limbic association cortex</td>
<td>Rolandic area</td>
<td>Cingulate gyrus, subcallosal area, retrosplenial area, and parahippocampal gyr</td>
</tr>
<tr>
<td>24, 25, 26, 27</td>
<td>Limbic association cortex</td>
<td>Rolandic area</td>
<td>Cingulate gyrus, subcallosal area, retrosplenial area, and parahippocampal gyr</td>
</tr>
<tr>
<td>28</td>
<td>Primary olfactory cortex; limbic association cortex</td>
<td>Rolandic area</td>
<td>Cingulate gyrus and retrosplenial area</td>
</tr>
<tr>
<td>29, 30, 31, 32, 33</td>
<td>Limbic association cortex</td>
<td>Rolandic area</td>
<td>Cingulate gyrus and retrosplenial area</td>
</tr>
<tr>
<td>34, 35, 36</td>
<td>Primary olfactory cortex; limbic association cortex</td>
<td>Rolandic area</td>
<td>Middle and inferior temporal gyr at junction of temporal and occipital lobes</td>
</tr>
<tr>
<td>37</td>
<td>Parietal-temporal-occipital association cortex</td>
<td>Rolandic area</td>
<td>Middle and inferior temporal gyr at junction of temporal and occipital lobes</td>
</tr>
<tr>
<td>38</td>
<td>Primary olfactory cortex</td>
<td>Rolandic area</td>
<td>Temporal pole</td>
</tr>
<tr>
<td>39</td>
<td>Parietal-temporal-occipital association cortex</td>
<td>Rolandic area</td>
<td>Inferior parietal lobe (angular gyrus)</td>
</tr>
<tr>
<td>40</td>
<td>Parietal-temporal-occipital association cortex</td>
<td>Rolandic area</td>
<td>Inferior parietal lobe (supramarginal gyr)</td>
</tr>
<tr>
<td>41</td>
<td>Primary auditory cortex</td>
<td>Rolandic area</td>
<td>Heschl's gyri and superior temporal gyrus</td>
</tr>
<tr>
<td>42</td>
<td>Secondary auditory cortex</td>
<td>Rolandic area</td>
<td>Heschl's gyri and superior temporal gyrus</td>
</tr>
<tr>
<td>43</td>
<td>Gustatory cortex</td>
<td>Rolandic area</td>
<td>Incisural gyr, frontaloparietal operculum</td>
</tr>
<tr>
<td>44</td>
<td>Broca's area, lateral premotor cortex</td>
<td>Rolandic area</td>
<td>Inferior frontal gyrus (frontal operculum)</td>
</tr>
<tr>
<td>45</td>
<td>Prefrontal association cortex</td>
<td>Rolandic area</td>
<td>Inferior frontal gyrus (frontal operculum)</td>
</tr>
<tr>
<td>46</td>
<td>Prefrontal association cortex (dominolateral prefrontal cortex)</td>
<td>Rolandic area</td>
<td>Middle frontal gyrus</td>
</tr>
<tr>
<td>47</td>
<td>Prefrontal association cortex</td>
<td>Rolandic area</td>
<td>Inferior frontal gyrus (frontal operculum)</td>
</tr>
</tbody>
</table>


*Areas 13, 14, 15, and 16 are part of the insular cortex.*
Motor Systems

Motor control involves a delicate balance between multiple parallel pathways and recurrent feedback loops. We will now provide an overview of the most important motor pathways, and of the cerebellum and basal ganglia, which are major feedback systems.

Main Motor Pathways

The most important motor pathway in humans is the corticospinal tract. The corticospinal tract begins mainly in the primary motor cortex, where neuron cell bodies project via axons down through the cerebral white matter and brainstem to reach the spinal cord (Figure 2.16). The majority of fibers in the corticospinal tract (about 85%) cross over to control movement of the opposite side of the body. This crossing over, known as the pyramidal decussation, occurs at the junction between the medulla and the spinal cord. Thus, lesions occurring above the pyramidal decussation produce contralateral (opposite-sided) weakness with respect to the lesion, while lesions below the pyramidal decussation will produce ipsilateral (same-sided) weakness. Several other descending motor pathways that exist in addition to the corticospinal tract will be discussed in Chapter 6.

Motor neurons that project from the cortex down to the spinal cord or brainstem are referred to as upper motor neurons (UMNs). UMNs form synapses onto the lower motor neurons (LMNs), which are located in the anterior horns of the central gray matter of the spinal cord (see Figure 2.16B) or in brainstem motor nuclei. The axons of LMNs project out of the CNS via the anterior spinal roots or via the cranial nerves to finally reach muscle cells in the periphery. Lesions affecting UMNs and LMNs have certain distinct clinical features, which we will learn about in Chapter 3.
Cerebellum and Basal Ganglia

The motor system is called upon to perform many delicate and complicated tasks. Therefore, in order to refine the output of the motor system, multiple feedback systems are employed, including the cerebellum and basal ganglia (Figure 2.17). These two systems do not themselves project directly to the LMsNs. Instead, the cerebellum and basal ganglia act by modulating the output of the corticospinal and other descending motor systems. The cerebellum and basal ganglia both receive major inputs from the motor cortex. The cerebellum also receives significant inputs from the brainstem and spinal cord, as discussed in Chapter 15. The cerebellum and basal ganglia, in turn, project back to the motor cortex via the thalamus. Lesions in the cerebellum lead to disorders in coordination and balance, often referred to as ataxia. Lesions in the basal ganglia cause hypokinetic movement disorders, such as Parkinsonism, in which movements are infrequent, slow, and rigid, and hyperkinetic movement disorders, such as Huntington's disease, which is characterized by dystonic involuntary movements.

Somatosensory Systems

Sensation from the body is conveyed by parallel pathways mediating different sensory modalities that travel to the central nervous system. We will now review the most important sensory pathways and introduce the thalamus, a major relay center for signals of all kinds (sensory and other) that travel to the cerebral cortex.

Main Somatosensory Pathways

Somatosensation refers to the conscious perceptions of touch, pain, temperature, vibration, and proprioception (limb or joint position sense). There are two major pathways in the spinal cord for somatosensation:

1. The posterior column pathways (Figure 2.18) convey proprioception, vibration sense, and fine, discriminative touch.
2. The anterolateral pathways (Figure 2.19) convey pain, temperature sense, and crude touch.

Some aspects of touch sensation are carried by both pathways, so touch sensation is not eliminated in isolated lesions of either pathway. Note that the primary sensory neurons cell bodies are located outside the CNS in the dorsal root ganglia and that they have bifurcating axons, with one long process extending to the periphery and one into the spinal cord (see Figures 2.18 and 2.19). Equally as important as the knowledge that the corticospinal tract crosses over at the pyramidal decussation, which allows us to localize lesions, is the knowledge of where in the CNS the two main sensory pathways cross over. These major sensory pathways are, therefore, briefly outlined here.

POSTERIOR COLUMN PATHWAY: Primary sensory neurons carrying information about proprioception, vibration sense, and fine touch enter first the spinal cord via the dorsal roots and then the ipsilateral white matter dorsal (posterior) columns to ascend all the way to the dorsal column nuclei in the medulla (see Figure 2.18). It is here that they make synapses onto the secondary sensory neurons, which send out axons that cross over to the other side of the medulla. These axons continue to ascend, now on the contralateral side, and synapse in the thalamus. From there neurens project to the primary somatosensory cortex in the postcentral gyrus.

ANTEROLATERAL PATHWAY: Primary sensory neurons carrying information about pain, temperature sense, and crude touch also enter the spinal cord via the dorsal roots (see Figure 2.19). However, these axons make their first synapses immediately in the gray matter of the spinal cord. Axons from the secondary sensory neurons cross over to the other side of the spinal cord and ascend in the anterolateral white matter, forming the spinothalamic tract. After synapsing in the thalamus, the pathway again continues to the primary somatosensory cortex.

Thalamus

The thalamus is an important relay center. Nearly all pathways that project to the cerebral cortex do so after synapsing in the thalamus. The thalamus are gray matter structures located deep within the cerebral white matter just above the brainstem and behind the basal ganglia (see Figures 2.17, 2.20). They are shaped somewhat like eggs, with their posterior ends angled out...
Figure 2.19 Spinothalamic Sensory Pathway: Pain and Temperature
(A) Pathway from periphery to somatosensory cortex. (B) Representative sections showing pathway through the spinal cord, thalamus and cerebral cortex.

ward, together forming an inverted V in horizontal sections (see Figures 2.7A, 2.20B). The thalamus consists of multiple nuclei. Each sensory modality, including vision, hearing, taste, and somatic sensation, has a different nuclear area where synapses occur before the information is relayed to the cortex (olfactory inputs are an exception and do not pass directly through the thalamus). Nonsensory pathways also relay in the thalamus. For example, there are thalamic nuclei that process information coming from the basal ganglia, cerebellum, limbic pathways, and brainstem reticular formation on the way to the cortex (see Figure 2.20A). An important feature of thalamic circuits is the reciprocal nature of cortical–thalamic connections. Thus, virtually all cortical regions project strongly via layer VI (see Table 2.3) back to the thalamic areas from which their major inputs arise.

As we discussed earlier in this chapter, the thalamus, together with the hypothalamus and epithalamus, form the diencephalon (see Figure 2.2). The hypothalamus is an important region for control of autonomic, neuroendocrine, limbic, and other circuits. The epithalamus encompasses several small nuclei, including the pineal body (Figure 2.11B), habenula, and parts of the pretectum.

Stretch Reflex
The monosynaptic stretch reflex is a well-studied reflex arc that provides rapid local feedback for motor control. The reflex arc begins with specialized receptors called muscle spindles, which detect the amount and rate of stretch in muscles (Figure 2.21). This information is transmitted to the distal processes of sensory neurons and is then conveyed via the dorsal roots into the spinal gray matter. In the spinal gray matter the sensory neurons form multiple synapses, including some direct synapses onto LMNs in the anterior horn. The LMNs project via the ventral roots back out to the muscle, causing...

Figure 2.20 The Thalamus
(A) Summary of thalamic inputs and reciprocal connections with the cortex.
(B) View of thalamus sitting on top of brainstem, demonstrating the major thalamic nuclear divisions. (The posterior portion of the reticular nucleus has been removed.)

Figure 2.21 Neural Circuit for Deep Tendon (Muscle Stretch) Reflex
Twitch muscle stretch elicited by tapping the tendon causes agonists (triceps) to contract and antagonists (biceps) to relax.
it to contract. Damage anywhere in this pathway (see Figure 2.21) can cause the reflex to be diminished or absent.

In addition to the monosynaptic pathway, theafferent sensory neuron forms synapses onto excitatory and inhibitory interneurons in the spinal gray matter, which in turn make synapses onto LMNs. Thus, local circuits in the spinal cord can use sensory information to regulate the activity of LMNs without conscious input from higher centers. There are, nevertheless, descending pathways that modulate the activity of the stretch reflex. As we will learn, if these higher centers or their descending pathways are damaged, the stretch reflex may become hyperactive or hypotactive. Thus, by testing the stretch reflex on neurologic exam, one obtains information about multiple pathways, including sensory neurons and motor neurons in the PNS, and descending modulatory pathways in the CNS. Since the stretch reflex is often tested on neurologic exam by tapping over a tendon with the reflex hammer (see Chapter 3, or www.neuroexam.com), this is also commonly known as a deep tendon reflex.

**Brainstem and Cranial Nerves**

The overall structure of the brainstem can be seen in Figure 2.22. As discussed earlier, it is composed of the midbrain, pons, and medulla. The brainstem is connected to the diencephalon rostrally, the cerebellum dorsally, and the spinal cord caudally (see Figure 2.21). Most of the cranial nerves arise from the brainstem. The cranial nerves are analogous in some ways to the spinal nerves, having both sensory and motor functions. However, they also
As was suggested with the cerebral hemispheres (Figure 2.11), at this point you should become acquainted with the brainstem and cranial nerves by covering the labels in Figure 2.22A-C and attempting to name as many structures as possible. Also, cover the right columns in Table 2.5 and name the cranial nerves and their main functions. Like the cerebral hemispheres, the brainstem and cranial nerves will become familiar companions throughout this text.

### Table 2.5 Overview of the Cranial Nerves

<table>
<thead>
<tr>
<th>NERVE</th>
<th>NAME</th>
<th>FUNCTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>CN I</td>
<td>Olfactory nerve</td>
<td>Olfaction</td>
</tr>
<tr>
<td>CN II</td>
<td>Optic nerve</td>
<td>Vision</td>
</tr>
<tr>
<td>CN III</td>
<td>Oculomotor nerve</td>
<td>Extraretinal muscles, those innervated by CN IV and VI; parasympathetic to pupil constrictor and ciliary muscles of lens for near vision</td>
</tr>
<tr>
<td>CN IV</td>
<td>Trochlear nerve</td>
<td>Superior oblique muscle; causes the eye to move downward and to rotate inward (depression and intorsion)</td>
</tr>
<tr>
<td>CN V</td>
<td>Trigeminal nerve</td>
<td>Sensations of touch, pain, temperature; vibration; and joint position for the face, mouth, nasal sinuses, and teeth; muscles of mastication; tensor tympani muscle</td>
</tr>
<tr>
<td>CN VI</td>
<td>Abducens nerve</td>
<td>Lateral rectus muscle; causes abduction (outward movement) of the eye</td>
</tr>
<tr>
<td>CN VII</td>
<td>Facial nerve</td>
<td>Muscles of facial expression; also stapedius muscle and part of gag reflex; taste from anterior two-thirds of tongue; sensation from a region near the ear; parasympathetic causing lacrimation and supplying the submaxillar and sublingual salivary glands</td>
</tr>
<tr>
<td>CN VIII</td>
<td>Vestibulocochlear nerve</td>
<td>Hearing; vestibular sensation</td>
</tr>
<tr>
<td>CN IX</td>
<td>Glossopharyngeal nerve</td>
<td>Stylopharyngeous muscle; taste from posterior one-third of tongue; sensation from posterior pharynx, and from a region near the ear; chemo- and baroreceptors of the carotid body; parasympathetics to the parotid gland</td>
</tr>
<tr>
<td>CN X</td>
<td>Vagus nerve</td>
<td>Pharyngeal muscles (swallowing); laryngeal muscles (voice box); parasympathetics to the heart, lungs, and digestive tract up to the esophageal fascia; taste from epiglottis and pharynx; sensation from the pharynx, posterior meninges, and a region near the ear; aortic arch chemo- and baroreceptors</td>
</tr>
<tr>
<td>CN XI</td>
<td>Spinal accessory nerve</td>
<td>Sternumostomal muscle; upper part of the trapezius muscle</td>
</tr>
<tr>
<td>CN XII</td>
<td>Hypoglossal nerve</td>
<td>Intrinsics muscles of the tongue</td>
</tr>
</tbody>
</table>

The brainstem often cause impaired consciousness indirectly when they exert pressure on the brainstem through mass effect, thus distorting or compressing the reticular formation.

### Limbic System

Several structures in the brain are referred to collectively as the limbic system because they are located near the medial edge or fringe (limbus in Latin) of the cerebral cortex (Figure 2.24A). These structures have evolved from a system devoted mainly to olfaction in simpler animals to perform diverse functions, including the regulation of emotions, memory, appetitive drives, and autonomic and neuroendocrine control. The limbic system includes certain cortical areas located in the medial and anterior temporal lobes (Figure 2.24A), anterior insula (Figure 2.24B), inferior medial frontal lobes, and cingulate gyri. It also includes deeper structures, such as the hippocampal formation and the amygdala, located within the medial temporal lobes (Figure 2.24A). Several nuclei in the medial thalamus, hypothalamus, basal ganglia, septal area, and brainstem. These areas are interconnected by a variety of pathways, including the fornix, a paired, arch-shaped white matter structure that connects the hippocampal formation to the hypothalamus and septal nuclei (Figure 2.24A).

Lesions in the limbic system can cause deficits in the consolidation of immediate recall into longer-term memories. Thus, patients with lesions in these areas may have no trouble recalling remote events but have difficulty forming new memories. In addition, limbic dysfunction can cause behavioral changes and may underlie a number of psychiatric disorders. Finally, epileptic seizures most commonly arise from the limbic structures of the medial temporal lobe, resulting in seizures that may begin with emotions such as fear, memory distortions such as déjà vu, or olfactory hallucinations.

### Association Cortex

In addition to the primary motor and sensory areas described earlier, the cerebral cortex contains a large amount of association cortex (Figure 2.25), which carries out higher-order information processing. In unimodal association cortex, higher-order processing takes place mostly for a single sensory or motor
Language is usually perceived first by the primary auditory cortex in the superior temporal lobe when we are listening to speech or by the primary visual cortex in the occipital lobes when we are reading. From here, cortical–cortical association fibers convey information to Wernicke's area in the dominant (usually left) hemisphere (see Figure 2.25). Lesions in Wernicke's area cause deficits in language comprehension, also sometimes called receptive or sensory aphasia, or Wernicke's aphasia. Broca's area is located in the frontal lobe, also in the left hemisphere, adjacent to the areas of primary motor cortex involved in moving the lips, tongue, face, and larynx. Lesions in Broca's area cause deficits in the production of language, with relative sparing of language comprehension. This is called expressive or motor aphasia, or Broca's aphasia, which can be remembered by the mnemonic "Broca's broken phonics." ("Phonics" means "mouth in Spanish.")

The parietal lobe is divided by the intraparietal sulcus into a superior and inferior parietal lobule (see Figures 2.11A and 2.25). Lesions in the inferior parietal lobule in the left hemisphere can produce an interesting constellation of abnormalities, including difficulty with calculations, right–left confusion, inability to identify fingers by name (finger agnosia), and difficulties with written language. This group of abnormalities is called Gerstmann's syndrome.

Performance of complex motor tasks, such as brushing one's teeth or throwing a baseball, requires higher-order planning before the primary motor cortex can be activated. Motor planning appears to be distributed in many different areas of cortex. Thus, diffuse lesions of the cortex, or even more focal lesions affecting the frontal or left parietal lobe, can produce abnormalities in motor conceptualization, planning, and execution called apraxia.
The parietal lobes also play an important role in spatial awareness. Thus, lesions in the parietal lobe, especially in the nondominant (usually right) hemisphere often cause a distortion of perceived space and neglect of the contralateral side. For example, right parietal lesions can cause left hemineglect. With this syndrome, patients will often ignore objects in their left visual field, but they may see them if their attention is strongly drawn to that side. They may draw a clock face without filling in any numbers on the left side of the clock. They may also be completely unaware of the left side of their body, thinking, for example, that their left arm belongs to someone else, and they may be unaware of any weakness or other deficits on that side. Unawareness of a deficit is called anosognosia (from the Greek a, "lack," nous, "disease," gnômi, "knowledge").

Patients may also display a phenomenon called extinction, in which a tactile or visual stimulus is perceived normally when it is presented to one side only, but when it is presented on the side opposite the lesion simultaneously with an identical stimulus on the normal side, the patient neglects the stimulus on the side opposite the lesion. These severe abnormalities in spatial orientation and awareness are less common in lesions of the dominant (usually left) parietal lobe, possibly because the dominant hemisphere is more specialized for language than it is for visuospatial functions.

The frontal lobes are the largest hemispheres and contain vast areas of association cortex (see Figure 2.25). Lesions in the frontal lobes cause a variety of disorders in personality and cognitive functioning. Frontal release signs are "primitive" reflexes that are normal in infants, such as grasp, root, suck, and snout reflexes, but that can also be seen in adults with frontal lobe lesions. In addition, patients with frontal lobe lesions may have particular difficulty when asked to perform a sequence of actions repeatedly, or to change from one activity to another. In doing these tasks they tend to perseverate, meaning that they repeat a single action over and over without moving on to the next one. Personality changes with frontal lobe lesions may include impaired judgment, a cheerful lack of concern about one's illness, inappropriate joking, and other disinhibited behaviors. Other patients with frontal lobe lesions may be abulia (opposite of ebuliunt), with a tendency to stare passively and to respond to commands only after a long delay. Frontal lesions can also cause a characteristic unsteady gait, in which the feet shuffle close to the floor, and urinary incontinence. Lesions in the visual association cortex in the parieto-occipital and inferior temporal lobes can produce a variety of interesting phenomena, including prosopagnosia (inability to recognize faces), achromatopsia (inability to recognize colors), palinopsia (perception or reappearance of an object viewed earlier), and other phenomena. Seizures in the visual association cortex can cause elaborate visual hallucinations.

### Blood Supply to the Brain and Spinal Cord

There are two pairs of arteries that carry all the blood supply to the brain and one pair of draining veins (Figure 2.26A, B). The internal carotid arteries form the anterior blood supply, and the vertebral arteries, which join together in a single basilar artery, form the posterior blood supply (see Figure 2.26A). The anterior and posterior blood supplies from the carotid and vertebral-basilar systems, respectively, join together in an anastomotic ring at the base of the brain called the circle of Willis (Figure 2.26C). The main arteries supplying the cerebral hemispheres arise from the circle of Willis. Ordinarily, however, the anterior and middle cerebral arteries derive their main blood supply...
supply from the internal carotid arteries (anterior circulation), while the posterior cerebral arteries derive their main supply from the vertebrobasilar system (posterior circulation). The main arteries supplying the brainstem and cerebellum also arise from the vertebral and basilar arteries. These include the superior, anterior inferior, and posterior inferior cerebellar arteries. Venous drainage for the brain is provided almost entirely by the internal jugular veins (see Figure 2.26B).

The spinal cord receives its blood supply from the anterior spinal artery, which runs along the ventral surface of the cord in the midline and from the paired posterior spinal arteries, running along the right and left dorsal surfaces of the cord (see Figure 6.5). The anterior and posterior spinal arteries are supplied in the cervical region mainly by branches arising from the vertebral arteries (see Figure 2.26C). In the thoracic and lumbar regions, the spinal arteries are supplied by radicular arteries arising from the aorta.

Conclusions

In this chapter we have reviewed the overall structure and organization of the nervous system. In addition, we have discussed in general terms the functions of each of the major areas in the brain, spinal cord, and peripheral nervous system, and we have briefly reviewed the blood supply to the brain. This overview should provide a framework upon which important details will be filled in and reinforced through clinical cases in the chapters that follow. It also provides the necessary background for the next chapter, in which we will introduce the neurologic exam and explore what each portion of the exam can teach us about neuroanatomy. Thus you, the reader, have completed the rough sketch and now have before you an undertaking that will require innumerable finer and finer brush strokes, each subtly enhancing the final composition.

References

Carpentier MB. 1991. Core Text of Neuroanatomy. 4th Ed. Williams & Wilkins, Baltimore, MD.
The Neurologic Exam as a Lesson in Neuroanatomy

Throughout this book, we will encounter case presentations that include findings from the neurologic exam: "A 37-year-old woman suddenly developed pain and numbness in her right shoulder and fingers. Her general physical exam was unremarkable. A neurologic exam showed that her mental status and cranial nerves were normal; motor exam was notable for diminished right triceps strength; reflexes were absent in the right triceps muscle; coordination and gait were normal; and sensation was normal except for diminished pain and temperature sensation in her right index and middle fingers." Performing the neurologic exam carefully, and presenting findings clearly, are crucial to accurately diagnosing and effectively treating patients. Here we will learn about each part of the neurologic exam and its basis in functional neuroanatomy.
Overview of the Neurologic Exam

The neurologic exam as a diagnostic tool gained mythical proportions in the pre-CT/MRI era, when great clinicians could pigeonhole a lesion in the nervous system with often astounding accuracy. Decisions for surgery and other interventions were frequently made entirely on the basis of the neurologic history and physical findings. Today, with the availability of modern imaging techniques, the neurologic exam takes on a new and equally important role in diagnosis and management. Rather than serving as an end in and of itself, the neurologic exam today is a critical way station in the clinical decision-making process. Does the patient who just collapsed on the street have cardiac disease or an intracranial bleed? Is the patient with leg weakness and numbness suffering from degenerative joint disease or from impinging spinal cord compression? Does the patient with nausea and vomiting need a gastroenterology consult, a head CT, or emergency interventions to lower dangerously elevated intracranial pressure? These, and many similar questions that frequently arise for health care providers in all subspecialties, can quickly be answered by a carefully performed neurologic exam.

We will study the neurologic exam in this chapter with two goals in mind. First, since most of the remainder of the book is based on clinical case presentations, it is important for you to become familiar with the neurologic exam and how to interpret normal and abnormal findings. Second, we will use the neurologic exam in conjunction with the material presented in Chapter 2 to attain an overview of neuroanatomical function and clinical localization.

Although there are some variations in style among clinicians, we will describe the neurologic exam here with a fairly conventional format. This consists of the following six subdivisions:

1. Mental status
2. Cranial nerves
3. Motor exam
4. Reflexes
5. Coordination and gait
6. Sensory exam

Table 3.1 provides a more detailed outline of the neurologic exam as it will be presented here.

As we discussed in Chapter 1, the neurologic exam is just one part of patient evaluation. Although we discuss it here separately, the neurologic exam should always be performed and interpreted in the context of a more general assessment. This includes the patient history, general physical exam, which includes the neurologic exam as one part, and finally, other diagnostic tests, such as radiological studies and blood tests. Review the neurologic information that can be learned from the general physical exam as discussed in Chapter 1. Some parts of the general exam with special neurologic significance are again summarized in Table 3.2.

A unique feature of the neurologic exam is that it tests function. Each part of the neurologic exam should be used to titrate the patient's level of function. To do this, several tests should be used, ranging from the easiest to the most difficult. With each examination, record the tests a patient can and cannot perform. This allows comparison with subsequent examinations, so that changes in the patient's status can be determined accurately.

In the first section of this chapter we will describe how each part of the neurologic exam is performed. We will include discussions of what is being tested, correlating clinical findings with neuroanatomy. Much of the material in this first section is also covered in neuroexam.com (discussed next), where it is supplemented by video demonstrations.

Table 3.1 Outline of the Neurologic Exam

| I. MENTAL STATUS | 1. Level of alertness, attention, and cooperation |
| 2. Orientation |
| 3. Memory |
| Remote memory |
| II. LANGUAGE |
| 1. Spontaneous speech |
| Comprehension |
| Naming |
| Repetition |
| Reading |
| Writing |
| III. MOTOR EXAM |
| 1. Observation |
| Enervatory movements, tremor, hypokinesia |
| IV. SENSORY EXAM |
| 1. Primary sensation— asymmetry, sensory level |
| 2. Sensory snowballing |
| 3. Vibratory sensation |
| 4. Position sense |
| 5. Tactile (two-point) discrimination |

The remaining sections of this chapter describe the usefulness of the neurologic exam in a variety of special circumstances. Since impairment on any portion of the exam may interfere with the ability to test many other functions, examination strategies and limitations in these situations are discussed. Cont is a special situation in which the neurologic exam is pivotal in evaluation; therefore, a separate section is devoted to this topic. We also briefly discuss the neurologic exam in brain death and in patients with conversion disorder, malingering, and related disorders, before presenting a minimal screening form of the neurologic exam at the conclusion of the chapter.

Table 3.2 Parts of the General Physical Exam with Special Neurologic Significance

| Vital signs, including orthostatic |
| Ophthalmoscopic exam |
| Signs of cranial trauma |
| Brain death |
| Meningismus |
| Straight-leg raising |
| Racial tone |

Note: See also Chapter 1.
The material presented here may be difficult to absorb fully on the first pass, either in print or on the Web. However, by referring back to it while attempting to localize lesions in the clinical cases, you will gradually become proficient in understanding both the neurologic exam and neuroanatomy.

neuroexam.com

A picture, or better yet, a moving picture is worth a thousand words. It is difficult to adequately describe in print the technique used in performing many aspects of the neurologic exam. Therefore, we have provided an interactive website, neuroexam.com, which demonstrates through brief streaming video clips how to perform each part of the neurologic exam. The website includes much of the text contained in the next section, "The Neurologic Exam: Examination Technique and What Is Being Tested." Therefore, if you have access to the Internet, we suggest that you now surf over to neuroexam.com while reading the next section (text from this section also appears on the website). Note, however, that the second half of this chapter, covering the neurologic exam in a variety of special situations, including coma, does not appear on the website.

Some may prefer to read from the book and view video segments selectively. Therefore, in this chapter, and elsewhere in the book when discussing the neurologic exam, we will provide a cross-reference to the relevant video segment on neuroexam.com. The segments can be accessed directly through the "Video Menu" on the website. Alternatively, rather than viewing individual segments, the complete exam can be viewed from start to finish by watching The NeuroExam Video (see "How to Use This Book").

The Neurologic Exam: Examination Technique and What Is Being Tested

In this section we will describe the neurologic examination (see Table 3.1) and what is being tested by each part of the exam. Like the general physical examination, different parts of the neurologic exam may be done in more or less detail depending on the clinical suspicion that a particular lesion is present. For example, an emergency neurologic exam in a comatose patient can be performed in less than 2 minutes (see the "Coma Exam" section). In a patient where the suspicion for focal findings on neurological exam is low, a "screening exam" can be completed in the office setting in about 10 minutes, as described at the end of this chapter. In contrast, in a patient with unusual findings, where the diagnosis is uncertain, detailed testing for up to an hour may be required. Sometimes, certain parts of the exam can be combined, or performed in a slightly different order, to minimize the number of times the patient has to change positions. Understanding how to best tailor the exam to the clinical situation comes with experience and practice. The accomplished clinician uses the neurologic exam as a flexible tool. In experienced hands, the neurologic exam remains an unparalleled method both to screen for unexpected lesions and to test hypotheses for localization.

1. Mental Status

There are many different versions of the mental status exam. The structure provided here follows a fairly standard format and is organized around the anatomy of the brain, as discussed in the section "Association Cortex" in Chapter 2 (see also Chapters 16, 18, and 19). Thus, we begin with tests that involve global brain function and that determine how well we will be able to perform the rest of the exam (level of alertness, attention, and cooperation). We next ask a few standard questions that make for easy comparisons between different patients or different exams of the same patient (orientation). This part of the exam is followed by testing of limbic and global functions (memory); testing of dominant (usually left) hemisphere language functions (language); and additional testing for left parietal dysfunction (Korsakoff's syndrome), right parietal dysfunction (neglect and construction), and frontal dysfunction (sequencing tasks and frontal release signs). Finally, we conclude with a few more tests that are less localizing but provide important clues about brain dysfunction (apaxia, logic and abstraction, delusions, hallucinations, and mood).

LEVEL OF AWARENESS, ATTENTION, AND COOPERATION. Be as specific as possible in documenting the level of alertness, making note of what the patient can or cannot do in response to which stimuli (see the section "Coma Exam" later in this chapter). One can test attention by seeing if the patient can remain focused on a single task, such as spelling a short word forward and backward (W-O-R-L-D/L-R-O-W is a standard), repeating a string of integers forward and backward (digit span), or naming the months forward and then backward (see neuroexam.com Video 4). Normal digit span is six or more forward, and four or more backward, depending slightly on age and education. It normally takes up to twice as long to recite months backward as forward. Note that these tests of attention depend on language, memory, and some logic functions as well. Degree of cooperation should be noted, especially if it is abnormal, since this will influence many aspects of the exam.

What Is Being Tested? Level of consciousness is severely impaired in damage to the brainstem reticular formation, and in bilateral lesions of the thalamus or cerebral hemispheres (see Figure 2.23). It may also be mildly impaired in unilateral cortical or thalamic lesions. Toxic or metabolic factors are also common causes of impaired consciousness because of their effects on the structures mentioned here (see KCC 14.2).

Generalized impaired attention and cooperation are relatively non-specific abnormalities that can occur in many different focal brain lesions, in diffuse abnormalities such as dementias or encephalitis, and in behavioral or mood disorders (see KCC 19.14-19.16).

ORIENTATION: A CAVEAT TO THOSE WHO WRITE "AOKO." Ask for the patient's full name, the location, and the date, and note the exact response (see neuroexam.com Video 5). It is common practice to use brief phrases in clinical notes such as "alert and oriented" or "alert and oriented to person, place, and time"—abbreviated as "AOKO"—as a substitute for documenting the full mental status exam. Given realistic time constraints, it is probably reasonable in non-neurologic patients with normal mental status to write "AOKO," as long as the meaning is clear. For patients with compromised mental status, however, it is very important to document specifically the questions they were asked and how they answered. This is really the only way to detect changes in a patient's mental status when different doctors are following a patient. For example, for the orientation section on a patient Harry Smith, you should write the following:

Name: "Harry Smith"
Location: "Hospital," but does not know which one
Date: "19/2," and does not know month, date, or season
You should never write instead: "The patient was A&O," since this is ambiguous and makes it hard to know what the patient’s true mental status was at the time of the exam.

**What Is Being Tested?** The main usefulness of this set of questions is that it is so standard. It tests mainly recent and longer-term memory (see below), but as in all other parts of the exam, the response is also influenced by level of alertness, attention, and language capabilities.

**MEMORY.** Recent memory. Ask the patient to recall three items or a brief story for a delay of 3 to 5 minutes (see neuroexam.com Video 6). Be sure the information has been registered by asking the patient to repeat it immediately before (initiating the delay). Provide distractions during the delay to prevent the patient from rehearsing the items repeatedly. A timer, such as a digital watch alarm, should be used to provide a consistent interval from patient to patient—and to prevent the examiner from forgetting to ask for the test items!

**Remote memory.** Ask the patient about historical or verifiable personal events (see neuroexam.com Video 7).

**What Is Being Tested?** Memory can be impaired on many different timescales. Impaired ability to register and recall something within a few seconds after it was said is an abnormality that bleeds into the category of impaired attention discussed earlier. If immediate recall is intact, then difficulty with recall after about 1 to 5 minutes usually signifies damage to the limbic memory structures located in the medial temporal lobes and medial diencephalon (see Figure 2.24; see also KCC 18.1). Dysfunction of these structures characteristically causes anterograde amnesia, meaning difficulty remembering new facts and events occurring after lesion onset, and retrograde amnesia, meaning impaired memory of events for a period of time immediately before lesion onset, with relative sparing of earlier memories. Loss of memory without these time characteristics may signify damage to areas other than the medial temporal and medial diencephalic structures, and can also occur in psychiatric amnesia.

**LANGUAGE.**
1. **Spontaneous speech.** Note the patient’s fluency, including phrase length, rate, and abundance of spontaneous speech (see neuroexam.com Video 8). Also note tonal modulation and whether there are inappropriate or inadvertently substituted words or syllables, neologisms (nonsense words), or errors in grammar are present.
2. **Comprehension.** Can the patient understand simple questions and commands? Comprehension of grammatical structure should be tested as well; for example, “Mike was shot by John. Is John dead?” (See neuroexam.com Video 9.)
3. **Naming.** Ask the patient to name some easy (pen, watch, tie, etc.) and some more difficult (fingerboard, belt buckle, stethoscope, etc.) objects (see neuroexam.com Video 10). Naming parts of objects is often more difficult and should also be tested. Write down what was said to enable follow-up comparisons.
4. **Repetition.** Can the patient repeat single words and sentences (a standard is “no ifs, ands, or buts”)? Again, titrate function using tasks that range from easy to difficult, and write down what the patient says. (See neuroexam.com Video 11.)
5. **Reading.** Ask the patient to read aloud single words, a brief passage, and the front page of the newspaper and test for comprehension.
6. **Writing.** Ask the patient to write their name and write a sentence. (See neuroexam.com Video 12.)

**What Is Being Tested?** Different kinds of language abnormalities are caused by lesions in the dominant (usually left) frontal lobe, including Broca’s area; the left temporal and parietal lobes, including Wernicke’s area (see Figure 2.25); subcortical white matter and gray matter structures, including thalamus and caudate nucleus; as well as the nondominant hemisphere. For further details regarding the neuroanatomy of specific language disorders, see Chapters 2 and 19.

**CALCULATIONS.** Right-left confusion and finger agnosia can both be quickly screened for with the classic command, “Touch your right ear with your left thumb.” (See neuroexam.com Video 14.)

**APPRA XIA.** The term apraxia will be used here to mean inability to follow a motor command that is not due to a primary motor deficit or a language impairment. It is caused by a deficit in higher-order planning or conceptualization of the motor task. “You can test for apraxia by asking the patient to do complex tasks, using commands such as ‘pretend to comb your hair’ or ‘pretend to strike a match and blow it out,’ or ‘see neuroexam.com Video 15.” Patients with apraxia perform awkward movements that only minimally resemble those requested, despite having intact comprehension and an otherwise normal motor exam. This kind of apraxia is sometimes called ideomotor apraxia. In some patients, rather than affecting the distal extremities, apraxia can involve primarily the mouth and face, or movements of the whole body, such as walking or turning around.

Unfortunately, the term “apraxia” has also been attached to a variety of other abnormalities—for example, “constructional apraxia” in patients who have visuospatial difficulty drawing complex figures, “ocular apraxia” in patients who have difficulty directing their gaze, “dressing apraxia” in patients who have difficulty getting dressed, and so on. It is unclear at present whether these various types of “apraxia” are related in some way or are caused by completely different mechanisms.

**What Is Being Tested?** Although apraxia indicates brain dysfunction, it can be caused by lesions in many different regions, so exact localization is often difficult. Apraxia is commonly present in lesions affecting the language areas and adjacent structures of the dominant hemisphere.
This may make it challenging to prove that the deficit is apraxia rather than impaired language comprehension. The distinction can often be made by asking patients to perform a task, and then if they fail, demonstrating several tasks and asking them to choose the correct one.

**NEGLIGENCE AND CONSTRUCTIONS.** Hemineglect is an abnormality in attention to one side of the universe that is not due to a primary sensory or motor disturbance. In sensory neglect, patients ignore visual, somatosensory, or auditory stimuli on the affected side, despite intact primary sensation (see KCC 19.9). This can often be demonstrated by testing for **extinction on double simultaneous stimulation.** Thus, patients may detect a stimulus on the affected side when presented alone, but when stimuli are presented simultaneously on both sides, only the stimulus on the unaffected side may be detected. In motor neglect, normal strength may be present; however, the patient does not move the affected limb unless attention is strongly directed toward it. Sensory and motor neglect are usually tested as part of the visual, auditory, somatosensory, and motor exams (to be described shortly). During the reading and writing portions of the language exam, patients may be noted to neglect one side of the page.

During the mental status exam, certain other aspects of neglect should be screened for. Patients should be asked, "Is anything wrong with you right now?" because patients with anosognosia may be strikingly unaware of severe deficits on the affected side of their body. For example, some patients with acute stroke who are completely paralyzed on the left side believe there is nothing wrong and may even be perplexed about why they are in the hospital. Some patients do not even comprehend that affected limbs belong to them. In addition, certain drawing tasks, such as asking the patient to trace a line on a clock face, can demonstrate neglect (see neuroexam.com Video 16). "**Construction tasks** involving drawing complex figures or manipulating blocks or other objects in space may be abnormal as a result of neglect or other visuospatial impairments (see neuroexam.com Video 17). However, constructional abilities can also be abnormal because of other cognitive difficulties, such as impaired sequencing (see next section) or apraxia.

**What Is Being Tested?** Hemineglect is most common in lesions of the right (nondominant) parietal lobe, causing patients to neglect the left side. Left-sided neglect can also occasionally be seen in right frontal lesions, right thalamic or basal ganglia lesions, and, rarely, in lesions of the right midbrain. In left parietal lesions a much milder neglect is usually seen affecting the patient’s right side. Abnormal constructions demonstrating neglect can occur with right parietal lesions. In addition, other abnormalities in constructions can occur as well, as a result of lesions in many other parts of the brain. Generally, however, impaired visuospatial function is more severe with damage to the nondominant (right) hemisphere (see also KCC 19.9, 19.10).

**SEQUENCING TASKS AND FRONTAL RELEASE SIGNS.** Patients with frontal lobe dysfunction may have particular difficulty in changing from one action to the next when asked to perform a repeated sequence of actions. For example, when asked to continue drawing a silhouette pattern of alternating triangles and squares, they may get stuck on one shape and keep drawing triangles (Figure 3.3); see also neuroexam.com Video 20). This phenomenon is called perseveration. The **Luria manual sequencing task,** in which the patient is asked to tap the table with a fist, open palm, and side of open hand and then to repeat the sequence as quickly as possible, is also a useful test for perseveration (see neuroexam.com Video 19). Another common finding is motor **impersistence,** a form of distractibility in which patients only briefly sustain a motor action in response to a command such as "Raise your arms" or "Look to the right." Ability to suppress inappropriate behaviors can be tested by the **Auditory Go-No-Go Test,** in which the patient moves a finger in response to one tap on the table, but must keep it still in response to two taps (see neuroexam.com Video 21). Additional support for frontal lobe pathology comes from the presence of frontal release signs, such as the grasp reflex (see neuroexam.com Video 18) described in the section on reflexes later in the chapter. Patients with frontal lobe lesions may also exhibit very slow responses termed **abulia** or may have changes in personality and judgment based on consecutive exams or reported by family members.

**What Is Being Tested?** The constellation of abnormalities just described helps localize lesions to the frontal lobes (see "Association Cortex" in Chapter 2 and KCC 19.11).

**LOGIC AND ABSTRACTION.** Can the patients solve simple problems such as the following (see neuroexam.com Video 22): "If Mary is taller than Jane, and Jane is taller than Ann, who is the tallest?" How do they interpret proverbs such as "Don’t cry over spilt milk"? How well can they understand similarities such as "How a car and an airplane alike?" How well can they generalize a complete series—for example, "Continue the following: AZ BY CX D?" A more detailed evaluation can be done, indicated, using formal neuropsychological testing batteries. Educational background must always be taken into account in interpretations of these tests.

**What Is Being Tested?** These functions can be abnormal in damage to a variety of brain areas involving higher-order association cortex and are not well localized.

**DELIUSIONS AND HALLUCINATIONS.** Does the patient have any delusional thought processes? Does the patient have auditory or visual hallucinations? Ask questions such as, "Do you ever hear things that other people don’t hear or see things that other people don’t see?" "Do you feel that someone is watching you or trying to hurt you?" "Do you have any special abilities or powers?" (See neuroexam.com Video 23.)

**What Is Being Tested?** These abnormalities can be seen in toxic or metabolic abnormalities and in other causes of diffuse brain dysfunction, and in primary psychiatric disorders (see KCC 18.3). In addition, abnormal sensory phenomena can be caused by focal lesions or seizures in visual, somatosensory, or auditory cortex, and thought disorders can be caused by lesions in the association cortex and limbic system.

**MOOD.** Does the patient have signs of depression, anxiety, or mania? Signs of major depression include depressed mood, changes in eating and sleeping patterns, loss of energy and initiative, low self-esteem, poor concentration, lack of enjoyment of previously pleasurable activities, and self-destructive or suicidal thoughts and behavior. Anxiety disorders are characterized by preoccupation with worrisome thoughts. Mania causes patients to be abnormally active and cognitively disorganized.

**What Is Being Tested?** These disorders are often considered psychiatric in origin and may be due to imbalances in neurotransmitter systems.
in several different areas of the brain (see KCC 18.3, 19.9). However, features of these disorders are also seen in focal brain lesions and in toxic or metabolic abnormalities such as thyroid dysfunction.

Some of the most difficult and interesting diagnostic dilemmas arise because of overlap and confusion between psychiatric and neurologic disorders. Thus, depressed patients with somatization or conversion disorders (which will be discussed later in the chapter) often have complaints such as pain, numbness, weakness, or even seizure-like activity and are therefore referred to neurologists for evaluation. Likewise, neurologic disorders such as brain tumors, strokes, metabolic derangements, encephalitis, vasculitis, and so on can produce confusion states or bizarre behavior that may be misinterpreted as psychiatric in origin.

2. Cranial Nerves

Perhaps more than any other part of the neurologic exam, cranial nerve testing can raise red flags that suggest specific neurologic dysfunction rather than a systemic disorder. For example, there are many medical causes of lethargy, unsteadiness, headaches, or disorientation. However, any of these symptoms in conjunction with cranial nerve abnormalities strongly suggests brainstem dysfunction as the cause (see Chapters 12-14). Careful testing of the cranial nerves, therefore, can reveal crucial information to help pinpoint disorders in the nervous system. While learning to test the cranial nerves, refer to Figure 2.22 and Table 2.5.

Olfaction (CN II). Can the patient smell coffee or soap with each nostril? (see neuroexam.com Video 24.) Do not use noxious odors, since they may stimulate pain fibers (from CN V; CN II) is often not tested unless specific pathology such as a subfrontal brain tumor is suspected.

- **What Is Being Tested?** Impairment can be due to nasal obstruction, damage to the olfactory nerves in the nasal mucosa, damage to the nerves as they cross the cribiform plate, or intracranial lesions affecting the olfactory bulbs (see Figure 2.12C).

Optic Nerve Exam (CN II). Examine both retinas carefully with an ophthalmoscope (see neuroexam.com Video 25).

- **What Is Being Tested?** This exam allows direct visualization of damage to the retina or retinal vessels, optic nerve atrophic changes, papilledema (see KCC 5.3), and other important abnormalities.

**VISION (CN II).**

1. **Visual Acuity.** Test visual acuity for each eye separately (by covering one eye at a time) using an eye chart.

2. **Color Vision.** Test each eye separately for ability to distinguish colors. Test for red desaturation, a sign of subtle asymmetry in optic nerve function (as seen, for example, in optic neuritis described in KCC 11.4). By asking the patient to cover each eye alternately while looking at a red object and to report any relative dullness of the color in one eye (see neuroexam.com Video 26).

3. **Visual Fields.** Test visual fields for each eye by asking the patient to fixate straight ahead and to report when a finger can be seen moving in each quadrant. Alternatively, ask the patient to report how many fingers are being shown in each quadrant (see neuroexam.com Video 27). More precise mapping of visual fields can be done in the laboratory for patients who will be followed over time (see KCC 11.2). In comatose or uncooperative patients (discussed later in the chapter), visual fields can be tested roughly using blink-to-threat.

4. **Visual Extinction.** Test for visual extinction on double simultaneous stimulation by asking patients how many fingers they see when fingers are presented to both sides at the same time (see neuroexam.com Video 27). In visual extinction, a form of hemineglect, patients do not report seeing the fingers on the affected (usually left) side of the visual field, although they can see fingers when they are presented to that side alone.

- **What Is Being Tested?** Damage anywhere in the visual pathway from the eye to the cortex can cause specific deficits in the visual fields of one or both eyes (see also Figure 11.19). Importantly, some visual information from each eye crosses to the opposite side at the optic chiasm. Therefore, lesions in front of the optic chiasm (eye, optic nerve) cause visual deficits in one eye, while lesions behind the optic chiasm (optic tract, thalamus, white matter, visual cortex) cause visual field defects that are similar for both eyes.

Visual hemineglect or extinction is usually caused by contralateral parietal lesions, and less often by frontal or thalamic lesions. Neglect is usually more robust in lesions of the right hemisphere (see KCC 19.9).

Pupillary Responses (CN II, III). First, record the pupil size and shape at rest. Next, note the direct response, meaning constriction of the illuminated pupil, as well as the consensual response, meaning constriction of the opposite pupil (see neuroexam.com Video 29).

In an **afferent pupillary defect** there is a decreased direct response caused by decreased visual function in one eye. This can be demonstrated with the **swinging flashlight test**, in which the light is moved back and forth between the eyes every 2 to 3 seconds (see neuroexam.com Video 30). The afferent pupillary defect becomes obvious when the flashlight is moved from the normal to the affected eye, and the affected pupil dilates in response to light. Under normal conditions, the pupil constricts in response to light. Brief oscillations of pupillary size called ***hippus*** occur normally in response to light and should not be confused with an afferent pupillary defect.

Finally, test the pupillary response to accommodation. Normally the pupils constrict while fixating on an object being moved toward the eyes (see neuroexam.com Video 31).

- **What Is Being Tested?**

  1. **Direct Response (pupil illuminated).** The direct response is impaired in lesions of the ipsilateral optic nerve, the pretectal area, the ipsilateral parasympathetics traveling in CN III, or the pupillary constrictor muscle of the iris (see Figure 13.8).

  2. **Conensual Response (contralateral pupil illuminated).** The consensual response is impaired in lesions of the contralateral optic nerve, the pretectal area, the ipsilateral parasympathetics traveling in CN III, or the pupillary constrictor muscle (see Figure 13.8).

  3. **Accommodation (response to looking at something moving toward the eye).** Accommodation is impaired in lesions of the ipsilateral optic nerve, the ipsilateral parasympathetics traveling in CN III, or the pupillary constrictor muscle, or in bilateral lesions of the pathways from the optic tracts to the visual cortex. Accommodation is spared in lesions of the pretectal area that may impair the pupillary light response. See Chapter 13 for further details on the neuroanatomy of pupillary reflexes and pupillary abnormalities (see KCC 13.5).

Extraocular Movements (CN III, IV, VI). Check extraocular movements (eye movements) by having the patient look in all directions without moving their
head. While doing this, ask them if they experience any double vision. Test smooth pursuit by having the patient follow an object moved across their full range of horizontal and vertical eye movements (see neuromax.com Video 32).

Test convergence movements by having the patient fixate on an object as it is moved slowly toward a point right between the patient’s eyes. Also, observe the eyes at rest to see if there are any abnormalities such as spontaneous nystagmus (discussed shortly) or dysconjugate gaze (eyes not both fixated on the same point), resulting in diplopia (double vision).

Saccades are eye movements used to rapidly reposition one object to another. The examiner can test saccades by holding two widely spaced targets in front of the patient (such as the examiner’s thumb on one hand and index finger on the other) and asking the patient to look back and forth between the targets, e.g., by saying, “Now look at my finger . . . thumb . . . finger . . . thumb” (see neuromax.com Video 33).

Test optokinetic nystagmus (OKN) by moving a strip with parallel stripes on it in front of the patient’s eyes and asking them to watch the stripes go by (see neuromax.com Video 34). Normally, eye movements called nystagmus occur, consisting of an alternating slow phase with slow pursuit movements in the direction of strip movement, and a rapid phase with quick, saccadic re-orientations back to midline. OKN testing can be very useful in detecting subtle abnormalities or asymmetries in saccadic or smooth pursuit eye movements.

In certain or severely lethargic patients, eye movements can also be evaluated with oculocephalic or caloric testing (see “Coma Exam,” later in this chapter; see neuromax.com Video 35).

What Is Being Tested? Careful testing can often identify abnormalities in individual muscles or in particular cranial nerves (oculomotor, trochlear, or abducens)—in their course from the brainstem to the orbit, in the brainstem nuclei, or, finally, in the higher-order centers and pathways in the cortex and brainstem that control eye movements (review Table 2.5; see also Chapter 13 for more details). Spontaneous nystagmus can indicate toxic or metabolic conditions such as drug overdose or alcohol intoxication, or peripheral or central vestibular dysfunction (see “Hearing and Vestibular Sense” [CN VIII] below).

FACIAL SENSATION AND MUSCLES OF MASTICATION (CN V). Test facial sensation using a cotton wisp and a sharp object. Also test for tactile extinction using double simultaneous stimulation (see above). The corneal reflex, which involves both CN V and CN VII, is tested by touching each cornea gently with a cotton wisp and observing any asymmetries in the blink response (see neuromax.com Video 37).

Feel the masseter muscles during jaw clench (see neuromax.com Video 38). Test for a jaw jerk reflex by gently tapping on the jaw with the mouth slightly open (see neuromax.com Video 39).

What Is Being Tested? Facial sensation can be impaired by lesions of the trigeminal nerve (CN V), the trigeminal sensory nuclei in the brainstem, or ascending sensory pathways to the thalamus and somatosensory cortex in the postcentral gyrus (see Figures 7.9, 12.8). The corneal reflex is mediated by polysynaptic connections in the brainstem between the trigeminal (CN V) and facial (CN VII) nerves and can be impaired by lesions anywhere in this circuit (see KCC 12.4).

Extinction in the presence of intact primary sensation is usually caused by right parietal lesions.

Weakness of the muscles of mastication can be due to lesions in the upper motor neuron pathways synapsing upon the trigeminal (CN V) motor nucleus, in the lower motor neurons of the trigeminal motor nucleus in the pons or as they exit the brainstem to reach the muscles of mastication, in the neurovascular junctions, or in the muscles themselves.

Presence of a jaw jerk reflex is abnormal, especially if it is prominent. It is a sign of hyperreflexia associated with lesions of upper motor neuron pathways projecting to the trigeminal motor nucleus. Both the afferent and the efferent limbs of the jaw jerk reflex are mediated by CN V (see KCC 12.4).

MUSCLES OF FACIAL EXPRESSION AND TASTE (CN VII). Look for asymmetry in facial shape or in depth of frowns such as the nasolabial fold. Also look for asymmetries in spontaneous facial expressions and blinking. Facial weakness may be difficult to detect in cases where it occurs bilaterally, also known as facial diplegia, because the facial weakness is asymmetrical. Ask patients to smile, puff out their cheeks, clench their eyes tight, wrinkle their brow, and so on (see neuromax.com Video 40). Old photographs of the patient can often aid your recognition of subtle changes.

Check taste with sugar, salt, or lemon juice on cotton swabs applied to the lateral aspect of each side of the tongue (see neuromax.com Video 41). Like olfaction, taste is often tested only when specific pathology is suspected, such as in lesions of the facial nerve or in lesions of the gustatory nucleus (nucleus solitarius).

What Is Being Tested? Facial weakness can be caused by lesions of upper motor neurons in the corticobulbar motor cortex or descending CNS pathways, lower motor neurons in the ipsilateral facial nerve nucleus (CN VII) or exiting nerve fibers, the neuromuscular junction, or the face muscles. Note that the upper motor neurons for the upper face (the upper portions of the orbicularis oculi and the frontalis muscles of the forehead) project to the facial nuclei bilaterally (see Figure 12.13). Therefore, upper motor neuron lesions such as a stroke cause contralateral face weakness sparing the forehead, while lower motor neuron lesions such as a facial nerve injury typically cause weakness involving the whole ipsilateral face.

HEARING AND VESTIBULAR SENSE (CN VIII). Can the patient hear fingers rubbed together or words whispered just outside of the auditory canal and identify which ear hears the sound? (see neuromax.com Video 42). A tuning fork can be used to distinguish neural from mechanical conductive hearing problems (see KCC 12.5). Vestibular sense is generally not specifically tested except in the following important situations:

1. Patients with vertigo. Certain maneuvers can help distinguish central from peripheral lesions (see KCC 12.6; see also neuromax.com Video 43).

2. Patients with limitations of horizontal or vertical gaze. Testing the vestibulo-ocular reflex can help localize the lesion (see Chapter 13). The vestibulo-ocular reflex can be tested either using the oculocephalic maneuver, in which the eyes are held open and the head is turned rapidly either side to side or up and down, or by using caloric testing, in which cold or warm water is instilled into one ear, producing asymmetrical stimulation of the semicircular canals. Further details of these tests and their significance are provided in the section “Coma Exam” later in this chapter, and in KCC 12.6.

3. Patients in coma. The vestibulo-ocular reflex is often the only way to test eye movements in these patients (see discussion of comatose patients later in this chapter).

What Is Being Tested? Hearing loss can be caused by lesions in the acoustic and mechanical elements of the ear, the neural elements of the cochlea, or the acoustic nerve (CN VIII) (see Figure 12.15). After the hearing pathways enter the brainstem, they cross over at multiple levels and ascend bilaterally to the thalamus and auditory cortex (see Figure 12.16).
Therefore, clinically significant unilateral hearing loss is invariably caused by peripheral neural or mechanical lesions. Abnormalities in vestibular testing can be associated with lesions in the vestibular apparatus of the inner ear (see Figure 12.15), the vestibular portion of CN VIII, the vestibular nuclei in the brainstem, the cerebellum, or pathways in the brainstem (such as the medial longitudinal fasciculus) that connect the vestibular and oculomotor systems (see Figure 12.18). Further details are provided in Chapter 12 and in the section "The Neurologic Exam in the Comatose or Uncooperative Patient" later in this chapter.

PALATE ELEVATION AND GAG REFLEX (CN IX, X). Does the palate elevate symmetrically when the patient says, "Ahh" (see neuroexam.com Video 44)? Does the gag reflex when the posterior pharynx is brushed? The gag reflex needs to be tested only in patients with suspected brainstem pathology, impaired consciousness, or impaired swallowing. 

What Is Being Tested? Palate elevation and the gag reflex are impaired in lesions involving CN IX, CN X, the neuromuscular junction, or the pharyngeal muscles.

MUSCLES OF ARTICULATION (CN V, VII, IX, X, XII). Is the patient's speech hoarse, slurred, quiet, breathy, nasal, low or high pitched, and so on (see neuroexam.com Video 45)? It is often important to ask if the patient's speech has changed from baseline. Note that dysarthria (see KCC 12.8), or abnormally pronounced speech, is not the same as aphasia, which is an abnormality in language production or comprehension. 

What Is Being Tested? Abnormal articulation of speech can occur in lesions involving the muscles of articulation, the neuromuscular junction, or the peripheral or central portions of CN V, VII, IX, X, or XII. Furthermore, speech production can be abnormal as a result of lesions in the motor cortex, cerebellum, basal ganglia, or descending pathways to the brainstem.

STERNOCELOIDOMASTOID AND TRAPEZIUS MUSCLES (CN XI, XII). Ask the patient to shrug their shoulders, turn their head in both directions, and raise their head from the bed flexing forward against the force of your hands (see neuroexam.com Video 46).

What Is Being Tested? Weakness in the sternocleidomastoid or trapezius muscles can be caused by lesions in the muscles, neuromuscular junction, or lower motor neurons of the accessory spinal nerve (CN XII) (see KCC 12.7). Unilateral upper motor neuron lesions in the cortex or descending pathways cause contralateral weakness of the trapezius, with relative sparing of sternocleidomastoid strength. This may be analogous to upper motor neuron facial lesions sparing the upper portion of the face. When sternocleidomastoid weakness is present with upper motor neuron lesions, there is weakness of head turning away from the side of the lesion (see also KCC 13.10).

TONGUE MUSCLES (CN XII). Note any atrophy or fasciculations (spontaneous quivering movements) of the tongue while it is resting, on the floor of the mouth. Ask the patient to stick their tongue straight out and note whether it curves to one side or the other (see neuroexam.com Video 47). Ask the patient to move their tongue from side to side and push it forcefully against the inside of each cheek.

What Is Being Tested? Fasciculations and atrophy are signs of lower motor neuron lesions (see Table 3.3). Unilateral tongue weakness causes the tongue to deviate toward the weak side. Tongue weakness can result from lesions of the tongue muscles, a neuromuscular junction, the lower motor neurons of the hypoglossal nerve (CN XII), or the upper motor neurons originating in the motor cortex. Lesions of the motor cortex cause contralateral tongue weakness.

3. Motor Exam

The motor exam has several steps, including (1) observation, (2) inspection, (3) palpation, (4) muscle tone testing, (5) functional testing, and (6) strength testing of individual muscle groups. Each of these steps will now be discussed in turn.

Observation. Carefully observe the patient to detect any twitches, tremors, or other involuntary movements, as well as any unusual paucity of movement (see KCC 15.2, KCC 16.1). Note also the patient's posture.

What Is Being Tested? Involuntary movements and tremors are commonly associated with lesions of the basal ganglia or cerebellum (see KCC 15.2, KCC 16.1). Tremors can also occasionally be seen with peripheral nerve lesions.

Inspection. Inspect several individual muscles to see if muscle wasting, hypertrophy, or fasciculations are present (see neuroexam.com Video 48). The best muscles to look at for fasciculations in generalized lower motor neuron disorders are the intrinsic hand muscles, shoulder girdle, and thigh.

Palpation. In cases of suspected myositis, palpate the muscles to see if there is tenderness.

Muscle Tone Testing. Next test muscle tone. Ask the patient to relax, and then passively move each limb at several joints to get a feeling for any resistance or rigidity that may be present (see neuroexam.com Videos 49, 50).

What Is Being Tested? Many parts of the motor exam can help distinguish between upper motor neuron and lower motor neuron lesions (see Chapters 2 and 6). Recall that upper motor neurons project via the corticospinal tract to lower motor neurons located in the anterior horn of the spinal cord. Signs of lower motor neuron lesions (Table 3.3) include weakness, atrophy, fasciculations, and hyperreflexia (increased reflexes; see the section "Reflexes" later in this chapter). Signs of upper motor neuron lesions include weakness, hyperreflexia (increased reflexes), and increased tone. The hyperreflexia and increased tone seen with corticospinal lesions is apparently caused by damage to pathways that travel in close association with the corticospinal tract rather than directly by damage to the cor

| TABLE 3.3 Signs of Upper Motor Neuron (UMN) and Lower Motor Neuron (LMN) Lesions |
|------------------|------------------|------------------|
| SIGN             | UMN LESIONS      | LMN LESIONS      |
| Weakness         | Yes              | Yes              |
| Atrophy          | No¹              |                |
| Fasciculations   | No               | Yes              |
| Reflexes         | Increased⁶       | Decreased        |
| Tone             | Increased⁶       | Decreased        |

¹Mild atrophy may develop as a result of disease.
²With acute upper motor neuron lesions, reflexes and tone may be decreased.
Increased tone can occur in upper motor neuron lesions, but can also occur in basal ganglia dysfunction (see KCC 16.1). In addition, slow or awkward fine finger movements or toe tapping, in the absence of weakness, can signify a subtle abnormality of the corticospinal pathways, but can also occur in lesions of the cerebellum or basal ganglia.

**FUNCTIONAL TESTING.** Before formally testing strength in each muscle, it is useful to do a few general functional tests that help detect subtle abnormalities. Check for **drift** by having the patient hold up both arms or both legs and note whether there is any increase in tone and hyperreflexia. With time (hours to weeks), increased tone and hyperreflexia usually develop.

**STRENGTH OF INDIVIDUAL MUSCLE GROUPS.** Patterns of weakness can help localize a lesion to a particular cortical or white matter region, spinal cord level, nerve root, peripheral nerve, or muscle. Test the strength of each muscle group and record in a systematic fashion. It is wise to pair the testing of each muscle group, immediately with testing of its contralateral counterpart to enhance detection of any asymmetries. Muscle strength is often rated on a scale of 0/5 to 5/5 as follows:

- 0/5: no contraction
- 1/5: muscle flicker, but no movement
- 2/5: movement possible, but not against gravity (test the joint in its horizontal plane)
- 3/5: movement possible against gravity, but not against resistance by the examiner
- 4/5: movement possible against some resistance by the examiner (sometimes this category is subdivided further into 4+/5, 4/5, and 5/5)
- 5/5: normal strength

While testing muscle strength, it is important to keep in mind anatomical information such as which nerves, nerve roots, and brain areas control each muscle and to allow this information to guide the exam (see neuroexam.com Video 54-57). Also, compare proximal vs. distal weakness, because these features can sometimes suggest muscle versus nerve disease, respectively.

**What Is Being Tested?** A detailed discussion of patterns of muscle weakness and localization is provided in KCC 6.3 and in Chapters 8 and 9. The actions tested are also demonstrated through video clips on the website neuroexam.com. In Tables 3.4 and 3.5, we briefly summarize some of the main actions, muscle groups, peripheral nerves, and nerve roots tested during the motor exam.

### Table 3.4 Upper Extremity Strength Testing

<table>
<thead>
<tr>
<th>ACTION</th>
<th>MUSCLES</th>
<th>NERVES</th>
<th>NERVE ROOTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finger extension</td>
<td>Extensor digitorum, extensor indicis, extensor digiti minimi</td>
<td>Radial nerve (posterior interosseous nerve)</td>
<td>C7, C8</td>
</tr>
<tr>
<td>Thumb abduction in plane of palm</td>
<td>Abductor pollicis longus</td>
<td>Radial nerve (posterior interosseous nerve)</td>
<td>C7, C8</td>
</tr>
<tr>
<td>Finger abduction</td>
<td>Dorsal interossei, abductor digiti minimi</td>
<td>Ulnar nerve</td>
<td>C8, T1</td>
</tr>
<tr>
<td>Finger and thumb abduction in plane of palm</td>
<td>Adductor pollicis, palmar interossei</td>
<td>Ulnar nerve</td>
<td>C8, T1</td>
</tr>
<tr>
<td>Thumb opposition</td>
<td>Opponens pollicis</td>
<td>Median nerve</td>
<td>C8, T1</td>
</tr>
<tr>
<td>Thumb abduction perpendicular to plane of palm</td>
<td>Abductor pollicis brevis</td>
<td>Median nerve</td>
<td>C8, T1</td>
</tr>
<tr>
<td>Flexion at distal interphalangeal joints, digits 2, 3</td>
<td>Flexor digitorum profundus to digits 2, 3</td>
<td>Median nerve</td>
<td>C7, C8</td>
</tr>
<tr>
<td>Flexion at distal interphalangeal joints, digits 4, 5</td>
<td>Flexor digitorum profundus to digits 4, 5</td>
<td>Ulnar nerve</td>
<td>C7, C8</td>
</tr>
<tr>
<td>Wrist flexion and hand abduction</td>
<td>Flexor carpi radialis</td>
<td>Median nerve</td>
<td>C6, C7</td>
</tr>
<tr>
<td>Wrist flexion and hand abduction</td>
<td>Flexor carpi ulnaris</td>
<td>Ulnar nerve</td>
<td>C7, C6, T1</td>
</tr>
<tr>
<td>Wrist extension and hand abduction</td>
<td>Extensor carpi radialis</td>
<td>Radial nerve</td>
<td>C6, C6</td>
</tr>
<tr>
<td>Elbow flexion (with forearm supinated)</td>
<td>Brachioradialis</td>
<td>Musculocutaneous nerve</td>
<td>C5, C6</td>
</tr>
<tr>
<td>Elbow extension</td>
<td>Triceps</td>
<td>Radial nerve</td>
<td>C6, C7, C8</td>
</tr>
<tr>
<td>Arm abduction at shoulder</td>
<td>Deltoide</td>
<td>Axillar nerve</td>
<td>C5, C6</td>
</tr>
</tbody>
</table>

Note: When one nerve root is more important than the others, it is shown in boldface.

### Table 3.5 Lower Extremity Strength Testing

<table>
<thead>
<tr>
<th>ACTION</th>
<th>MUSCLES</th>
<th>NERVES</th>
<th>NERVE ROOTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hip flexion</td>
<td>Iliopsoas</td>
<td>Femoral nerve, and L1-L3 nerve roots</td>
<td>L1, L2, L3, L4</td>
</tr>
<tr>
<td>Knee flexion</td>
<td>Quadriceps</td>
<td>Femoral nerve</td>
<td>L2, L3, L4</td>
</tr>
<tr>
<td>Knee flexion</td>
<td>Hamstrings (semimembranosus, semitendinosus, biceps femoris)</td>
<td>Sciatic nerve</td>
<td>L5, S1, S2</td>
</tr>
<tr>
<td>Leg abduction</td>
<td>Gluteus medius, gluteus minimus, tensor fasciae latae</td>
<td>Superior gluteal nerve</td>
<td>L4, L5, S1</td>
</tr>
<tr>
<td>Leg adduction</td>
<td>Obturator externus, adductor longus, magnus, and brevis gracilis</td>
<td>Obturator nerve</td>
<td>L2, L3, L4</td>
</tr>
<tr>
<td>Toe dorsiflexion</td>
<td>Extensor hallucis longus, extensor digitorum longus</td>
<td>Deep peroneal nerve</td>
<td>L5, S1</td>
</tr>
<tr>
<td>Foot dorsiflexion</td>
<td>Tibialis anterior</td>
<td>Deep peroneal nerve</td>
<td>L4, L5</td>
</tr>
<tr>
<td>Foot plantar flexion</td>
<td>Triceps surae (gastrocnemius, soleus)</td>
<td>Tibial nerve</td>
<td>S1, S2</td>
</tr>
<tr>
<td>Foot eversion</td>
<td>Peroneus longus, peroneus brevis</td>
<td>Superficial peroneal nerve</td>
<td>L5, S1</td>
</tr>
<tr>
<td>Foot inversion</td>
<td>Tibialis posterior</td>
<td>Tibial nerve</td>
<td>L4, L5</td>
</tr>
</tbody>
</table>

Note: When one nerve root is more important than the others, it is shown in boldface.
tons can influence reflex amplitude. As in muscle strength testing, it is important to compare each reflex immediately with its contralateral counterpart so that any asymmetries can be detected. If you cannot elicit a reflex, you can sometimes bring it out by certain reinforcement procedures. For example, have the patient gently contract the muscle being tested by instructing the patient to raise the limb very slightly, or to concentrate on forcefully contracting a different muscle group just at the moment when the reflex is tested. When reflexes are very brisk, clonus is sometimes seen. This is a repetitive, vibratory contraction of the muscle that occurs in response to muscle and tendon stretch. Deep tendon reflexes are often rated according to the following scale:

- 0 absent reflex
- 1* trace, or seen only with reinforcement
- 2* normal
- 3* brisk
- 4* nonsustained clonus (i.e., repetitive vibratory movements)
- 5* sustained clonus

Deep tendon reflexes are normal if they are 1*, 2*, or 3* unless they are asymmetric or there is a dramatic difference between the arms and the legs. Reflexes rated as 0, 4*, or 5* are usually considered abnormal. In addition to clonus, other signs of hyperreflexia include spreading of reflexes to other muscles not directly being tested and crossed adduction of the opposite leg when the muscular aspect of the knee is tapped. Hoffmann's sign also indicates heightened reflexes. You can elicit this sign by having the patient's middle finger loosely and flicking the finger nail downward, causing the fingers to rebound slightly into extension (see neuroexam.com Video 69). If the thumb flexes and adducts in response, Hoffmann's sign is present.

- **What Is Being Tested?** Deep tendon reflexes (see Figure 2.21) may be diminished by abnormalities in muscles, sensory neurons, lower motor neurons, and the neuromuscular junction; acute upper motor neuron lesions; and mechanical factors such as joint disease. Abnormally increased reflexes are associated with upper motor neuron lesions (see Table 3.3).

Note that deep tendon reflexes can be influenced by age, metabolic factors such as thyroid dysfunction or electrolyte abnormalities, and the anxiety level of the patient. The main spinal nerve roots involved in testing the deep tendon reflexes are summarized in Table 3.6.

**PLANTAR RESPONSE.** Test the plantar response by scraping an object across the sole of the foot beginning from the heel, moving forward toward the small toe, and then arching medially toward the big toe (Figure 3.2). If normal, the response is downward contraction of the toes. The abnormal response, called Babinski's sign, is characterized by an upgoing big toe and fanning outward of the other toes. In some patients the toes are "silent," moving neither up nor down. If the toes are downgoing on one side and silent on the other, the side is considered abnormal. The presence of Babinski’s sign in an adult is always abnormal, but it is often present in infants, up to the age of about 1 year.

**What Is Being Tested?** Babinski's sign is associated with upper motor neuron lesions anywhere along the corticospinal tract. Note that it may not be possible to elicit Babinski's sign if there is severe weakness of the toe extensors.

A concise way to document reflexes at the biceps, triceps, brachioradialis, patellar, and Achilles tendons, as well as the plantar responses, is to illustrate them with a stick figure. An example for a normal patient is shown in Figure 3.3.

**TABLE 3.6 Deep Tendon Reflexes**

<table>
<thead>
<tr>
<th>REFLEX</th>
<th>MAIN SPINAL NERVE ROOTS INVOLVED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biceps</td>
<td>C5, C6</td>
</tr>
<tr>
<td>Brachioradialis</td>
<td>C5</td>
</tr>
<tr>
<td>Triceps</td>
<td>C7</td>
</tr>
<tr>
<td>Patellar</td>
<td>L4, L5</td>
</tr>
<tr>
<td>Achilles tendon</td>
<td>S1</td>
</tr>
</tbody>
</table>

**Figure 3.2 Plantar Response**

**REFLEXES TESTED IN SPECIAL SITUATIONS.** Additional reflexes are tested in special situations such as coma, spinal cord injury, frontal lobe dysfunction, and neurodegenerative disorders.

With suspected spinal cord damage, absence of certain normal reflexes can help localize the level and ascertain the severity of the lesion (Table 3.7). Elicit abdominal cutaneous reflexes by scraping the abdominal skin on each side, above and below the umbilicus, and observing the abdominal muscle contractions. Elicit the cremasteric reflex in males by scraping the upper inner thigh and observing ascent of the testicle. The bulbocavernous reflex is contraction of the rectal sphincter in response to pressure on the bulbocavernous muscle. In males this response can be elicited by compressing of the glans penis in females, since a Foley catheter is usually present in the urethra in this clinical setting, traction on the Foley catheter can elicit the response. Anal wink is contraction of the rectal sphincter in response to a sharp stimulus in the perianal area. Frontal lobe lesions in adults can cause the reemergence of certain primitive reflexes that are normally present in infants but are pathologic in adults. These so-called frontal release signs include the grasp, snout, root, and suck reflexes (see neuroexam.com Video 18 for a demonstration of the grasp reflex). Frontal release signs are sometimes tested for during the mental status exam if suspicion of frontal lobe pathology arises. Two other reflexes deserve mention, although they are less specific and can be seen in a wide variety of neurodegenerative conditions. Elicit the glabellar response by tapping with a finger repeatedly in the midline between the eyes and asking the patient to keep their eyes open. The normal patient may blink a few times, but the response then extinguishes. The abnormal response—continuing blinking with each tap (Myerson's sign)—is most commonly seen in neurodegenerative movement disorders such as Parkinson's disease. In the palmenmental reflex, squeezing the hypothenar eminence causes ipsilateral contraction of the mentalis muscles of the chin. This response is very nonspecific, and is present in some normal individuals.

**Figure 3.3 Reflex Stick Figure**

Commonly tested deep tendon reflexes and plantar responses are summarized pictorially using stick figures, a widespread clinical shorthand.

**TABLE 3.7 Additional Reflexes for Localizing Spinal Cord Lesions**

<table>
<thead>
<tr>
<th>REFLEX</th>
<th>SPINAL NERVE ROOTS INVOLVED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal cutaneous reflexes</td>
<td>T10-T12</td>
</tr>
<tr>
<td>Above umbilicus</td>
<td>T10-T12</td>
</tr>
<tr>
<td>Below umbilicus</td>
<td>L1-L2</td>
</tr>
<tr>
<td>Cremasteric reflex</td>
<td>S2-S4</td>
</tr>
<tr>
<td>Bulbocavernous reflex</td>
<td>S2-S4</td>
</tr>
<tr>
<td>Anal wink</td>
<td>S2-S4</td>
</tr>
</tbody>
</table>

**Figure 3.4 Reflex Stick Figure**

Commonly tested deep tendon reflexes and plantar responses are summarized pictorially using stick figures, a widespread clinical shorthand.
In patients with damage to descending motor pathways, posturing can sometimes be seen. Posturing consists of complex reflexes involving brainstem and spinal cord circuitry and will be described further in the section on the coma exam later in this chapter.

**What Is Being Tested?** Special reflexes tested in spinal cord lesions help localize the level of the damage (see Table 8.37, see also Table 8.1 and Figure 8.4). Frontal release signs support the localization of lesions to the frontal lobes (see KCC 19.11). The localizing value of posturing will be discussed in the "Coma Exam" section.

### 5. Coordination and Gait

Coordination and gait are usually described under a separate section because cerebellar disorders can disrupt coordination or gait while leaving other motor functions relatively intact. There is much overlap, however, between the systems being examined in this section and those examined in the earlier general motor exam section as well as in parts of the exam. Keep in mind that disturbances of coordination and gait can be caused by lesions in many systems other than the cerebellum.

The term **ataxia** is often used to describe the abnormal movements seen in coordination disorders (see KCC 15.2). In ataxia there are medium- to large-amplitude involuntary movements with an irregular oscillatory quality superimposed on and interfering with the normal smooth trajectory of movement (see Figure 3.4B). **Overshoot** is also commonly seen as part of atactic movements and is sometimes referred to as **past pointing** when target-oriented movements are being discussed. Another feature of coordination disorders is **dyssynergia**—that is, abnormal alternating movements.

Cerebellar lesions can cause different kinds of coordination problems depending on their location. One important distinction is between truncal ataxia and appendicular ataxia (see KCC 15.2). **Appendicular ataxia** affects movements of the extremities and is usually caused by lesions of the cerebellar hemispheres and associated pathways (see Figure 15.3). **Truncal ataxia** affects the proximal musculature, especially that involved in gait stability, and is caused by midline damage to the cerebellar vermis and associated pathways.

**APPENDICULAR COORDINATION.** Fine movements of the hands and feet, as discussed earlier under the general motor exam, should be tested. **Rapid alternating movements**, such as wiping one palm alternately with the palm and dorsum of the other hand, should be tested as well (see neuroexam.com Video 62). Perhaps the most popular test of coordination, however, is the **finger-nose-finger test**, in which the patient is asked to alternate touching the examiner's finger with his thumb and then back again (Figure 3.4; see also neuroexam.com Video 64). Ataxia is best revealed if the examiner's finger is held at the extreme of the patient's reach, and if the examiner's finger is occasionally moved suddenly to a different location. Test for overshoot by having the patient raise both arms suddenly from their lap to the level of your hand (see neuroexam.com Video 65). In addition, you can apply pressure to the patient's outstretched arms and then suddenly release it. To test the accuracy of movements in a way that requires very little strength, you can draw a line on the crease of the patient's thumb and then ask the patient to touch the line repeatedly with the tip of their forefinger (see neuroexam.com Video 63). This test can help distinguish between irregular waving movements caused by limb weakness and abnormal movements caused by ataxia.

Similar tests can be done with the legs. In the **heel-shin test** the patient is asked to touch the heel of one foot to the opposite knee and then to drag their

![Image](image-url)

Figure 3.4 Finger-Nose-Finger Test

(A) Normal patient. (B) Patient with ataxia.

**What Is Being Tested?** Normal performance of these motor tasks depends on the integrated functioning of multiple sensory and motor subsystems. These include position sense pathways, visual pathways, lower motor neurons, upper motor neurons, the basal ganglia, and the cerebellum. Thus, in order to convincingly demonstrate that abnormalities are due to a cerebellar lesion, one must first test for normal joint position sense, visuomotor strength, and reflexes and confirm the absence of involuntary movements caused by basal ganglia lesions. As already mentioned, appendicular ataxia is usually caused by lesions of the cerebellar hemispheres and associated pathways, while truncal ataxia (see the next two sections, on the Romberg test and gait) is often caused by damage to the midline cerebellar vermis and associated pathways (see Figures 15.3 and 15.9).

**ROMBERG TEST.** Ask the patient to stand with their feet together (touching each other). Then ask the patient to close their eyes. Remain close at hand in case the patient begins to sway or fall (see neuroexam.com Video 67).
What Is Being Tested? With the eyes open, three sensory systems provide input to the cerebellum to maintain truncal stability. These are vision, proprioception, and vestibular sense. If there is a mild lesion in the vestibular or proprioceptive systems, when the eyes are open the patient is usually able to compensate and remain stable. When the patient closes their eyes, however, visual input is removed and instability can be brought out. If there is a more severe proprioceptive or vestibular lesion, or if there is a midline cerebellar lesion causing truncal instability, the patient will be unable to maintain this position even with their eyes open. Note that instability can also be seen with lesions in other parts of the nervous system, such as upper or lower motor neurons or the basal ganglia, so these should be tested separately in other parts of the exam.

GAIT
A patient’s gait can be difficult to describe in a reproducible fashion. Observe the patient walking toward you and away from you in an open area with plenty of room. Note stance (how far apart the feet are), posture, stability, how high the feet are raised off the floor, trajectory of leg swing and whether there is circumduction (an arched trajectory in the sagittal plane), in the frontal plane, and degree of knee bending, arm swing, tendency to fall or sway in any particular direction, rate and speed, difficulty initiating or stopping gait, and any involuntary movements that are brought out by walking. Turn should also be observed closely. When following a patient over several visits, it may be useful to time them walking a fixed distance and to count the number of steps they took and the number of steps required to turn around. The patient’s ability to rise from a chair without assistance should also be recorded.

To bring out abnormalities in gait and balance, ask the patient to do more difficult maneuvers. Test tandem gait by asking the patient to walk a straight line while touching the heel of one foot to the toe of the other with each step (see neuroexam.com Video 68). Patients with unilateral ataxia caused by damage to the cerebellum (see Figure 15.3) or associated pathways will have particular difficulty with this task, since they tend to have a wide-based, unsteady gait, and become more unsteady when attempting to keep their feet close together. To bring out subtle gait abnormalities or ataxias, it may be appropriate in some cases to ask patients to perform so-called forced gait testing by asking them to walk on their heels, walk on their toes, walk on the insides or outsides of their feet, to stand or hop on one leg, or to walk up steps (see neuroexam.com Video 69).

Gait apraxia is a perplexing, and somewhat controversial, abnormality in which the patient is able to carry out all of the movements required for gait normally when lying down, but is unable to walk in the standing position. It is thought to be associated with frontal disorders or normal pressure hydrocephalus (see KCC 5.7).

What Is Being Tested? As with tests of appendicular coordination, gait involves multiple sensory and motor systems. These include vision, proprioception, vestibular sense, lower motor neurons, upper motor neurons, basal ganglia, the cerebellum, and higher-order motor planning systems in the association cortex. Once again, it is important to test each of these systems for normal function before concluding that a gait disturbance is caused by a cerebellar lesion. Localization and diagnosis of gait disorders is described further in KCC 6.5 and Table 6.6.

6. Sensory Exam
The sensory exam relies to a large extent on the ability or willingness of patients to report what they are feeling. It can therefore often be the most difficult part of the exam to interpret with certainty. Tests should be performed in all extremities, as well as on the face and trunk, with the patient’s eyes closed or covered to improve objectivity.

PRIMARY SENSATION, ASYMMETRY, SENSORY LEVEL
Light touch is best tested with a cotton-tipped swab, but a light finger touch will often suffice, as long as care is taken to make the stimulus fairly reproducible. You can test the relative sharpness of pain sensation by randomly alternating stimuli with the sharp or dull end of a safety pin (always use a new pin for each patient; see neuroexam.com Video 70). Temperature sensation can be tested with a cool piece of metal such as a tuning fork (see neuroexam.com Video 71). Test vibration sense by placing a vibrating tuning fork on the ball of the patient’s right or left large toe or fingers and asking them to report when the vibration stops (see neuroexam.com Video 72). Take care not to place the tuning fork on a bone, since bones conduct the vibration to much more proximal sites, where they can be detected by nerves far from the location being tested. Test joint position sense by moving one of the patient’s fingers or toes up and down and asking the patient to report which way it moves (see neuroexam.com Video 73). Hold the digit lightly by the sides while doing this so that tactile inputs don’t provide significant clues to the direction of movement. The digit should be moved very slightly because normal individuals can detect movements that are barely perceptible by eye. Two-point discrimination can be tested with a special pair of calipers, or with a bent paper clip, alternating randomly between touching the patient with one or both points (see neuroexam.com Video 74). The minimal separation (in millimeters) at which the patient can distinguish these stimuli should be recorded in each extremity, and compared side to side.

As in other parts of the exam, the patient’s deficits, as well as the anatomy of the nerves, nerve roots, and central pathways, should be used to guide the exam (see Chapters 7–9). Considerations should be made from one side of the body to the other and from proximal to distal on each extremity. Note especially if there is a sensory level corresponding to a particular spinal segment (see Figure 8.4) below which sensation abruptly changes, since such a change may indicate a spinal cord lesion requiring emergency intervention. Whenever there are uncertainties in the sensory exam, or other parts of the exam, a good strategy is to repeat the relevant portions of the exam several times.

CORTICAL SENSATION, INCLUDING EXTINCTION
Higher-order aspects of sensation, or cortical sensation, should be tested as well. To test graphesthesia, ask patients to close their eyes and identify letters or numbers that are being traced onto their palm or the tip of their finger (see neuroexam.com Video 75). To test stereognosis, ask patients to close their eyes and identify various objects by touch, using one hand at a time (see neuroexam.com Video 76). Test also for tactile extinction on double simultaneous stimulation (as described earlier; see neuroexam.com Video 77). Note that graphesthesia, stereognosis, and extinction cannot reliably be tested for unless primary sensation is intact bilaterally.

What Is Being Tested? Somatosensory deficits can be caused by lesions in peripheral nerves, nerve roots, the posterior columns or anterolateral sensory systems in the spinal cord or brainstem, the thalamus, or sensory cortex. Recall that position and vibration sense ascend in the posterior column pathway and cross over in the medulla, while pain and temperature sense cross shortly after entering the spinal cord and then ascend in the anterolateral pathway (see Figures 2.13, 2.18, and 2.19). Intact primary sensation with deficits in cortical sensation such as
agranulocytosis or osteoporosis suggests a lesion in the contralateral sensory cortex. Note, however, that severe cortical lesions can cause deficits in primary sensation as well. Extinction with intact primary sensation is a form of hemineglect that is most commonly associated with lesions of the right parietal lobes. Like other forms of neglect, extinction can also occasionally be seen in right frontal or subcortical lesions, or in left hemisphere lesions causing mild right hemineglect.

The pattern of sensory loss can provide important information that helps localize lesions to particular nerves, nerve roots, and regions of the spinal cord, brainstem, thalamus, or cortex (see KCC 7.5, and Chapters 8 and 9).

The Neurologic Exam as a Flexible Tool

In actual clinical practice, the neurologic exam just described is hardly ever performed in its entirety from start to finish. As we mentioned earlier, with experience, one learns how to perform a screening exam covering the most important parts of the assessment and then focuses on relevant portions in greater detail depending on the clinical situation. In the sections that follow, we will discuss some alternative exam strategies and limitations in interpretation in certain situations, as well as examination techniques used for the following special circumstances: coma, brain death, and somnolence.

Exam Limitations and Strategies

One of the more challenging aspects of the neurologic exam is that impairments in one area can affect the patient's ability to perform other parts of the exam. For example, during the mental status exam a patient is not fully alert, attentive, cooperative, and possessing intact language functions, then during the motor exam, detailed testing of each individual muscle group will not be possible. Therefore, the examiner must be prepared to modify the exam appropriately in the patient's limitations.

In addition to strategies for working around limitations, it is important to know when parts of the exam cannot be done reliably in different situations. Documentation of the patient's limitations and how they affected the exam are essential. For example, if a patient in a patient with impaired attention, it is preferable to write “joint position sense testing was unreliable due to impaired attention” rather than “joint position sense was poor.”

We will now describe a few specific strategies for examining patients with deficits. In mild to moderate impairment of alertness or attention, most aspects of the exam can be done with repeated stimulation of the patient. Patience is required. In severe impairment, the various strategies outlined later.

With mild to moderate impairment of language comprehension, patients can often understand some simple questions or commands, and sometimes have an easier time understanding gestures or demonstrations of the action desired. For impaired expression, the patient can be asked yes-no or multiple-choice questions. For testing memory, several objects can be hidden around the room and the patient can be asked to find them after a delay. Again, patience and creativity are essential.

With sensory and motor neglect, some patients will show an improvement when the beam is turned towards the affected side. With motor neglect, some patients show improved performance when their attention is repeatedly directed to the affected side, in response to pain, or during activities requiring bimanual coordination. When performing the motor exam on patients with apraxia, they may show improved strength if the movement is demonstrated or if their limbs are moved through the desired motion before allowing them to continue on their own. Sometimes, midline and appendicular motor functions are differentially affected. For example, some patients can close their eyes and stick out their tongue on command but cannot squeeze the examiner's hand. In motor impersistence, estimates of limb weakness or of gait deficits must be made based on any deficits in the brief movements achieved by the patient.

In patients with bilateral deafness, communication can usually be achieved by writing or using a sign language interpreter, and nonauditory language comprehension can still be tested. In patients who are unable to speak due to motor deficits, or who are intubated, expressive communication can often be achieved by providing the patient with a pen and paper, computer keyboard, or other device or code, that can be used for movements or blinking for patients with severe motor impairment (see KCC 14.1).

Numerous additional strategies can be employed for examining patients in special situations, some of which will be described in the sections that follow.

Coma Exam

The coma exam is much simpler than the exam in the awake patient. The same general format is used; however, the exam is shorter because many things cannot be tested without the patient's cooperation. An advantage of the short length of the coma exam is that it can be done quickly in emergency situations, thus enabling a rapid assessment of neurologic status that often yields critical information for patient care.

For patients who are neither fully awake nor fully unconscious, various elements of the coma exam and the exam in the awake patient should be combined. Similarly, for the unconscious but awake patient, some elements of the coma exam may be useful. Review the overall format of the coma exam shown in Table 3.8. Since many aspects of the coma exam are the same as in the general neurologic exam, these elements will be described more briefly here; refer to the previous discussion and earlier sections titled "What Is Being Tested?" for details.

General Physical Exam

As always, a good general physical exam should be performed in the comatose patient. Particular attention should be paid to parts of the exam that could reveal the cause of coma (see Table 3.2), such as acute focal signs, irregular breathing, signs of cranial trauma (Table 3.9), midsagittal ridge (see KCC 5.9), and so on. If trauma is suspected, the neck should be immobilized with a rigid cervical collar.

1. Mental Status

Coma is defined by Plum and Posner (1981) as unarousable unresponsiveness in which the patient lies with eyes closed. There is a wide continuum of levels of consciousness between coma and the fully awake state. A variety of more
TABLE 3.8 Outline of the Neurologic Exam in the Comatose Patient

I. MENTAL STATUS
Document level of consciousness with a specific statement of what the patient did in response to particular stimuli.

II. CRANIAL NERVES
1. Ophthalmoscopic exam (CN II)
2. Vision (CN II)
   - Blink to threat
3. Pupillary responses (CN II, III)
4. Extraocular movements and vestibulo-ocular reflex (CN III, IV, VI, VIII)
   - Spontaneous extraocular movements
   - Dysconjugate gaze
   - Oculocephalic maneuver (doll’s eyes test)
5. Caloric testing
6. Cervical reflexes, facial asymmetry, grimace response (CN V, VII)
7. Gag reflex (CN IX, X)

III. SENSORY AND IV. MOTOR EXAM
1. Spontaneous movements
2. Withdrawal from a painful stimulus

V. REFLEXES
1. Deep tendon reflexes
2. Plantar response
3. Posturing reflexes
4. Special reflexes in cases of suspected spinal cord lesions (see Table 3.7)

VI. COORDINATION AND GAIT
Usually not testable

poorly defined terms are sometimes used to describe different states along the
continuum, such as lethargy, stupor, obtundation, semicoma, and so on. Use
these terms without further details can be confusing to other physicians
when they read the chart and try to assess the patient’s progress. Therefore, it
is essential to document the patient’s level of alertness with a specific statement
of what the patient did in response to particular stimuli, for example:

“The patient opens eyes and turns toward voice but obey no verbal com-
mands,” or

“The patient responds only to painful sternal rub by moving the right arm
and grunting,” or

“The patient is unresponsive to voice and sternal rub.”

Level of consciousness is often the only part of the mental status exam that
can be performed in these patients. Recall that consciousness can be impaired
by damage to the brainstem reticular formation, and in bilateral lesions of the
thalamus or cerebral hemispheres (see Figure 2.1). It may also be mildly im-
paired in unilateral cortical or thalamic lesions. Toxic or metabolic factors are
also common causes of impaired consciousness because of their effects on those
structures (see KCC 14.2; KCC 19.14-19.16).

TABLE 3.9 Important External Signs of Cranial Trauma

<table>
<thead>
<tr>
<th>NAME</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bony step-off</td>
<td>Palpable discontinuity in shape of skull due to displaced fracture</td>
</tr>
<tr>
<td>CSF rhinorrhea</td>
<td>Exudation of cerebrospinal fluid from the nose due to base-of-skull fracture usually involving the ethmoid bone</td>
</tr>
<tr>
<td>CSF otorrhea</td>
<td>Exudation of cerebrospinal fluid from the ear due to base-of-skull fracture usually involving the temporal bone</td>
</tr>
<tr>
<td>Frank ecchymosis</td>
<td>Dark purple blood visible behind the tympanic membrane caused by base-of-skull fracture usually involving the temporal bone</td>
</tr>
<tr>
<td>Battle’s sign</td>
<td>Dark purple ecchymoses visible in the skin overlying the mastoid processes due to base-of-skull fracture and blood extravasation into the subcutaneous tissues</td>
</tr>
<tr>
<td>Raccoon eyes</td>
<td>Dark purple ecchymoses visible in the skin around the eyes due to base-of-skull fracture and blood extravasation into the subcutaneous tissues</td>
</tr>
</tbody>
</table>

A number of conditions can be mistaken for coma; but are actually quite dif-
f erent from coma in anatomy and pathophysiology. Large lesions involving
the frontal lobes or their connections can cause a condition resembling coma
called akinesthesia or abulia (see Table 14.3). In this state, the patient has
progressively decreased initiative and minimal responsiveness, but the eyes are usu-
ally open and there may be occasional normal appearing movements. Cata-
tonia is another condition in which there is profoundly decreased re-
ponsiveness due to psychiatric illness. In locked-in syndrome, consciousness
and sensation may be normal, but the patient is unable to move because of
a lesion in the brainstem motor pathways or because of peripheral neuro-
muscular blockade (see KCC 14.1).

2. Cranial Nerves

Examination of the cranial nerves provides crucial information about brain
stem dysfunction as the possible cause of coma.

OPHTHALMOSCOPIC EXAM (CN II). Examine both retinas carefully with an op-
thalmoscope, looking especially for papilledema, suggesting elevated intracrani-
al pressure (see KCC 5.3) (see also neuroexam.com Video 25).

VISION (CN II). If the patient cannot cooperate with visual field testing, the
blink-to-throat test can be used to roughly map visual fields. Observe whether
the patient blinks in response to moving your hand rapidly toward their eyes
from different directions (see neuroexam.com Video 28).

PUPILLARY RESPONSES (CN II, III). This is one of the most important parts of
the exam in patients with impaired consciousness. Pupil size and reactivity can
be a helpful guide to the cause of coma (see Table 14.5; neuroexam.com Video 29).
Although many exceptions exist, toxic or metabolic causes of coma often produce
normal-sized, reactive pupils. Asymmetrical or bilateral dilated, unreactive
(“blown”) pupils can indicate transtentorial herniation (see KCC 5.4) or other dis-
orders affecting the midbrain. Bilateral small but responsive pupils are often seen
in pontine lesions. Bilateral pinpoint pupils are seen in optic atrophy.

OPHTALMOSCOPIC EXAM

Blink to threat

Pupils light reflex
EXTRAOCULAR MOVEMENTS AND VESTIBULO-OCULAR REFLEX (CN III, IV, VI, VIII).
Check for spontaneous extraocular movements, nystagmus, dysconjugate gaze, or fixed deviation of the eyes in a particular direction (see neuroexam.com Videos 22-25). OKN can sometimes be useful in eliciting eye movements and testing vision in uncooperative patients, but it is often suppressed when consciousness is impaired. If the patient cannot follow commands to move their eyes, the vestibulo-ocular reflex can be used to test whether brainstem eye movement pathways are intact (see Figures 12.10, 13.12). Elicit the oculococephalic reflex by holding the eyes open and rotating the head from side to side or up and down. These maneuvers obviously should not be performed in cases of head or neck injury until possible cervical spinal trauma has been ruled out by appropriate radiological and other studies. The oculococephalic reflex is present if the eyes move in the opposite direction of the head movements, and it is therefore sometimes called doll's eyes. Note that in awake patients, doll's eyes are usually not present. This is because voluntary eye movements mask the reflex. Thus, the absence of doll's eyes suggests brainstem dysfunction in the comatose patient but can be normal in the awake patient.

Another, more potent stimulus of the vestibulo-ocular reflex is caloric stimulation. An appropriate caloric test can be performed with an oto scope. Then, with the patient lying in the supine position and the head elevated at 30°, infuse ice water into one ear. If the brainstem vestibulo-ocular reflex pathways are intact, this will produce nystagmus, with the fast phase directed opposite to the side of the cold water infusion. A useful mnemonic for interpreting the results of this test is COWS (cold opposite, warm same). After waiting 5 to 10 minutes for equilibration, try the second ear to drive the eyes in the opposite direction.

CORNEAL REFLEX, FACIAL ASYMMETRY, GRIMACE RESPONSE (CN V, VII). Look for facial asymmetry at rest, and asymmetrical spontaneous blinking or grimacing. Test the corneal reflex by touching each cornea gently with a cotton wisp (see KCC 12.4; see also neuroexam.com Video 37). Facial grimacing should also be observed in response to pain during the sensory and motor exam (to be discussed shortly) or in response to firm pressure applied to each orbital ridge.

GAG REFLEX (CN IX, X). Test the gag reflex by touching the posterior pharynx on each side with a cotton swab. In intubated patients the endotracheal tube can be leaned slightly to elicit a gag reflex. It is also helpful to ask personnel who were present at the time of intubation if a gag reflex was observed, or if a gag or cough reflex occurs during suctioning of the tracheal passages.

Look for spontaneous movements of all extremities. Test resting muscle tone.
You can assess asymmetries in tone by raising each limb and letting it fall to the bed (see neuroexam.com Videos 49, 50).
Test each limb for withdrawal from a painful stimulus, such as nail bed pressure or skin pinch. Several different responses are possible, depending on the severity of damage to the nervous system. Beginning with the least severe, a lethargic but otherwise intact patient may wake up and shout at the examiner. Thus, out of consideration to the patient, painful stimuli should be used only when absolutely necessary. A more lethargic patient may not wake up fully, but may localize the stimulus by turning toward it and may use other limbs to attempt to stop the stimulus in addition to withdrawing the limb from the pain. Grimacing provides additional evidence that the pain sensory pathways are functioning. More severely impaired patients may simply withdraw the limb from the pain. The examiner must be careful to distinguish purposeful withdrawal from posturing (discussed in the next section). Finally, if the pain sensory pathways or motor pathways for the limb are not functional, there may be no response.

5. Reflexes
Test deep tendon reflexes and the plantar response as in the awake patient (see Tables 3.6, 12.18, 13.12; neuroexam.com Videos 58, 59).
Posturing reflexes can be seen in patients with damage to the descending upper motor neuron pathways. These reflexes depend on brainstem and spinal circuitry and are often seen in severe lesions associated with coma. Sherrington studied the effects of lesions at various levels in the brainstem on postural reflexes in the cat. In the decorticate preparation, the brainstem was transected above the level of the red nucleus; in the decerebrate preparation, the transection was performed below the red nucleus. In response to a painful stimulus the decorticate cat flexes its upper limbs and extends its lower limbs, while the decerebrate cat extends both upper and lower limbs. In humans, the anatomical interpretation of flexor or extensor posturing has not been localized to particular brainstem structures. Thus, although the terms "decorticate" and "decerebrate posturing" are sometimes used with patients, it is probably more correct instead to use the terms flexor and extensor posturing and to mention which limb is involved. Although there are many exceptions, in humans as well as animals, flexor (decorticate) posturing tends to occur with lesions higher in the neuraxis at the midbrain or above, whereas extensor (decerebrate) posturing tends to occur with more severe lesions extending lower down in the brainstem. (Mnemonic: in decorticate posturing the lesion is higher, and flexed arms point up toward the cortex; in decerebrate posturing the lesion is lower, and extended arms point down.) Extensor posturing may carry a slightly worse prognosis.
Flexor posturing of the upper extremities is shown in Figure 3.5A. In extensor posturing of the upper extremities, the arms are extended and rotated inward, as shown in Figure 3.5A, B. Extensor posturing of the lower extremities often accompanies either flexor or extensor upper extremity posturing, as is shown in Figure 3.5A, B. These reflexes depend on brainstem function. Their presence thus suggests damage to descending motor pathways, with some brainstem function left intact. They can occur unilaterally or bilaterally and can be different on the two sides. It is important to distinguish these reflexes from purposeful withdrawal. You can make this distinction by pinching the skin on the extensor and flexor sides of the limb and noting the direction of movement. For example,
in flexor posturing the arm flexes even when the flexor side of the arm is pinched, thus moving toward the painful stimulus. In purposeful withdrawal, on the other hand, the movement is always away from the painful stimulus.

A flexion reflex in the lower extremity can sometimes be seen as well. This is called triple flexion because it involves flexion at the thigh and knee, and dorsiflexion at the ankle (see Figure 3.3C). In contrast to the other posterior reflexes already mentioned, triple flexion does not require brainstem function and depends only on spinal cord circuitry. Once again, you can distinguish this reflex from purposeful withdrawal by pinch- ing the dorsal and ventral aspects of the leg or foot.

In patients with suspected spinal cord injuries, the special reflexes listed in Table 3.7 may further aid in localization.

6. Coordination and Gait

These are usually not testable in this setting.

Brain Death

The definition of brain death is irreversible lack of brain function. The exact criteria used for brain death depend on the hospital; however, the mainstay of the evaluation is the neurologic exam. Generally speaking, there must be no evidence of brain function, including the brainstem. In addition to conducting the usual neurologic exam, in order to ensure that no brainstem function is present, the examiner does ocular testing, as well as an apnea test, in which lack of spontaneous respirations without the ventilator must be demonstrated despite certain standard changes in blood pH or PCO2. In the United States, a patient with posturing reflexes involving the brainstem (see Figure 3.5) does not meet brain death criteria, although a patient with only triple flexion and deep tendon reflexes may. Reversible causes such as hypoxia, hypoglycemia, hypothermia, drug overdose, and so on must be considered. At least two separate brain death examinations should be done to confirm the diagnosis. If part of the clinical evaluation is inconclusive, then confirmatory tests are done for example, an angiogram that demonstrates no flow to the brain or an EEG that demonstrates electrocerebral inactivity. These tests, however, play a confirmatory role only, and the diagnosis of brain death remains a clinical one.

Specific practice parameters for determining brain death have been published by the American Academy of Neurology (see References), and by similar organizations in other countries.

Conversion Disorder, Malingering, and Related Disorders

A number of disorders can mimic neurologic illness but in fact are psychiatric in origin. We have already discussed, under the mood portion of the mental status exam, how difficult this distinction can be. One such disorder is conversion disorder, in which psychiatric illness causes the patient to have sensory or motor deficits without a corresponding focal lesion in the nervous system. In somatization disorder, patients have multiple somatic complaints that change over time. In these two disorders patients are not consciously "faking" their symptoms, and they usually believe that they have a nonpsychiatric illness. It is essential to avoid being judgmental regarding such patients, since they usually suffer distress and functional impairment from their condition that is equal to or even worse than that of patients with identifiable lesions.

Other terms that are sometimes used for these types of disorders include hypochondriasis and hysteria. Some other related examples include psychogenic amnesia and psychogenic coma.

In a second, much less common class of disorders, patients do have conscious control over their symptoms, and they are intentionally using them for an ulterior motive. In factitious disorder (formerly known in severe cases as Munchausen syndrome) the ulterior motive is internal to the patient. It is believed that these patients lie about illness, including neurologic illness, because they gain some form of emotional pleasure from assuming the role of patient. In malingering, the ulterior motive involves some external gain for the patient, such as avoiding work, obtaining disability benefits, or the like.

While it is difficult to distinguish these disorders from neurologic illness, it can often be even more difficult to distinguish these disorders from each other, and sometimes there is overlap. There is an unfortunate tendency to dismiss all such patients as "fakers." However, these patients may be severely impaired by their illnesses, and they deserve psychiatric care to help them recover and to help avoid future confusion with neurologic disease. In addition, overzealous labeling of a patient's symptoms as psychiatric in origin without appropriate investigation can lead to misdiagnosis, particularly when the neurologic findings are subtle or when neurologic and psychogenic diseases overlap, as is often the case.

The most important tool for identifying these patients and for ruling out focal lesions in the nervous system is a thorough knowledge of the neurologic exam and histopathology. Of the many techniques that can be used, only a few of the most clear-cut methods are described here (see the references at the end of this chapter for more complete discussion).

Hand-dropping test in pseudocoma. When a patient is truly in coma and their hand is released directly above their face, their hand should strike their face on its way down.

Saccadic eye movements in pseudocoma. Saccades should not be present in coma. Note, however, that they may be present if the patient is locked in (see KCC 14.1), or if they are experiencing sleep paralysis, as is seen in narcolepsy (see Chapter 14).

Variable resistance. A patient with psychogenic weakness of a limb may vary their resistance over a wide range up to normal strength when their strength is tested by variable resistance from the examiner. This must be distinguished from a similar condition called parasthria, often seen in frontal lobe lesions (see KCC 19.11).

Hooer test. In unilateral leg weakness, palpate the contralateral gastrocnemius while the patient tries to raise the affected leg off the bed. In normal individuals the contralateral gastrocnemious is used to exert force against the bed, and it should contract. Lack of gastrocnemius contraction demonstrates lack of effort.

Unconscious movements. Patients with psychogenic paralysis may be observed to move the affected limbs during sleep, or while being transferred onto a stretcher, or in other situations when distracted.

Midline change in vibration sense. Loss of vibration sense on only one side of the sternum or one side of the skull is nonphysiological, since vibration is readily conducted through the bone to the contralateral side.
Other neuroanatomical inconsistencies can sometimes be detected if the examiner uses common sense, a little experience, and a thorough neurologic exam in which uncertain portions of the exam are repeated. It is important, once again, to be cautious because lesions in the nervous system often present with atypical and unusual symptoms and signs for a given location, leading to apparent inconsistencies in the exam. Finally, it should be noted that a substantial number of patients have disorders in which neither a clear-cut neurologic nor a psychiatric diagnosis can be made. Patients of this kind are in danger of being treated by neither neurologists nor psychiatrists, who both might consider them out of their area of expertise. A better approach would be for these patients to be followed by both neurologists and psychiatrists until either a clear-cut diagnosis emerges, or they respond to empiric therapy.

The Screening Neurologic Exam

When evaluating patients, it is useful to be proficient in a brief form of the neurologic exam that can be performed in less than 10 minutes. Performing this abbreviated exam is essential to be highly vigilant for any suggestion of a subtle abnormality. Any suspicious part of the examination should be repeated and evaluated more carefully with more detailed tests, including those described earlier in this chapter. In addition, any suspicion that arises from the patient history should be investigated more closely. For example, if a patient with visual complaints should have a detailed visual exam. A patient with complaints of weakness should have a detailed motor exam.

There is no single standard for a screening neurologic exam. However, an example is listed in Table 3.10 that may be useful as a minimal starting point, from which more detailed testing should be done when appropriate.

### TABLE 3.10 Minimal Screening Neurologic Exam

<table>
<thead>
<tr>
<th>PART OF EXAM</th>
<th>TESTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mental status</td>
<td>Level of alertness and orientation; Assess attention using months forward/backward; Immediate registration and delayed recall of 3 objects for 4 minutes (timed); Naming of watch parts; Note behavior, language, affect, etc., while taking history.</td>
</tr>
<tr>
<td>Cranial nerves</td>
<td>Pupil light reflexes; Ophthalmoscopic exam; Visual fields, including extinction testing; Horizontal and vertical smooth pursuit eye movements; Facial sensation to light touch including extinction testing; Facial symmetry during emotional smile; Hearing of finger rub bilaterally; Palate elevation; Note quality of voice during remainder of exam; Head turning and shoulder shrug against resistance; Tongue protrusion.</td>
</tr>
<tr>
<td>Motor exam</td>
<td>Delt, Rapid hand and foot tapping; Upper and lower extremity tone; Strength in several proximal and distal muscle groups in the upper and lower extremities bilaterally (e.g., finger flexors, finger abductors, wrist extensors, biceps, triceps, deltoids; lips/quads, foot and toe dorsifusors, and knee flexors).</td>
</tr>
<tr>
<td>Reflexes</td>
<td>Bilateral biceps, brachioradialis, patellar, Achilles tendon, and plantar reflexes.</td>
</tr>
<tr>
<td>Coordination and gait</td>
<td>Finger-nose-finger and heel-shin tests bilaterally; Gait and tandem gait.</td>
</tr>
<tr>
<td>Sensory exam</td>
<td>Light touch in hands and feet, including extinction testing; Pin prick or temperature testing in feet bilaterally; Vibration and joint position sense in feet bilaterally.</td>
</tr>
</tbody>
</table>

*Duration - 5 to 10 minutes

Conclusions

In this chapter we have reviewed techniques for performing the neurologic exam in many different situations. We have seen how the exam may be adapted to test patients who are awake and cooperative; comatose; or suffering from psychiatric disorders, malingering, or any combination of other ailments. In addition, we have begun to explore the neuroanatomical systems being tested and the effects of disease on function.

The lessons learned here will serve as the basis for understanding the clinical cases in Chapters 5 through 19 and will help localize lesions to particular areas of the nervous system. Once the clinical suspicion of a lesion has been raised as a result of the history and physical exam, several important decisions need to be made. Depending on the type and location of the lesion that is suspected, the options include emergency surgical or medical therapy; less urgent therapy; or further investigations, including blood tests, cerebrospinal fluid tests, electrophysiological studies, or neuroradiological imaging.

The clinician is guided in these difficult decisions by the information obtained from the history and the exam. For example, the decision to do neuroimaging, which method to use, and what areas of the nervous system to study are based on conclusions made about the probable location and nature of the lesion derived from the history and physical exam. In the next chapter we will discuss the use of neuroimaging and its applications to understanding clinical cases in the context of the complete patient assessment.

References


Russe RT. 1990. How to Examine the Nervous System, 3rd Ed. Appleton & Lange, Stamford, CT.

Advances in clinical imaging, particularly in neuroradiology, are some of the most exciting recent advances in medicine. One patient, a 52-year-old woman, suddenly developed left-sided weakness and increased reflexes. Although her initial head CT and conventional MRI scans were normal, a diffusion-weighted MRI revealed an infarct involving the right motor cortex. An MR angiogram and carotid Doppler studies suggested severe narrowing of the right internal carotid artery, later confirmed by conventional neuroangiography. Based on these findings, a surgical procedure was performed to open the narrowing in her carotid artery, and she subsequently did well. In this chapter, we will learn about current neuroimaging techniques and their clinical applications.
Introduction

Modern techniques of neuroimaging have revolutionized both clinical practice and neuroscience research. This chapter will focus on the three imaging modalities most commonly used in clinical practice: computerized tomography (CT), magnetic resonance imaging (MRI), and neuroangiography (including ultrasound, magnetic resonance angiography [MRA], and CT angiography). We will briefly touch on functional imaging modalities such as positron emission tomography (PET), single photon emission computerized tomography (SPECT), and functional MRI (fMRI).

Imaging Planes

Most CT and MRI scan images are two-dimensional "slices" through the brain. The imaging planes used are similar to the horizontal (axial), coronal, and sagittal planes described in Chapter 2 (see Figure 2.5). However, the angle of the axial slices in CT scans is sometimes adjusted by a few degrees off the true axial plane (Figure 4.1). This adjustment enables the whole brain to be covered using fewer slices and decreases radiation exposure to the eyes. In MRI scans, the axial slices are usually true horizontal slices, although this may vary slightly depending on the institution. Scout or localizer images, such as that shown in Figure 4.1, should be included on all CT and MRI films so that the exact angle of scanning can be documented. Although in practice a slight angulation off the horizontal plane does not greatly affect the appearance of images, it should be kept in mind, especially when comparing scans for differences between them.

Computerized Tomography

Computerized tomography (CT) was developed directly from conventional X-ray technology and therefore shares many of the same principles. Like conventional X-ray radiographs, CT scans measure density of the tissues being studied. There are really only two differences from conventional X-rays:

1. Rather than taking one view, the X-ray beam is rotated around the patient to take many different views of a single slice of the patient, hence the term "tomography."

2. The X-ray data acquired in this way are then reconstructed by a computer to obtain a detailed image of all the structures in the slice (including soft tissues, liquids, and air, as well as bone) hence the term "computerized."

Recent advances in CT technology have made it possible to acquire multiple CT slices simultaneously. For simplicity, we will first describe single-slice CT. The patient lies on a special table, which moves the patient in small steps through the scanner to obtain many horizontal slices. The scanner is shaped like a large ring (Figure 4.2). At each step of the table, a thin beam of X-rays is scanned through the patient from many different points around the ring and picked up by detectors on the opposite side of the ring. As a single beam of X-rays passes through the patient in a CT scanner, it is partially absorbed by the tissues it encounters. The amount of energy absorbed depends on the density of the tissues traversed. Since the X-ray beam is passed through the patient from many different directions, crossing and re-crossing the same structure from different angles, enough information is obtained for the computer to calculate the density for every point within the horizontal slice. These densities are then displayed as an image that looks like a cross section through the head (Figure 4.3). More recently, helical CT scanners have been developed that can acquire data continuously as the patient moves through the scanner ring, without requiring stops. In addition, instead of acquiring single slices, up to four rows of detectors are now being used so that multiple overlapping slices can be obtained. These technical advances have greatly improved the resolution and speed of CT scanning.

As in conventional X-rays, dense structures like bone or other calcifications appear white in CT scans, and less dense materials such as air appear black (see Figure 4.3). The terms hyperdense and hypodense are frequently used to refer to brighter and darker areas, respectively, on CT scans. Structures of intermediate density similar to that of brain tissue appear gray and are called isodense. Cerebrospinal fluid (CSF) is dark gray, and fat tissue (seen subcutaneously just outside the skull) appears nearly black. Since fat is less dense than water, white matter (which has a high myelin content) appears slightly darker than the cellular gray matter (which has a high water content). Density in CT scans is often expressed in Hounsfield units (HU). The HU scale is based on the following values: HU = 0 for water, and HU = -1000 for air. Table 4.1 lists the HU numbers for several materials commonly imaged with CT scans. Take a few moments to review the series of normal CT scan images in Figure 4.2.4 in the Neuroradiological Atlas at the end of this chapter and to become acquainted with normal anatomy as seen in CT scans. Note that in horizontal (axial) sections, the brain (see Figures 4.2, 4.3) is shown dramatically.
4.11C, 4.123.K, and 4.13(J.K), several important gyri form a sideways “T” shape, facilitating localization of the central sulcus. The superior frontal gyrus and the superior parietal lobule form the top of the “T,” and the stem of the “T” is formed by the pre- and postcentral gyri together.

CT scans can be used to visualize a variety of different intracranial abnormalities. The appearance of hemorrhage on CT depends on how recently it occurred (see Figure 5.19). Fresh intracranial hemorrhage coagulates nearly immediately and therefore shows up on CT scans as hyperdense areas relative to brain. With typical image display settings, fresh hemorrhage may appear about as white as bone, although the actual HU is significantly lower (see Table 4.1). As the clot is broken down, after about a week it becomes isodense with brain tissue, and after 2 to 3 weeks it becomes hypodense (see Figure 5.19).

Acute cerebral infarctions often cannot be seen by CT scanning in the first 6 to 12 hours after the event. Subsequently, cell death and edema lead to an area of hypodensity seen in the distribution of the artery that has been occluded, along with some distortion of the local anatomy due to the edema (see Figures 10.19, 10.21). Over weeks to months, the brain tissue surrounding the infarct may shrink, producing a local area of prominent sulci or enlarged ventricles. Persistent areas of hypodensity in the brain tissue may be present as a result of gliosis, and of brain necrosis with replacement by CSF.

Neoplasms may appear hypodense, hypodense, or isodense depending on the type and stage (see Figures 15.17, 19.19, and 19.24). They may contain areas of calcification, hemorrhage, or fluid-attened cysts. Neoplasms may produce surrounding edema that is hypodense. Intracranial contrast dye (discussed shortly) is often helpful in visualizing neoplasms.

Mass effect is anything that distorts the brain’s usual anatomy by displacement. This can occur with edema, neoplasms, hemorrhage, and other conditions. It can be detected on CT by localized compression of the ventricles, effacement of sulci, or distortion of other brain structures seen, for example, in subarachnoid hemiation of brain structures across the midline (see Figure 5.28).

Intravenous contrast material is sometimes used in CT scanning, especially to facilitate visualization of suspected neoplasms or brain abscess. The contrast material contains iodine, which is denser than brain and will therefore appear hypodense or brain (white) in areas of increased vascularity or brain edema. Moreover, the contrast material can be used to help define the size and extent of a lesion. It is often used in conjunction with intravenous contrast for comparison. Review the contrast contrast CT image in Figure 4.4 and identify the structures that normally take up contrast by comparison to the noncontrast images. These structures include arteries, venous sinuses, the choroid plexus, and dura. In suspected intracranial hemorrhage, it is very important to obtain a noncontrast CT scan. This is because small hemorrhages often appear on CT as whithis areas at the base of the brain, which could be masked by the normal hypodense contrast material in blood vessels and meninges at the brain base.

CT scanning is combined with another form of contrast enhancement in magnetoencephalography. A needle is introduced into the CSF space, usually by lumbar puncture (see KCC 5.10), and an iodinated contrast dye is introduced into the CSF space. This allows radiographic visualization of nerve roots and of abnormal impingements on the spinal CSF space—caused, for example, by a herniated intervertebral disc. In conventional magnetoencephalography, plain films are made (see Figure 8.17). In CT magnetoencephalography, a CT scan of the spine is performed as well, providing very clear visualization of the vertebral bones and the contents of the spinal canal (see Figure 8.23).

Images produced by CT can be adjusted to improve the contrast for tissues over a particular density range. To optimize contrast we adjust two parameters, the window and level, which determine the conversion between the calculated density values and the gray scale used for display. Thus, for example, images displayed with bone windows are used to carefully study the skull for fractures (see Figure 5.3), while soft tissue windows are used to look at brain structures.

CT versus MRI

MRI (see the next section) provides high-contrast, high-resolution imaging of the nervous system with striking anatomical detail. It is therefore the imaging method of choice for detecting low-contrast or small lesions such as multiple sclerosis plaques, low-grade astrocytomas, acoustic neuromas, and so on. In addition, unlike CT scanning, in which the dense bones at the base of the skull obscure the adjacent areas with "shadowing" artifact (see Figure 4.12B), MRI provides remarkably clear images of crucial basilar structures such as the brainstem, cerebellum, and pituitary fossa. The spinal cord is also much more clearly visible on MRI for similar reasons.

MRI has its disadvantages as well. The main drawbacks are time, cost, and inferior performance in imaging fresh hemorrhage and bony structures. A typical MRI scan takes about 45 minutes to complete, while a quick CT scan from an emergency patient can be done in 5 to 10 minutes. A CT scan usually costs about two-thirds as much as an MRI. Finally, CT images depend on overall tissue density, while MRI depends on proton density and proton environment (see the next section). Therefore, bone (high overall density but low proton density) and fresh hemorrhage (high overall density due to fibrinogen but low proton density and environment similar to CSF) are image better with CT than with MRI.

In summary (Table 4.2), CT is the preferred technique in patients with head trauma or suspected intracranial hemorrhage, and as a first screening method to detect most intracranial lesions, especially in the emergency setting. MRI is reserved for patients who, on the basis of the clinical story, are suspected of having low-contrast lesions or brainstem or skull-base lesions, or as a secondary technique when a lesion is suspected but not visible on CT. In nonsurgical situations, in which a single more definitive imaging method is desired, MRI is often the test of choice.

Magnetic Resonance Imaging

The detailed physics of MRI are beyond the scope of this section (see the references at the end of this chapter for greater depth). We will consider only a few basic

<table>
<thead>
<tr>
<th>TABLE 4.2 CT versus MRI in Different Situations</th>
<th>CT BETTER</th>
<th>MRI BETTER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head trauma</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Lower cost needed</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Subdural area of tumor, infant, demyelination, etc.</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Brainstem lesion</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Fresh hemorrhage</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Old hemorrhage</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Skull fracture</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Calcified lesions</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Cystostrophic or obese</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>(+250 lb) patient</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Facemask, or metallic fragments in heart or eye</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Anatomical detail needed</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

*CT is prone to shadowing artifact.
*MRI technique, when available, is mostly as fast as CT.
The choice of TR determines the time during T1 relaxation when the MRI image is obtained, while TE determines when during T2 relaxation the MRI image is obtained. Contrast between different tissues is enhanced early during T1 relaxation, and late during T2 relaxation. Thus, a short TR (660 ms) and a short TE (30 ms) enhance T1 contrast maximally, and the resulting image is called a T1-weighted image. Conversely, a long TR (2000 ms) and a long TE (280 ms) enhance T2 contrast maximally, and the resulting image is called a T2-weighted image. A compromise—that is, an image obtained with a long TR and a short TE—is neither T1 nor T2 weighted and depends mainly on proton density.

So what does all this mean for looking at MRI scans? T1- and T2-weighted images look different from each other. As a rule of thumb, T1-weighted images look like anatomical brain sections, while T2-weighted images look a bit like a film magazine. Thus, in T1-weighted images gray matter is gray and white matter is white, while in T2-weighted images the opposite is true (Table 4.3). T1-weighted images are often useful for identifying anatomy; T2-weighted images are better for detecting pathologic changes.

How can these differences between T1- and T2-weighted images be explained? Taking a somewhat simplified approach, the brightness in the images is determined mainly by:

1. Water content
2. Fat content

Rather than talking about density, as in CT scans, MRI scans are described in terms of intensity, or brightness of the signal. Thus, brighter areas are referred to as hyperintense and darker areas as hypointense. The relative brightness of various tissues in T1, T2, and proton density images is summarized in Table 4.3. In T1-weighted images, water appears dark while fatty tissues appear bright (Figure 4.6A). Thus, T1-weighted images have the appearance of anatomical brain sections, with CSF appearing dark, gray matter appearing gray (higher water content), and white matter appearing white.

### Table 4.3 MRI Appearance of Commonly Scanned Tissues

<table>
<thead>
<tr>
<th>TISSUE</th>
<th>T1-WEIGHTED</th>
<th>T2-WEIGHTED</th>
<th>PROTON DENSITY-WEIGHTED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gray matter</td>
<td>Light gray</td>
<td>Light gray</td>
<td></td>
</tr>
<tr>
<td>White matter</td>
<td>White</td>
<td>Dark gray</td>
<td>Grey</td>
</tr>
<tr>
<td>CSF or water</td>
<td>Dark gray</td>
<td>White</td>
<td>Dark gray</td>
</tr>
<tr>
<td>Fat</td>
<td>Black</td>
<td>Black</td>
<td>Black</td>
</tr>
<tr>
<td>Air</td>
<td>Black</td>
<td>Black</td>
<td>Black</td>
</tr>
<tr>
<td>Bone or calcification</td>
<td>Black</td>
<td>Black</td>
<td>Black</td>
</tr>
<tr>
<td>Edema</td>
<td>White</td>
<td>White</td>
<td>White</td>
</tr>
<tr>
<td>Demyelination or gliosis</td>
<td>White</td>
<td>White</td>
<td>White</td>
</tr>
<tr>
<td>Periosteal deposits (e.g., in basal ganglia)</td>
<td>Black</td>
<td>Black</td>
<td>Black</td>
</tr>
<tr>
<td>Ca(^2) bound to protein</td>
<td>White</td>
<td>Dark gray</td>
<td>Dark gray</td>
</tr>
<tr>
<td>Proteinaceous fluid</td>
<td>White</td>
<td>White</td>
<td>White</td>
</tr>
</tbody>
</table>

*In fast spin echo (FSE) sequences (a faster variant of the SE sequence), fat appears bright in T2- and proton density-weighted images.*
Typical MRI Images

1. T1, T2, and proton density-weighted images were obtained in an axial plane, without gadolinium contrast. See also Table 4.3. (A) T1-weighted image, acquired with spin echo (SE) pulse sequence. TR = 500, TE = 15. (B) T2-weighted image, acquired with fast spin echo (FSE) pulse sequence. TR = 4000, effective TE = 120. (C) Proton density-weighted image, acquired with FSE pulse sequence. TR = 4000, effective TE = 13.

In T2-weighted images, on the other hand, water appears bright, and fat appears dark (see Figure 4.6B). Thus, CSF appears bright, while areas of brain edema, gray matter, and myelinated areas are progressively less bright, and epidural fat is very dark. T2-weighted images are generally noisier and have less resolution than T1-weighted images, but they have better contrast.

In proton density-weighted images (sometimes called first echo images), contrast between gray and white matter is generally reduced (see Figure 4.6C). The main utility of proton density images is that subtle abnormalities in the parenchyma, such as small areas of edema or infarction adjacent to the CSF, can be easily seen as bright regions. These small, bright abnormalities will also be present on T2 images; however, they are often harder to see on T2 images because of the relative brightness of adjacent CSF. A variety of additional specialized MRI pulse sequences and techniques exist that are beyond the scope of this discussion, but they are reviewed in the references listed at the end of the chapter.

In addition to fat and water content, the intensity of all MRI images depends on the number of measurable protons in the sample, or proton density. Simply put, the reason is that protons must be present in order for a signal to be generated. Therefore, on T1-weighted, T2-weighted, and proton density-weighted images, air appears black, and bone or calcified structures appear dark, because of the relative absence of water protons (see Table 4.3, Figure 4.6).

A number of other factors affect the intensity of MRI signals as well. Paramagnetic substances such as Ca²⁺ bound to protein, or in blood degra-
dation products, can cause either relatively bright or dark signals depending on the exact circumstances (see Tables 4.3 and 4.4). When special pulse sequences for magnetic susceptibility are used, even minute amounts of hemosiderin from an old hemorrhage can be detected as black areas on the scan. The paramagnetic substance gadolinium is used in MRI for intravascular contrast. In analogy with CT, gadolinium contrast injection produces a bright signal in regions of increased vascularity or breakdown of the blood-brain barrier. Gadolinium contrast agents are much less nephrotoxic and less prone to cause allergic reactions than are the iodinated contrast agents used in CT.

Another factor that can affect MRI signals is flow artifact in blood vessels and, to a lesser extent, in CSF. Flow artifact occurs as a result of protons moving rapidly into or out of the area being imaged. Some protons appear or disappear between the time that the excitation and recording radio frequency pulses occur. This change can cause increases or decreases in MRI signal intensity depending on the rate and direction of flow and on the pulse sequence used. Magnetic resonance angiography (MRA) takes advantage of these effects to create images of arterial blood flow (see the next section). MRI scans are also distorted by artifacts in patients with metallic implants in the skull. Metallic fragments in the eye, pacemakers, cochlear implants, metallic heart valves, and older aneurysm clips can be moved or damaged by the powerful MRI magnet, and therefore will preclude MRI scanning in certain patients. Intracranial hemorrhage undergoes a characteristic series of changes on MRI images over time (Table 4.4). In simple terms, on both T1- and T2-weighted images, acute hemorrhage may be difficult to see because it is gray and resembles CSF. Subacute hemorrhage contains methemoglobin, causing it to appear white. Chronic hemorrhage contains dark areas resulting from hemosiderin deposition. Usually the center of the hemorrhage has a different composition from the periphery so that, particularly for older hemorrhages, there is a characteristic bright center with a dark rim. Eventually, the center of the hemorrhage may resorb, forming a fluid-filled cavity that is dark on T1-weighted images and bright on T2-weighted images (not shown in table).

We will now briefly summarize the above discussion (see Tables 4.3 and 4.4), and provide some examples. On MRI imaging, abnormal areas of increased fluid such as cysts, infarcts, edema, gliosis, or demyelination, appear dark on T1-weighted images (see Figures 7.20, 19.21) and bright on T2-weighted images (see Figures 6.16, 7.25, and 10.18). Regions of inflammation or neoplasms often enhance with intravenous gadolinium (see Figures 12.21, 15.18, and 18.18). Hemorrhage is difficult to see acutely, but becomes bright on subsequent imaging (see Figure 14.35), and then often develops both bright and dark regions (Table 4.4). New pulse sequences continually improve the clinical usefulness of MRI. For example, diffusion-weighted MRI (discussed later, in the section “Functional Neuroimaging”) often allows visualization of acute cerebral infarcts far earlier than was possible previously (see Figures 14.23, 14.31).

Take a few moments now to review the series of normal T1-weighted MRI scan images in the Neuroradiological Atlas at the end of this chapter (see Figures 4.13-4.15) to become acquainted with normal anatomy as seen by MRI. The images in Figure 4.13 were obtained in approximately the same imaging planes as the CT images in Figure 4.12 (although the angle of the slices is somewhat more horizontal for the MRI images). Note the markedly superior resolution for the MRI images. In addition, note that the administration of intravenous gadolinium (Figure 4.7) causes enhancement of the arteries, venous sinuses, choroid plexus, and ducts.

MRI scans are sometimes reformatted into three-dimensional surface representations. An example is shown in Figure 4.8. This method enables the detection of subtle abnormalities in sulcal morphology that may not be appreciated in two-dimensional sections. In addition, it can be helpful to represent functional neuroimaging data on a three-dimensional representation of the brain surface (see Figure 4.10).

**TABLE 4.4 MRI Appearance of Intracranial Hemorrhage**

<table>
<thead>
<tr>
<th>TIME SINCE HEMORRHAGE</th>
<th>T1-WEIGHTED</th>
<th>T2-WEIGHTED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute: first 6-24 hours (intracellular oxyhemoglobin)</td>
<td>Gray</td>
<td>Light gray</td>
</tr>
<tr>
<td>Early subacute: 3-5 days (intracellular deoxyhemoglobin)</td>
<td>Gray</td>
<td>Dark gray</td>
</tr>
<tr>
<td>Middle sub acute: 3-7 days (intracellular methemoglobin)</td>
<td>White</td>
<td>Bluish-gray</td>
</tr>
<tr>
<td>Late sub acute: 3-38 days (extracellular methemoglobin)</td>
<td>White</td>
<td>White</td>
</tr>
<tr>
<td>Chronic: &gt;14 days (hemosiderin, mainly on outer rim)</td>
<td>White</td>
<td>White</td>
</tr>
</tbody>
</table>

Note: The actual sequence of changes in the appearance of hemorrhage on MRI scans can be fairly complicated and variable, depending on individual scenarios.

### Neuroangiography

Cerebral angiography is one of the oldest neuroradiological techniques, and its role has therefore evolved in many ways. Before the availability of CT and MRI, neuroangiography was often used to detect slight distortions in the patterns of blood vessels suggestive of intracranial mass lesions. These subtle angiographic changes were combined with findings from other techniques no longer used for this purpose (plain skull films, pneumoencephalography, and EEG) to provide circumstantial evidence for intracranial lesions that today can easily be visualized with CT or MRI.

Now that CT and MRI are widely available, neuroangiography is used mainly to visualize lesions of the blood vessels themselves, rather than to provide indirect information about surrounding structures. Lesions optimally seen by angiography include atherosclerotic plaques and other vessel nar-

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**REVIEW EXERCISE**

Study the MRI images in the Neuroradiological Atlas (see Figures 4.13-4.15) and identify (1) whether they are axial (horizontal), coronal, or sagittal (see Figure 2.3), and (2) whether they are T1-, T2-, or proton-density weighted. Then, cover the labels and try to name as many structures as possible.
Doppler ultrasound can be used to measure flow and lumen diameter of large blood vessels in the head and neck. It is most useful for assessing the proximal portions of the internal carotid, middle cerebral, anterior cerebral, posterior cerebral, vertebral, and basilar arteries. Smaller, more distal branches cannot be assessed. However, the technique is still quite useful because most significant atherosclerotic narrowings occur proximally. This technique usually cannot detect aneurysms or other vascular abnormalities.

Magnetic resonance angiography (MRA) takes advantage of the change in magnetic resonance signal that occurs in areas of flow as a result of the movement of protons into and out of the region being assessed between the time that the radio frequency excitation pulse is emitted and the time that the signal is collected. The direction and speed of flow to be detected can be selected via the computer. A series of normal MRA images of the intracranial vessels is shown in Figure 4.18. These images should be compared to the conventional angiographic images in Figures 4.16 and 4.17. Note that with MRA, although the major vessels can be seen, the smaller, more distal branches cannot. Like conventional angiography, MRA can also be used to image potential sites of narrowing or other pathology of the carotid and vertebral arteries in the neck (Figure 4.19), or even as they arise from the aortic arch (Figure 4.20A), MRA is used mainly to detect regions of decreased or absent arterial blood flow caused by atherosclerotic narrowing, thrombosis, or dissection. In addition, MRA can be useful for detecting some aneurysms and other vascular abnormalities. Venous flow can be visualized using magnetic resonance venography (MRV). An example of MRV used to detect venous sinus thrombosis is shown in Figure 10.26.

Spiral CT angiography (CTA) is a relatively new method in which rapid injection of intravenous contrast is used together with helical CT scan techniques to obtain images of blood vessels quickly. The blood vessels are reconstructed in three dimensions by means of a computer. Information obtained from CTA can sometimes supplement what obtained from MRA, and CTA can be performed in patients in which MRA is contraindicated (e.g., patients with pacemakers).

Although noninvasive techniques have further narrowed the role of angiography in diagnosis, a new role has emerged for neuroangiography in invasive functional testing and therapy. This field is known as interventional neuroradiology. For example, in the angiogram Wada test, a sedative medication (anesthetic) is selectively infused into each carotid artery with the patient awake. This test can help localize the side of language and memory function and is useful in planning neurosurgery (see KCC 18.2). Brain aneurysms and arteriovenous malformations, which can cause massive intracranial hemmorhage (see Chapter 5), can sometimes be clotted off and rendered harmless by filling them with glue-like material or tiny metal screws via the angiography catheter. Finally, therapeutic trials are under way in acute stroke in which thrombolytic agents are infused via the catheter directly at the site of the clot to try to reestablish perfusion.

**Functional Neuroimaging**

In most clinical situations, the most important radiological information comes from a structural anatomical image of the abnormality produced by one of the techniques already described. Sometimes, however, it is also useful to assess the physiological function of the structures in question. Several different techniques can be used for measuring various aspects of brain function, and, as we will discuss in this section, exciting clinical applications...
are beginning to emerge. Research applications of functional neuroimaging have seen a remarkable growth in recent years, giving rise to speculation that with some techniques we may soon be able to virtually "peer into someone's head and see what they are thinking."

The original method for measuring brain activity was the electroencephalogram (EEG). In this technique an array of electrodes is applied to the surface of the scalp and connected to amplifiers to detect the weak electrical signals transmitted from the brain through the skull. The normal EEG pattern consists of waveforms of various frequencies that vary with the level of alertness of the patient. Abnormalities in large regions of brain produce abnormal or asymmetrical waveforms that can be detected with EEG. The sensitivity and spatial resolution of EEG in detecting focal brain lesions is poor, however, compared to modern neuroimaging methods. EEG remains very useful today in evaluating patients for epileptic (seizure-producing) brain activity (see KCC 18.2), or for detecting widespread abnormalities in brain function (see KCC 39.15, 39.16). Evoked potentials are a method similar to EEG in which brain electrical signals are recorded in response to specific stimuli. Additional refinements in electrical measurements of brain function have been developed. These include quantitative EEG analysis and magnetoencephalography (MEG), which uses a superconducting quantum interference device (SQUID) to detect the very weak magnetic signals from the brain. These techniques are presently used mainly for research purposes.

Other methods of functional assessment depend on brain metabolic activity. Brain metabolic activity is used as an indirect measure of brain electrical activity, or neuronal firing. Increased local neuronal firing causes increased brain metabolism which, in turn, leads to increased local blood flow and increased turnover of local blood volume. Techniques that can produce images based on blood flow or dynamic blood volume include: Xenon regional cerebral blood flow mapping (Xe CBF), positron emission tomography (PET), single photon emission computerized tomography (SPECT), dynamic contrast functional MRI (perfusion MRI), and blood oxygen level-dependent functional MRI (BOLD MRI). In addition to measuring cerebral blood flow, many of these techniques can be used to more directly measure brain function by other methods. For example, PET scanning can also be used to map local brain consumption of glucose, or local binding of various neurotransmitters.

Functional MRI (fMRI) refers to several different MRI techniques used to measure different aspects of brain function:

1. Dynamic contrast MRI (perfusion MRI) involves rapid injection of gadolinium and rapid measurements using "echo planar" imaging to produce an image of dynamic blood volume.
2. Blood oxygen level-dependent fMRI (BOLD fMRI) measures relative changes in oxy- and deoxyhemoglobin, which occur with changes in regional cerebral blood flow.
3. Diffusion MRI uses rapid echo planar imaging and strong gradients to measure the diffusion coefficient of water in brain tissue. This sensitive technique can be used to detect early areas of ischemia long before conventional MRI shows any abnormalities.
4. Magnetic resonance spectroscopy (MRS) can be used to detect local concentrations of certain chemicals in the brain including some neurotransmitters.

The functional neuroimaging methods discussed in this section have caused a virtual explosion in neuroscience research and are greatly advancing our knowledge of localized brain function. In addition, some important clinical applications are beginning to emerge. For example, fluorodeoxyglucose PET scans are often used in patients with dementia or epilepsy to localize regions of abnormal glucose metabolism (see Figure 18.22); they may also be useful for distinguishing metabolically active recurrent brain tumors from stably-induced necrosis. Diffusion MRI is increasing in popularity as a method for detecting acute cerebral infarcts far earlier than conventional MRI or CT scans (see Figures 14.23, 14.31). SPECT scans can be used to indirectly measure regional brain activity during seizures and to help localize their region of onset. An example is shown in Figure 4.10, BOLD fMRI is being investigated as a method to help plan neurosurgery by allowing the neurosurgeon to know in advance where vital regions of brain function are located—as shown in Figure 4.11, BOLD fMRI can be used to localize the potent sensory-motor function and language function. Eventually, with further investigation, this method may replace the angiogram Wada test (see KCC 18.2). As time goes on, additional clinical applications of these powerful functional neuroimaging methods are likely to be found.

Conclusions

Neuroimaging plays an essential role in the diagnosis, and sometimes treatment, of patients with disease of the nervous system. However, it is the role of the clinician to decide, on the basis of the history and physical exam, what the most likely diagnoses are, so that neuroimaging methods are used appropriately. The clinician must first decide if a neuroimaging study is needed at all. Then the history and physical exam must be used to formulate hypotheses about both localization and the pathophysiology of lesions. Using this information, the clinician can decide whether CT, MRI, angiography, or other methods of evaluation are most appropriate, as well as whether regions of the nervous system should be the focus so that an optimal study is obtained. By combining the clinical history, examination, and other methods of assessment together with the powerful neuroimaging methods available today, clinicians are able to offer an ever-increasing number of patients accurate neurologic diagnosis and appropriate treatment.
Figure 4.12 CT Images  Unenhanced axial CT images with major structures labeled.

(A)  (B)  (C)  (D)
NEURORADIOLOGICAL ATLAS

Figure 4.12 (continued)

(F) Frontal horn of lateral ventricle
Sylvian fissure
Optic tract
Mammillary body (hypothalamus)
Cerebral peduncle
Midbrain tegmentum
Superior colliculus
Tentorial cerebellum

(G) Pons
Frontal horn
Sylvian fissure
Sylvian fissure
Forebrain
Temporal lobe
Calcarine fissure
Visual cortex
Occipital horn
Occipital lobe
Superior frontal gyrus
Middle frontal gyrus
Corpus callosum ( genu)
Caudate head
Internal capsule
Putamen
Thalamus
Calcified choroid plexus

(H) Pons
Sylvian fissure
Frontal horn
Sylvian fissure
Pons
Calcified choroid plexus
Atrium of lateral ventricle
Occipital lobe
Superior sagittal sinus
Corpus callosum ( genu)
Caudate head
Corpus callosum (splenium)
Figure 4.12 (continued)

(a) 
- Falc
- Septum pellucidum
- Central sulcus
- Body of lateral ventricle
- Choroid plexus
- Falc
- Parietal lobe
- Superior sagittal sinus

(b) 
- Superior frontal gyrus
- Precentral gyrus
- Central sulcus
- Postcentral gyrus
- Intraparietal sulcus
- Interior parietal lobe
- Marginal ramus of cingulate sulcus
- Superior parietal lobe
Figure 4.13 MRI: Axial T1-Weighted Images

Unenhanced axial MR images with major structures labeled. TR = 500, TE = 11.
Figure 4.13 (continued)

(j) 

- Corpus callosum (body) 
- Body of lateral ventricle 
- Central sulcus 
- Superior parietal lobule 
- Intraparietal sulcus 
- Inferior parietal lobule 
- Superior sagittal sinus

(k) 

- Superior frontal gyrus 
- Middle frontal gyrus 
- Precentral gyrus 
- Central sulcus 
- Postcentral gyrus 
- Central sulcus 
- Superior parietal lobule 
- Marginal ramus of cingulate sulcus 
- Precentral gyrus 
- Central sulcus 
- Postcentral gyrus 
- Parietal lobule 
- Marginal ramus of cingulate sulcus
Figure 4.14 MRI: Coronal T1-Weighted Images  Unenhanced coronal MRI images with major structures labeled. Images acquired using 3D SPGR sequence with TR = 23, TE = 4.

(A) Cingulate gyrus  Superior sagittal sinus  Pyriform sinus  Corpus callosum (splenium)

- Tail of caudate
- Precentral gyrus
- Superior frontal gyrus
- Middle frontal gyrus
- Frontal pole
- Supramarginal gyrus
- Superior temporal gyrus
- Middle temporal gyrus
- Inferior temporal gyrus
- Mammillary body (hypothalamus)
- Corpus callosum (body)
- Body of lateral ventricle
- Body of caudate
- Frontal pole
- Thalamus
- Sylvian fissure
- Temporal pole
- Third ventricle
- Temporal horn of lateral ventricle
- Hippocampus
- Lithostriatum
- Posterior cerebellar artery
- Superior cerebellar artery
- Basilar artery
- Corpus collosum (body)
- Septum pellucidum
- Anterior horn of lateral ventricle
- Fornix
- Internal capsule, anterior limb
- Septal nucleus
- Substantia innominata (medial basal)
- Optic tract
- Pituitary stalk

(B) Cingulate gyrus

- Septum pellucidum
- Fornix
- Internal capsule ( genu)
- Putamen
- Superior temporal gyrus
- Middle temporal gyrus
- Inferior temporal gyrus
- Mammillary body (hypothalamus)
- Superior sagittal sinus
- Body of lateral ventricle
- Body of caudate
- Frontal pole
- Thalamus
- Sylvian fissure
- Temporal pole
- Third ventricle
- Temporal horn of lateral ventricle
- Hippocampus
- Lithostriatum
- Posterior cerebellar artery
- Superior cerebellar artery
- Basilar artery
- Superior frontal gyrus
- Middle frontal gyrus
- Septum pellucidum
- Anterior horn of lateral ventricle
- Fornix
- Internal capsule, anterior limb
- Putamen
- Sylvian fissure
- Nucleus accumbens
- Optic chiasm
- Cavernous sinus
- (venous blood)
- Pituitary
- Sphenoid sinus
- (left)
Figure 4.16 Angiographic Images: Anterior Circulation
(A) Anterior-posterior view following injection of left internal carotid artery, demonstrating filling of left anterior and middle cerebral arteries (ACA, MCA). (B) Close-up view of recurrent artery of Heubner arising from anterior cerebral artery and lenticulostriate arteries arising from middle cerebral artery.

Figure 4.17 Angiographic Images: Posterior Circulation
(A) Anterior-posterior view following injection of left vertebral artery. Reflux into the right vertebral artery can be seen. (B) Lateral view following injection of left vertebral artery.

**Angiography**

(A)

- Posterior cerebral artery
- Posterior inferior cerebellar artery
- Vertebrobasilar artery

(B)

- Posterior chorioidal arteries
- Thalamoperforator arteries
- Posterior communicating artery
- Basilar artery
- Anterior inferior cerebellar artery
- Vertebral artery, intracranial
- Vertebral artery, extracranial
NEURORADIOLOGICAL ATLAS

Figure 4.20  MRA Images: Origins of Carotid and Vertebral Arteries  Anterior-posterior view with successive slices progressing from anterior (A) to posterior (B). (A) Origin of common carotid arteries from aortic arch and brachiocephalic artery. (B) Origin of vertebral arteries from subclavian arteries.

CT

MRI

Neuroangiography

Functional Neuroimaging
CHAPTER 5

Brain and Environs: Cranium, Ventricles, and Meninges

After a domestic altercation in which he had fallen down a flight of cement stairs and injured his head, a 51-year-old man was arrested and taken to prison. He had been conscious and smelled of alcohol when the police had arrived, but the next morning he was found unresponsive and thrashing aimlessly in his cell. His left pupil was dilated. His right side was paralyzed and had brisk reflexes. As we shall see in this chapter, this case illustrates how head injury can cause abnormal shifts among various compartments in the head, including the cranial vault, ventricles, and meninges. We will learn about the normal anatomy and function of each of these compartments, as well as clinical consequences of injury or illness.
ANATOMICAL AND CLINICAL REVIEW

In the sections that follow we will briefly discuss the brain in relation to its local environment, including the skull, meninges, blood vessels, and cerebrospinal fluid. In addition, we will summarize several important clinical abnormalities that involve these structures, including headache, intracranial mass lesions, elevated intracranial pressure, brain herniation, intracranial hemorrhage, hydrocephalus, brain tumors, and infections of the nervous system. Since this is the first chapter in the book containing clinical cases, we will introduce many Key Clinical Concepts that will be used not just here, but throughout the remainder of the book. For now, you can skim these Key Clinical Concepts (KCC 5.1–5.11) once briefly. Later, while you’re thinking through cases and attempting to make a diagnosis, it will be useful to refer back to these sections in more detail.

Cranial Vault and Meninges

The brain is encased in several protective layers that cushion it from trauma (Figure 5.1). Beneath the skin and subcutaneous tissues lie the hard bones that form the skull. The skull has many foramina, or holes, which allow the cranial nerves, spinal cord, and blood vessels to enter and leave the intracranial cavity. We will review these foramina in greater detail in Chapter 12, but for now it is important to recognize the largest foramen at the base of the skull: the foramen magnum (Figure 5.2). The point where the spinal cord meets the medulla, the cervicomedullary junction, occurs at the level of the foramen magnum (see Figures 2.25a and 3.10). You should be able to easily identify the foramen magnum and the other major foramina at the base of the skull on a CT scan (Figure 5.3).
Figure 5.3  CT Scan: Bone Windows Showing Major Foramina at the Base of the Skull  (A-C) Axial sections moving from inferior to superior through the posterior fossa.

On the inner surface of the skull are several ridges of bone that divide the base of the cranial cavity into different compartments, or fossae (see Figures 5.2B and 5.4). The anterior fossa on each side contains the frontal lobe. The middle fossa contains the temporal lobe. The posterior fossa contains the cerebellum and brainstem. The anterior fossa is divided from the middle fossa by the lesser wing of the sphenoid bone. The middle fossa is divided from the posterior fossa by the petrous ridge of the temporal bone, as well as by a sheet of meninges, which will be described next. These fossae can also be identified on CT and MRI scans (see Figures 4.1A–D and 4.13A–D).

The final layers of protection within the skull and surrounding the brain are the meninges and cerebral spinal fluid (see Figure 5.1). The three layers of meninges from inside to outside are:

1. Pia
2. Arachnoid
3. Dura

Thus, a mnemonic for the meningeal layers is PAD. The term “mater” (meaning “mother”) is sometimes added after these names—for example, pia mater, arachnoid mater, and dura mater. A mnemonic for the layers of the scalp (SCALP) is shown in Figure 5.1.
Moving now from outside to inside, the dura, meaning "hard," is composed of two tough fibrous layers (see Figure 5.1). The outer periosteal layer is adherent to the inner surface of the skull. This outer layer of dura is fused with the inner meningeal layer of dura except in a few places where the inner layer forms folds that descend far into the cranial cavity (see Figure 5.1). There are two main places where this occurs. The first is the falk cerebri, a flat sheet of dura that is suspended from the roof of the cranium and separates the right and left cerebral hemispheres, running in the interhemispheric fissure (Figure 5.5). The second is the tentorium cerebelli, a tentlike sheet of dura that covers the outer surface of the cerebellum (see Figures 5.5 and 5.6).

The tentorium cerebelli, together with the petrous portions of the temporal bones, divide the posterior fossa from the rest of the cranial vault. The portion of the intracranial cavity above the tentorium is referred to as supratentorial, while that below is called infratentorial. To understand the relationship between the tentorium cerebelli and the other intracranial structures, and how the tentorium is truly "tent" shaped, review the CT scan images in Figure 4.12D,E, and L and the MRI images in Figures 4.12F,E and 4.15A,B. Note that the occipital lobes and part of the temporal lobes rest on the upper surface of the tentorium. Recall that the midbrain connects the cerebral hemispheres with the brainstem and cerebellum. Thus, the midbrain can be seen to pass through an important narrow opening in the tentorium cerebelli called the tentorial incisura, or the tentorial notch (Figure 5.6).

The arachnoid is a wispy, "spidery" meningeal layer that adheres to the inner surface of the dura. Within the arachnoid, the cerebrospinal fluid percolates over the surface of the brain (see Figures 5.1, 5.10). The innermost meningeal layer is a very thin layer of cells called the pia. Unlike the arachnoid, the pia adheres closely to the surface of the brain and follows it along all the gyri and into the depths of the sulci. The pia also surrounds the initial portion of each blood vessel as it penetrates the brain surface, forming a perivascular space (Virchow-Robin space), and then fuses with the blood vessel wall (see Figure 5.1).

The meninges form three spaces or potential spaces with clinical significance:

1. Epidural space
2. Subarachnoid space
3. Subdural space

There are some important blood vessels that can give rise to hemorrhage in each of these spaces (see Figure 5.6). The epidural space is a potential space located between the inner surface of the skull and tightly adherent dura (see Figure 5.1). The middle meningeal artery enters the skull through the foramen spinosum (see Figures 5.2B, 5.3C) and runs in the epidural space between the dura and the skull (Figure 5.7). Grooves can often be seen on the inner surface of the skull that are formed by this artery and its many branches. Note that the middle meningeal artery is a branch of the external carotid artery (see Figure 2.26A) and supplies the dura, while the middle cerebral artery is a branch of the internal carotid artery and supplies the brain (see Figure 2.26C).

The subdural space is a potential space between the inner layer of dura and the loosely adherent arachnoid (see Figure 5.1). The bridging veins traverse the subdural space. These veins drain the cerebral hemispheres and pass...
**REVIEW EXERCISE**

For the epidural, subdural, and subarachnoid spaces:

1. Identify the two structures that bound each space (skull, dura, arachnoid, or pia).
2. State whether each space is a potential space or a CSF-filled space.
3. Name the main blood vessels running in each space.

through the subdural space en route to several large dural venous sinuses (Figures 5.8 and 5.9; see also Figure 5.1). Dural sinuses are large venous channels that lie enclosed within the two layers of dura. The dural sinuses drain blood mainly via the sigmoid sinuses to reach the internal jugular veins.

The cerebrospinal fluid-filled space between the arachnoid and the pia is called the subarachnoid space (see Figures 5.1, 5.10). In addition to cerebrospinal fluid, the major arteries of the brain travel within the subarachnoid space and then send smaller penetrating branches inward through the pia. As the spinal cord exits through the foramen magnum and continues downward through the bony spinal canal, it is enveloped by the same three meningeal layers (Figure 5.10). The only significant difference is that there is a layer of epidural fat in the spinal canal (see Figure 8.2), while in the cranium the outer layer of dura adheres tightly to bone (see Figure 5.1).

**Ventricles and Cerebrospinal Fluid**

During development the neural tube forms several cavities within the brain called ventricles (see Figure 2.2). The ventricles contain cerebrospinal fluid (CSF) that is produced by a specialized vascular structure called the choroid plexus, which lies inside the ventricles (see Figure 5.10). The inner walls of the ventricles are lined with a layer of cells called ependymal cells, and the blood vessels of the choroid plexus are lined with similar-appearing cuboidal cells called choroid epithelial cells (see Figure 5.13C). There are two lateral ventricles (one inside each cerebral hemisphere), a third ventricle located within the diencephalon, and the fourth ventricle, which is surrounded by the pons, medulla, and cerebellum (Figure 5.11, Table 5.1).
Figure 5.10 Cerebrospinal Fluid Circulation
Cerebrospinal fluid produced by choroid plexus flows from the lateral ventricles through the foramen of Monro, into the third ventricle, through the Sylvian aqueduct, into the fourth ventricle, out through the foramina of Luschka and Magendie, into the subarachnoid space, and up to the arachnoid granulations to be reabsorbed into the bloodstream.

Figure 5.11 Brain Ventricles
(A) Ventricles viewed from lateral surface of brain. (B) Ventricles viewed from anterior surface of brain. (C) Ventricles viewed from superi or surface of brain. (D) Details of ventricular structure.

The largest of the ventricles are the two lateral ventricles (see Figure 5.11), formerly called the first and second ventricles. The lateral ventricles have extensions called horns that are named after the lobes or after the direction in which they extend (see Table 5.1, Figure 5.11). The frontal or anterior horn of the lateral ventricle extends anteriorly from the body of the lateral ventricle into the frontal lobe. By definition, the frontal horn begins anterior
### Table 5.1 Brain Ventricles

<table>
<thead>
<tr>
<th>VENTRICLE</th>
<th>LOCATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lateral ventricle</td>
<td>Within the cerebral hemisphere</td>
</tr>
<tr>
<td>Frontal (anterior) horn</td>
<td>Begins anterior to the interventricular foramen of Monro and extends into the frontal lobe</td>
</tr>
<tr>
<td>Body</td>
<td>Posterior to the interventricular foramen of Monro, within the frontal and parietal lobes</td>
</tr>
<tr>
<td>Atrium (trigone)</td>
<td>Area of convergence of the occipital horn, the temporal horn, and the body of the lateral ventricle</td>
</tr>
<tr>
<td>Occipital (posterior) horn</td>
<td>Extends from the atrium posteriorly into the occipital lobe</td>
</tr>
<tr>
<td>Temporal (inferior) horn</td>
<td>Extends from the atrium inferiorly into the temporal lobe</td>
</tr>
<tr>
<td>Third ventricle</td>
<td>Within the thalamus and hypothalamus</td>
</tr>
<tr>
<td>Fourth ventricle</td>
<td>Within the pons, medulla, and cerebellum</td>
</tr>
</tbody>
</table>

**Review Exercise**

Cover the labels in Figure 5.10 and name each space or foramen that CSF travels through en route from the choroid plexus of the lateral ventricles to the arachnoid granulations.

Next, use the Neuroradiological Atlas CT and MRI images (see Figures 4.12-4.15) to identify each of the structures listed in the left column of Table 5.1 and to identify the foramen of Monro and the cerebral aqueduct.

---

The ambient cistern is located lateral to the midbrain; the quadrigeminal cistern is posterior to the midbrain, beneath the posterior portion of the corpus callosum (see Figure 5.12). The name "quadri-geminal" comes from the four bumps of the superior and inferior colliculi (see Figures 2.22B, 5.12). The interpeduncular cistern, also sometimes called the interpeduncular fossa, is located on the ventral surface of the midbrain, between the cerebral peduncles (see Figure 5.6). Note that the third nerve exits the midbrain through the interpeduncular fossa. The preoptic cistern is located just ventral to the pons. It contains the basilar artery and the sixth nerves (see Figures 2.22A, 2.26C) as they ascend from the pontomesencephalic junction up along the clivus (see Figure 5.3B). The cisterna magna, also known as the cerebellomedullary cistern, is the largest cistern and is located beneath the cerebellum near the foramen magnum (see Figure 5.12; see also Figure 4.15A). Finally, the lumbar cistern, located in the lumbar portions of the spinal column, contains the cauda equina (see Figure 2.8) and is the region from which cerebrospinal fluid is obtained during a lumbar puncture, or spinal tap (see KCC 5.10).

**Blood-Brain Barrier**

Anatomists discovered in the 1800s that when a colored dye is injected into the bloodstream of an animal, all of its organs become stained except the brain. This finding is the capillary endothelial cells in most of the body are separated from each other by clots, or fenestrations, allowing relatively free passage of fluids and solute molecules (Figure 5.3A). In the brain, however, capillary endothelial cells are linked by tight junctions (Figure 5.3B), and substances entering or leaving the brain must travel through the endothelial cells.

**Figure 5.12 Principal CSF Cisterns in the Subarachnoid Space**

- **A** Systemic capillary
- **B** Brain capillary
- **C** Choroid plexus
- **D** Arachnoid villi

**Figure 5.13 Blood-Brain and Blood-CSF Barriers**

A typical fenestrated capillary lying outside the nervous system, allowing the passage of water and solutes. (B) Brain capillary with tight junctions between endothelial cells, forming the blood-brain barrier. Cellular transport across the endothelial layer is required for the passage of water-soluble substances between blood and brain. (C) The choroid plexus is similar to the blood-brain barrier, allowing the passage of water and solutes, but chorioretinal epithelial cells form the blood-CSF barrier, requiring cellular transport for passage. (D) The arachnoid villus cells carry out one-way bulk flow of CSF from the subarachnoid space to venous sinuses via giant vacuoles.
Chapter Five

Cranium, Ventricles, and Meninges

Figure 5.14 Fluid Compartments of the Nervous System

- Blood-brain and blood-CSF barriers separate arterial blood from brain parenchyma and CSF. Substances pass relatively freely between brain parenchyma and CSF.
- Capillary endothelium
- Arachnoid granulations
- Subarachnoid space
- Intraventricular (interstitial) space
- Blood-brain and blood-CSF barrier
- Choroid plexus
- Ependyma
- Cerebrospinal fluid (CSF)
- Arachnoid villi

Figure 5.15 Circumventricular Organs

- Select regions where blood-brain barrier is interrupted, allowing chemical communication between the brain and the systemic circulation.
- Subcommissural organ
- Organum vasculosum
- Median eminence
- Neurohypophysis
- Area postrema
- Pinnae
- Sublenticular organ

Complements: The organum vasculosum of the lamina terminalis may have neuroendocrine functions. The subcommissural organ may regulate fluid balance. The pineal may be involved in melatonin-related circadian rhythms, and the function of the subcommissural organ is not known.

Brain tumors, infections, and other disorders can disrupt the blood-brain barrier, resulting in extravasation of fluids into the interstitial space (see Figure 5.14). This excessive extracellular fluid is called vasogenic edema. Cellular damage—for example, in cerebral infarction—can cause excessive intracellular fluid accumulation within brain cells, a condition known as cytotoxic edema. Both kinds of edema often occur simultaneously.

This concludes our anatomical review of the cranial vault, ventricles, and meninges. The sections that follow (KCC 5.1–5.13) introduce several clinical concepts that will be referred to frequently throughout this book. Therefore, you may choose to skim these sections only briefly now and move on to Clinical Cases 5.1–5.10 to solidify your knowledge of the anatomical material in this chapter.

52 Headache is one of the most common neurologic symptoms. Although usually benign, it occasionally signals life-threatening conditions. Interestingly, there are no pain receptors in the brain parenchyma itself. Therefore, headache is caused by mechanical traction, inflammation, or irritation of other structures in the head that are innervated, including the blood vessels, meninges, scalp, and skull. The supranuclear dura (most of the intracranial cavity) is innervated by the trigeminal nerve (CN V), while the dura of the posterior fossa is innervated mainly by CN IX and also by CN X and the first three cervical nerves. The side of the headache often, but not always, corresponds to the side of pathologic disease.

Most headaches can be classified as either vascular headache or tension headache (Table 5.2). A diverse list of other causes of headache is also found in Table 5.2, including chronic daily headaches, chronic tension-related headaches, and chronic supranuclear headaches.

In migraine, about 75% of patients have a positive family history, suggesting a genetic basis. Symptoms may be provoked by certain foods, stress, eye strain, the menstrual cycle, changes in sleep patterns, or a variety of other triggers. Migraine is often preceded by an aura, or warning symptoms, including visual blurring, shimmering, scintillating distortions, or fortification scotoma—a characteristic region of visual loss bordered by zigzagging lines resembling the walls of a fort. The headache is often unilateral, but if it is always on the same side, an MRI scan is warranted to exclude a vascular malformation or other lesion as a trigger for the headaches. The pain is often throbbing and may be exacerbated by light (photophobia), sound (phonophobia), or sudden head movements. Nausea and vomiting may occur, and the scalp may be tender to the touch.

Duration is typically 30 minutes to up to 24 hours, and relief often occurs after sleeping. The severity of migraine headaches ranges from mild to very severe in different individuals, and migraines may recur from once every few years to up to several times per week.

Complicated migraines may be accompanied by a variety of transient local neurologic deficits (see KCC 16.3), including sensory phenomena, motor deficits (e.g., hemiplegia), visual loss, brainstem findings in basilar migraine, and impaired eye movements in ophthalmoplegic migraine. Migraine is a cause of these deficits should be excluded.
### TABLE 5.2 Differential Diagnosis of Headache

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Vascular headache</th>
<th>Migraine</th>
<th>Cluster headache</th>
<th>Tension headache</th>
<th>Other causes*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carotid or vertebral artery dissection</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Venous sinus thrombosis</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Post-sinus headache</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Pseudotumor cerebri</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Low CSF pressure</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Toxic or metabolic derangements</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Meningitis</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Epidural abscess</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Trigeminal or occipital neuralgia</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Neoplasm</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Disorders of the eyes, ears, sinuses, teeth, joints, or scalp</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*Following format of Figure 1.1

should be accepted only in the setting of recurrent episodes, and only after appropriate tests have been done to exclude cerebrovascular disease, epilepsy, or other disorders.

Treatment of migraine is often quite effective. Acute attacks usually respond to nonsteroidal anti-inflammatory drugs, anti-emetics, or ergot derivatives, or other medications, and rest in a dark, quiet room. Preventive measures include avoiding triggers when possible, and for patients who have frequent attacks, treatment with prophylactic agents such as beta-blockers, calcium channel blockers, valproate, or metylergistine (note that metylergistine carries a risk of retroperitoneal fibrosis).

Cluster headache is less than one-tenth as common as migraine. It occurs about five times more often in males than in females. Typically, clusters of headaches occur from once to several times per day every day for a few weeks, and then vanish for several months. Headache pain is extremely severe, often described as a steady boring sensation behind one eye, lasting from about 30 to 90 minutes. It is usually accompanied by unilateral autonomic symptoms such as tearing, eye redness, Horner’s syndrome (see KCC 13.5), unilateral flushing, sweating, and nasal congestion. Treatment is similar to that for migraine. In addition, inhaled oxygen is often effective in aborting attacks.

**Tension headache**, recently renamed *tension-type headache*, is a steady dull ache, sometimes described as a bandlike sensation. Although possibly related to excessive contraction of scalp and neck muscles, the pathophysiologic distinction between tension headache and migraine has been questioned. Tension-type headache includes the common type of mild to moderate headache that most individuals experience from time to time, lasting up to a few hours. However, some patients have tension-type headaches that occur continuously every day for years. This chronic form of headache is commonly associated with psychological stress, but it is often unclear which is cause and which is effect. Chronic daily headache of this kind is also commonly seen in *posttraumatic headache*. Treatment for tension-type headache includes muscle relaxation techniques, nonsteroidal anti-inflammatory drugs, other analgesics, and tricyclic antidepressants.

It is important for clinicians to be familiar with the other causes of headache listed in Table 5.2, since diagnosis and intervention with many of these disorders can be potentially lifesaving. We will mention only a few salient points here, and the specific disorders will be discussed in greater detail in the sections and chapters that follow. Sudden "explosive" onset of severe headache should always be taken seriously. A CT scan should be done urgently to see if a subarachnoid hemorrhage has occurred (see KCC 5.6 Figure 5.19f). It is less well recognized that headache is common in cerebral ischemia and infarction (see KCC 10.4), and in the post-WE period following seizures (see KCC 18.2). Low CSF pressure can occur spontaneously, or following lumbar puncture (see KCC 5.10), resulting in headache that is worse when standing up but better when lying down. In contrast, increased intracranial pressure can occur such as neoplasms that can increase intracranial pressure, the headache may be worse when lying down during the night (see KCC 5.5).

Headache accompanied by fever or signs of meningitis, infection, such as neck stiffness and sensitivity to light (see Table 5.8), should be evaluated immediately for possible infectious meningitis, since patients with this condition can deteriorate rapidly if untreated.

**Pseudotumor cerebri** is a condition of unknown cause characterized by headache and papilledema, or optic disc edema. It is treated with acetazolamide or, when severe, with shunting procedures (see KCC 5.7). **Temporal arteritis**, also called giant cell arteritis, is an important treatable cause of headache, seen most commonly in elderly individuals. In this disorder, vasculitis affects the temporal arteries, as well as other vessels, including those supplying the eye. The temporal artery is characteristically enlarged and firm. Diagnosis is made by measurement of the blood erythrocyte sedimentation rate (ESR) and by temporal artery biopsy. Prompt diagnosis and treatment with steroids is essential to prevent possible vision loss.

**EXTERNAL MALIGNANT MASS LESIONS**

- Anything abnormal that occupies volume within the cranial vault functions as a mass. Examples include tumors, trauma, infection, edema, hydrocephalus, and other disorders. Intracranial mass lesions can cause neurologic symptoms and signs by the following mechanisms:
  1. Compression and destruction of adjacent regions of the brain can cause neurologic abnormalities.
  2. A mass located within the cranial vault can raise the intracranial pressure, which causes certain characteristic symptoms and signs.
  3. Mass lesions can displace nervous system structures so severely that they are shifted from one compartment into another, a situation called herniation.

In this section we will discuss local effects of the mass itself in the brain. In KCC 5.3 and 5.4 we will discuss elevated intracranial pressure and herniation.

Mass lesions can cause both local tissue damage and remote effects through mechanical distortion of adjacent structures. Mass effect is a descriptive term used for any distortion of normal brain geometry due to a mass lesion. Mass effect may be as subtle as a mild flattening, or effacement, of sulci next to a lesion seen on MRI scan but producing no symptoms. Depending on location and size, a mass can produce neurologic abnormalities due to local damage. For example, lesions located in the primary motor cortex will cause contralateral weakness. If the mass distorts or irritates blood vessels or meninges, it may cause headache (see KCC 5.1). Compression of blood vessels can also cause ischemic infarction, and erosion through blood vessel walls can cause hemorrhage.

Disruption of the blood-brain barrier results in extravasation of fluid into the extracellular spaces, producing vasogenic edema (see Figures 5.13, 5.14). Compression of the ventricular system can obstruct CSF flow, producing hydrocephalus (see KCC 5.7). Lesions can provoke abnormal electrical discharges in the cerebral cortex, resulting in seizures (see KCC 18.2). In addition, remote effects may result from functional changes in regions receiving important synaptic connections from the damaged areas. Large masses can produce dramatic midline shift of brain structures away from the side of the lesion. Displacement and stretching of the upper brainstem impairs function of the reticular activating systems (see Figure 2.23) causing impaired consciousness and, ultimately, coma. The pineal calcification (see Figure 4.12f) is a useful landmark for measuring extent of midline shift at the level of the upper brainstem. The amount of pineal shift has been shown to correlate with impairment of consciousness. In the extreme, mass effect causes brain structure to shift from one compartment into another, leading to herniation (see KCC 5.4).
Figure 5.16 Intracranial Pressure versus Intracranial Mass Volume
Small intracranial masses can be compensated for by reductions in intracranial CSF and blood volume. Larger masses lead to a steep increase in intracranial pressure, causing reduced cerebral perfusion and, ultimately, herniation. Note that the volume of CSF has been exaggerated in the equilibrium state (as seen in cerebral atrophy) for illustrative purposes.

![Diagram showing intracranial pressure and mass volume]

In Figure 5.16, larger lesions overcome this compensatory mechanism, and the intracranial pressure eventually begins to rise steeply. This can ultimately lead to herniation (see Figure 5.4) and death (right part of the curve in Figure 5.16).

Severely elevated intracranial pressure can cause decreased cerebral blood flow and brain ischemia. Cerebral blood flow depends on cerebral perfusion pressure, which is defined as the mean arterial pressure minus the intracranial pressure (CPP = MAP – ICP). Therefore, as the intracranial pressure increases, cerebral perfusion pressure decreases. Autoregulation of cerebral vessel caliber can compensate for modest reductions in cerebral perfusion pressure, leading to relatively stable cerebral blood flow. However, large increases in intracranial pressure can exceed the capacity of autoregulation, leading to reduced cerebral blood flow and brain ischemia. Depending on the type of lesion, intracranial pressure can change suddenly or more slowly over days to weeks. If left untreated, severely elevated intracranial pressure causes irreversible brain damage and death, sometimes within a few hours.

It is essential for clinicians to recognize the symptoms and signs of elevated intracranial pressure (Table 5.3) so that appropriate treatment can be instituted without delay. Let's discuss each of the symptoms and signs in Table 5.3 in turn. Headache associated with intracranial mass lesions is often worse in the morning, since brain edema increases overnight from the effects of gravity in the reclining position. Altered mental status, especially irritability and depressed level of alertness and attention, is often the most important indicator of elevated intracranial pressure. The mechanisms giving rise to nausea and vomiting in elevated intracranial pressure are not known. Vomiting occasionally occurs suddenly and without much nausea. This is called projectile vomiting.

Elevated intracranial pressure is transmitted through the subarachnoid space to the optic nerve sheath, obstructing axonal transport and venous return in the optic nerve. Ophthalmoscopic exam (see neuroexam.com Video 25) may, therefore, reveal papilledema, in which there is engorgement and elevation of the optic disc, sometimes accompanied by retinal hemorrhages (Figure 5.17). This classic sign of elevated intracranial pressure takes several hours to days to develop and is often not present in the acute setting. Transient or permanent optic nerve injury can occur in association with papilledema, leading to visual blurring or visual loss. Areas of decreased vision most commonly include an increased blind spot or a concentric visual field defect affecting mainly the peripheral margins of the visual field (see Figure 11.16A). Diplopia (double vision) can occur as a result of downward traction on CN VI, causing unilateral or bilateral abducens nerve palsies (see KCC 13.4). Finally, Cushing's triad—hypertension, bradycardia, and irregular respirations—is another classic sign of elevated intracranial pressure. Hypertension may be a reflex mechanism to maintain cerebral perfusion pressure, bradycardia may be a reflex response to the hypertension, and irregular respirations are caused by impaired brainstem function (see Figure 14.16). In reality, a variety of changes in vital signs other than Cushing's triad can be seen as a result of brainstem dysfunction, including hypertension and tachycardia.

The goal of treating elevated intracranial pressure is to reduce it to safe levels, providing time to treat the underlying disorder. Normal intracranial pressure in adults is less than 20 cm H₂O, or less than 15 mm Hg (torr). (1 cm H₂O = 0.735 mm Hg; 1 mm Hg = 1.36 cm H₂O.) Another critical goal of therapy is to keep cerebral perfusion pressure above 50 mm Hg so that cerebral blood flow is maintained. Intracranial pressure can be measured in clinically stable patients during lumbar puncture (see KCC 5.10). However, lumbar puncture should not be performed in patients suspected of having severely elevated intracranial pressure due to risk of precipitating herniation (see KCC 5.4).

### TABLE 5.3 Common Symptoms and Signs of Elevated Intracranial Pressure

<table>
<thead>
<tr>
<th>SYMPTOM OR SIGN</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>Altered mental status, especially irritability and depressed level of alertness and attention</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td></td>
</tr>
<tr>
<td>Papilledema</td>
<td>Visual loss</td>
</tr>
<tr>
<td>Diplopia (double vision)</td>
<td></td>
</tr>
<tr>
<td>Cushing's triad—hypertension, bradycardia, and irregular respirations</td>
<td></td>
</tr>
</tbody>
</table>

Note: This is often the most important indicator of elevated intracranial pressure.

Figure 5.17 Papilledema

(A) Funduscopic view of retina from a normal subject (left eye). Note sharp margins of the optic disc. (B) Papilledema in a patient with elevated intracranial pressure (left eye). This was a 43-year-old man who developed headaches, visual blurring, and horizontal diplopia. Lumbar puncture had an opening pressure of 40 cm H₂O. Magnetic resonance venogram revealed a bilateral sigmoid sinus venous thrombosis (see KCC 10.7). Blood studies showed an elevated anticardiolipin antibody (see KCC 10.4). The patient was treated successfully with chronic oral anticoagulation.
TABLE 5.4 Treatment Measures for Elevated Intracranial Pressure

<table>
<thead>
<tr>
<th>INTERVENTION</th>
<th>TIME TO ONSET OF EFFECT</th>
<th>PROPOSED MECHANISM/COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevate head of bed 30°, and maintain head straight to avoid obstructing jugular venous return</td>
<td>Immediate</td>
<td>Promotes venous drainage</td>
</tr>
<tr>
<td>Intubate and hyperventilate to Pco2 of 25-30 mm Hg.</td>
<td>30 seconds</td>
<td>Causes cerebral vasodilation</td>
</tr>
<tr>
<td>IV mannitol 1 g/kg bolus, then 0.25 mg/kg every 6 hours, aiming for serum osmolality of 300-310 while maintaining normalvolume status and normal blood pressure. Furosemide may also be added to promote diuresis of excess fluid.</td>
<td>5 minutes</td>
<td>Promotes removal of edema and other fluids from CNS while maintaining cerebral perfusion</td>
</tr>
<tr>
<td>Ventricular drainage</td>
<td>Minutes</td>
<td>Removal of CBF decreases intracranial pressure</td>
</tr>
<tr>
<td>If other measures fail, try barbiturate-induced coma</td>
<td>1 hour</td>
<td>Causes cerebral vasodilation and reduced metabolic demands</td>
</tr>
<tr>
<td>Hemicraniectomy (removal of skull overlying mass lesion)</td>
<td>Immediate</td>
<td>Decompresses intracranial cavity. Experiential.</td>
</tr>
<tr>
<td>Steroids</td>
<td>Hours</td>
<td>Reduces cerebral edema, possibly by strengthening blood-brain barrier. May also work by other mechanisms. Often used with brain tumors. Not shown to improve outcome in acute head trauma, stroke, or hemorrhage.</td>
</tr>
</tbody>
</table>

In critically ill patients, intracranial pressure can be monitored continuously with a ventricular drain, intraparenchymal monitor, subarachnoid bolt, or a variety of other devices placed neuroradiologically within the cranium and connected to a pressure transducer. Measures to lower intracranial pressure can then be instituted as described in Table 5.4 while the results are being monitored. Note that treatment of elevated intracranial pressure is somewhat controversial, and authorities differ as to which measures are actually beneficial (the list in Table 5.4 does not reflect this controversy). It should be reemphasized that all of these measures are temporary, and they are best used to buy time while treatment of the underlying cause of the elevated intracranial pressure is instituted.

KEY CLINICAL CONCEPT

581 As discussed in KCC 5.2, intracranial tumors, hemorrhage, edema, and other masses cause a displacement of intracranial structures called mass effect. Herniation occurs when mass effect is severe enough to push intracranial structures from one compartment into another. Herniation between different compartments is associated with certain distinct clinical features. Some authors argue that herniation does not actually cause these clinical features, and that it is merely an epiphenomenon. Nevertheless, herniation remains a clinically useful concept and will therefore be discussed in more traditional terms in this section.

The three most clinically important herniation syndromes are caused by herniation through the tentorial notch (transientorial herniation), herniation centrally and downward (central herniation), and herniation under the falk cerebri (subfalcial herniation), respectively (Figure 5.18).

Trans tentorial Herniation

Trans tentorial herniation (or simply, tentorial herniation) is herniation of the medial temporal lobe, especially the uncal (uncal herniation), inferiorly through the tentorial notch (see Figures 5.6, 5.18). Uncal herniation is her-
produce significant central herniation through the tentorial opening, resulting in bilateral uncal herniation (as described above). With severe elevations in intracranial pressure, large supratentorial mass lesions, or mass lesions in the posterior fossa, central herniation can progress downward through the foramen magnum (see Figure 5.18).

Herniation of the cerebellar tonsils downward through the foramen magnum is called tonsillar herniation (see Figure 5.18). This condition is associated with compression of the medulla and usually leads to respiratory arrest, blood pressure instability, and death. Some studies have called into question the pathophysiologic importance of central herniation, and there is controversy over whether central herniation is seen only as a postmortem phenomenon.

Subfalcial Herniation

Unilateral mass lesions can cause the cirrulate gyrus (see Figure 2.11B) and other brain structures to herniate under the falx cerebri (see Figure 5.5) from one side of the cranium to the other. The result is subfalcial herniation (see Figure 5.18). Usually no signs can be attributed directly to the subfalcine herniation. Sometimes, however, one or both anterior cerebral arteries can be occluded under the falx, leading to infarcts in the anterior cerebral artery territory (see Figures 10.5, 10.6).

KEY CLINICAL CONCEPT

HEAD TRAUMA

Head trauma is, unfortunately, a common cause of morbidity and mortality, especially in the young adult and adolescent population. Mild head trauma causes concussion, defined as reversible impairment of neurologic function for minutes to hours following a head injury. The mechanism of concussion is unknown, but it may involve transient diffuse neuronal dysfunction. CT and MRI scans are normal. Clinical features of concussion include loss of consciousness; "seeing stars," followed by headache, dizziness, and occasionally nausea; and vomiting. Some of these features may result from intracranial or intraventricular hemorrhages (see KCC 5.1) triggered by head injury. Occasionally, head trauma is accompanied by anoxia or retrograde amnesia (see KCC 18.1) for a period of several hours surrounding the injury. Recovery is usually complete, although occasional patients develop postconcussive syndrome even after relatively minor trauma, with headaches, lethargy, mental dullness, and other symptoms lasting up to several months after the accident. Even mildly relative head injuries can occasionally cause dissection of the carotid or vertebral arteries (see KCC 10.6), resulting in transient ischemic attacks or cerebral infarcts.

More severe head trauma can cause permanent injury to the brain through various mechanisms, including diffuse axonal shear injury, which causes widespread or patchy damage to the white matter and cranial nerves; petechial hemorrhages, or small spots of blood in the white matter; larger intracranial hemorrhages (see Figure 5.19; KCC 5.6); cerebellar contusion (see Figure 5.2); and direct tissue injury by penetrating trauma such as gunshot wounds or open skull fracture. Cerebral edema may occur as well, with or without other injuries, contributing to elevated intracranial pressure in head injury.

In addition to the neurologic exam, certain signs on general physical examination may provide clues of significant head trauma (see Table 3.9). In all head injuries, the spine should be evaluated carefully as well because the same mechanism of injury may cause an unnoted unstable spinal fracture. Spine X-rays are usually necessary in head injuries, especially when the patient is not fully responsive. Symptoms of intracranial hemorrhage resulting from head injury sometimes occur after a delay of up to several hours following the event (see KCC 5.6). Therefore, all patients with head injury that causes neurologic deficits, even when transient, should undergo a CT scan and be observed closely for signs of deterioration during the first 24 hours. Patients with more serious head injuries should be treated as described in KCC 5.3 and 5.6.

Intracranial hemorrhage can be traumatic or atraumatic. It can occur in several different compartments within the cranial vault (Figure 5.19). Intracranial hemorrhages are classified according to location and are often abbreviated as follows:

1. Epidural hematoma (EDH)
2. Subdural hematoma (SDH)
3. Subarachnoid hematoma (SAH)
4. Intracerebral or intraparenchymal hemorrhage (ICH)

Specific traumatic or atraumatic causes are most common in each of these locations, as indicated in the discussion that follows.

Epidural Hematoma

Location: In the potential space between the dura and the skull. Useful cause: Rupture of the middle meningeal artery (see Figure 5.7) due to fracture of the temporal bone by head trauma.

Clinical features and radiological appearance: Rapidly expanding hemorrhage under arterial pressure pools the dura away from the inner surface of the skull, forming a lens-shaped biconvex hematoma that often does not spread past the cranial sutures where the dura is tightly apposed to the skull (see Figure 5.19A). Initially the patient may have no symptoms (lucid interval). However, within a few hours the hematoma begins to compress brain tissue, often causing elevated intracranial pressure (see KCC 5.3) and, ultimately, herniation (see KCC 5.4) and death unless treated surgically.

Subdural Hematoma

Location: In the potential space between the dura and the loosely adherent arachnoid. Useful cause: Rupture of the bridging veins, which are particularly vulnerable to shear injury as they cross from the arachnoid into the dura (see Figure 5.1). Clinical features: Venous blood disperses relatively easily between the dura and the arachnoid, spreading out over a large area and forming a crescent-shaped hematoma. Two types of subdural hematoma—chronic and acute—are distinguished by different clinical features.

Chronic Subdural Hematoma

Often seen in elderly patients who atrophy allows the brain to move more freely within the cranial vault, thus making the bridging veins more susceptible to shear injury. This type of hematoma (see Figure 5.19D) may be seen with minimal or no known history of trauma. Cerebral edema collects over weeks to months, allowing the brain to accommodate and therefore causing vague symptoms such as headache, cognitive impairment, and unusual gait. In addition, focal dysfunction of the underlying cortex may result in focal neurologic deficits.

Acute Subdural Hematoma

For a significant subdural hematoma to occur immediately after an injury, the impact velocity must be quite high. Therefore, acute subdural hematoma is usually associated with other serious injuries, such as traumatic subarachnoid hemorrhage and brain contusion (to be discussed shortly). The prognos-
Figure 5.19 Types of Intracranial Hemorrhage Demonstrated by CT Scans

(A) Epidural hematoma

(B) Acute subdural hematoma

(C) Isodense subdural hematoma

(D) Chronic subdural hematoma

(E) Hematomat effect resulting from mixed acute and chronic subdural bleed

(F) Subarachnoid hemorrhage

(G) Contusion

(H) Intraparenchymal (basal ganglia) hemorrhage
sit is thus usually worse than with chronic subdural hematoma or even epidural hematoma.

Radiological appearance: Subdural hematomas are typically crescent shaped and spread over a large area (see Figures 5.18A–E, H). Density depends on the age of the blood. Recall that acute blood is hypodense (see Figure 5.19B) and therefore bright on CT scan (see Chapter 4). After 1 to 2 weeks the clot begins to liquefy and may appear isodense (see Figure 5.19C). If there is no further bleeding, after 3 to 4 weeks the hematoma will be completely liquefied and will appear uniformly hypodense (see Figure 5.19D). If there is continued occasional bleeding, however, there will be a mixed density appearance resulting from liquefied chronic blood mixed with clotted hypodense blood. Sometimes, with mixed-density hematomas, the denser acute blood settles to the bottom, giving a characteristic hematocrit effect (see Figure 5.19B). Subdural hematoma is treated by surgical evacuation, except for small to moderate-sized chronic subdural hematomas, which, depending on the severity of symptoms, can often be followed clinically because some will resolve spontaneously.

Subarachnoid Hemorrhage

Location: In the CSF-filled space between the arachnoid and the pia, which contains the major blood vessels of the brain (see Figure 5.1).

Radiological appearance: Unlike subdural hematoma, blood can be seen on CT to track down into the sulci following the contours of the pia (see Figure 5.19F).

Usual cause: Subarachnoid hemorrhage is seen in two clinical settings: nontraumatic (spontaneous) and traumatic.

Nontraumatic (Spontaneous) Subarachnoid Hemorrhage

Spontaneous subarachnoid hemorrhage usually presents with a sudden catastrophic headache. Patients may describe this as the "worst headache of my life" or as feeling like the head is suddenly about to explode. In the vast majority of cases (75–90%), spontaneous subarachnoid hemorrhage occurs as a result of rupture of an arterial aneurysm in the subarachnoid space. Less common (4–5%) is the result of bleeding from an arteriovenous malformation and from other rare or unknown causes. Risk factors for intracranial aneurysm include atherosclerotic disease, congenital anomalies in cerebral vessel walls, polycystic kidney disease, and connective tissue disorders such as Marfan's syndrome.

Saccular, or berry, aneurysms usually arise from arterial branch points near the circle of Willis (Figure 5.20). These are balloonlike outpouchings of the vessel wall that typically have a neck connecting it to the parent vessel and a fragile dome that can rupture. Over 85% occur in the anterior circulation (carotid artery and its branches). The most common locations, listed in descending order, are the anterior communicating artery (ACOM, about 30%), posterior communicating artery (PCOM, about 25%), and middle cerebral artery (MCA, about 20%). Saccular aneurysms can also occur in the branches of the posterior circulation (vertebral-basilar system, about 15%). Occasionally the main vessel itself becomes dilated, forming a fusiform aneurysm (see Figure 5.20), which is less prone to rupture than saccular aneurysms. Aside from symptoms caused by rupture, large unruptured aneurysms can occasionally present with symptoms due to mass effect or the compression of adjacent structures. An important example is PCOM aneurysm arising from the internal carotid artery (see Figure 5.20), which can cause a painful third-nerve palsy (see Figures 5.6, 13.2, KCJ 13.2). The PCOM junction with the posterior cerebral artery can also give rise to aneurysms, but much less commonly than the PCOM junction with the carotid.

Figure 5.20 Common Sites of Intracranial Aneurysms

Risk factors for aneurysmal rupture include hypertension, cigarette smoking, alcohol consumption, and situations causing sudden elevation in blood pressure. The clinical effects of subarachnoid hemorrhage can range from headache and meningeal irritation (Table 5.5), causing nuchal rigidity and photophobia, to cranial nerve and other focal neurologic deficits, to impaired consciousness, coma, and death. Perhaps 25% of all patients with subarachnoid hemorrhage die in the immediate aftermath of the event and thus never reach the hospital for treatment. The overall mortality of subarachnoid hemorrhage is about 50%; however, the prognosis is better in mild cases. In subarachnoid hemorrhage due to ruptured aneurysm, the risk of rebleeding is 4% on the first day and 20% in the first 2 weeks. Therefore, prompt diagnosis and early treatment of aneurysmal subarachnoid hemorrhage is essential.

<table>
<thead>
<tr>
<th>TABLE 5.5 Signs and Symptoms of Meningeal Irritation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
</tr>
<tr>
<td>Lethargy</td>
</tr>
<tr>
<td>Sensitivity to light (photophobia) and noise (phonophobia)</td>
</tr>
<tr>
<td>Fever</td>
</tr>
<tr>
<td>Nuchal rigidity (stiff neck): unable to touch chin to chest</td>
</tr>
<tr>
<td>Kernig's sign: pain in hamstring when knees are straightened with hips flexed</td>
</tr>
<tr>
<td>Broadsphendi's sign: flexion at neck causes hips to flex</td>
</tr>
</tbody>
</table>

Brainstem
CT scan performed within the first 3 days after rupture can detect the hemorrhage in over 95% of cases. It is important to perform a CT scan without contrast because both subarachnoid blood and contrast material appear white on the scan (see Figures 4.4, 5.19F), making it difficult to see a small hemorrhage. CT is better than MRI for detecting acute subarachnoid hemorrhage, although about 2 days subarachnoid hemorrhage may no longer be visible on CT (see Chapter 4). Lumbar puncture (see KCC 5.10) should be performed in suspected subarachnoid hemorrhage with a negative CT, but not with a positive CT because increased intracranial pressure across the aneurysm can occasionally precipitate rebleeding.

An angiogram (see Chapter 7) is next performed to define the exact location and size of the aneurysm. A four-vessel angiogram (both carotids and both vertebratlas) should be performed since multiple aneurysms are often seen in different vessels. In mild subarachnoid hemorrhage, most neurosurgeons now prefer to operate as soon as possible, placing a clip across the neck of the aneurysm to prevent a second potentially catastrophic event. The more traditional approach was to wait 1 to 2 weeks and then perform surgery (if the patient survived), with a somewhat lower risk of intraoperative rebleeding.

Following subarachnoid hemorrhage, delayed cerebral vasospasm occurs in about half of all patients, with a peak severity about 1 week after the hemorrhage. This can lead to cerebral ischemia or infarction. Vasospasm is often treated with volume expansion and induced hypertension in the intensive care unit. Such treatment can be done safely after the aneurysm has been clipped, which is another reason that early surgery is preferred. Administration of calcium channel blockers such as nimodipine early after hemorrhage can also improve the outcome, although the mechanism is uncertain because calcium channel blockers do not improve vasospasm angiographically.

**Traumatic Subarachnoid Hemorrhage**

Traumatic subarachnoid hemorrhage, which is caused by bleeding into the CSF from damaged blood vessels associated with cerebral contusions and other traumatic injuries, is actually more common than spontaneous subarachnoid hemorrhage. Like spontaneous subarachnoid hemorrhage, it is usually associated with severe headache due to meningeal irritation from blood in the CSF. Deficits are usually related to the presence of other cerebral injuries. Unlike aneurysmal subarachnoid hemorrhage, vasospasm is not usually seen.

**Intracerebral or Intraparenchymal Hemorrhage**

*Location:* Within the brain parenchyma in the cerebral hemispheres, brainstem, cerebellum, or spinal cord.

*Usual cause:* Once again, this type of hemorrhage may be traumatic or non-traumatic.

**Traumatic Intracerebral or Intraparenchymal Hemorrhage**

Contusions of the cerebral hemispheres occur in regions where cortical gyri are at the bony skull (Figure 5.21); see also Figures 5.2, 5.4). Thus, contusions are most common at the temporal and frontal poles (see Figure 5.16C). Interestingly, they are less common at the occipital poles. Contusions occur on the side of the impact (coup injury) as well as on the side opposite the impact (contrecoup injury) because of rebound of the brain against the skull. Shearing forces can produce areas of bleeding in the white matter as well, including small petechial or larger confluent intraparenchymal hemorrhage. Severe injuries are often accompanied by a combination of contusion, subarachnoid hemorrhage, and subdural hemorrhage. When a combination of intraparenchymal, subarachnoid, and acute subdural hemorrhage is seen on CT scan, head trauma can be assumed.

**Nontraumatic Intracerebral or Intraparenchymal Hemorrhage**

There are many different causes of intraparenchymal hemorrhage, including hyperextension, brain tumors, secondary hemorrhage after ischemic infarction, vascular malformations, blood coagulation abnormalities, infections, vessel fragility caused by deposition of amyloid protein in the blood vessel wall (amyloid angiopathy), vasculitis, myocytic (infectious) aneurysms in the setting of endocarditis, and so on.

**Hypertensive Hemorrhage** is the most common cause, and it tends to involve small penetrating blood vessels (see Figure 5.19F). The pathogenesis is uncertain, but it may be related to chronic pathologic effects of hypertension on the small vessels, such as the leptomeningeal arterioles (see Figures 4.16A, 10.7), including lipohyalinosis and microaneurysms of Charcot-Bouchard.

The most common locations for hypertensive hemorrhage, in decreasing order of frequency, are the basal ganglia (usually the putamen), thalamus, cerebellum, and pons. Some hemorrhages may involve the ventricles, either by extending from adjacent parenchyma or by arising from blood vessels in the ventricles themselves. These are described as intraventricular extension of an intraparenchymal hemorrhage or as intraventricular hemorrhage, respectively. Unlike aneurysmal hemorrhage, the rebleeding rate for hypertensive hemorrhage is low, although the hematoma often continues to enlarge, causing worsening clinical status for several hours after onset. Edema also gradually develops in the tissue surrounding the hemorrhage, causing a slow clinical worsening that reaches its peak about 5 days after onset.

In lobar hemorrhage, bleeding involves the occipital, parietal, temporal, or frontal lobe. The most common cause of lobar hemorrhage is probably amyloid (congoophilic) angiopathy. In this condition, deposits of amyloid in the vessel wall of older patients (usually >50 years old) cause vascular fragility. Unlike hypertensive hemorrhage, in amyloid angiopathy the hemorrhages tend to be recurrent or multiple, and they are often more superficial in
location. Transient symptoms resembling transient ischemic attack (see KCC 10.3) or seizures can occur in amyloid angiopathy for weeks or months preceding hemorrhage. Lobar hemorrhage can also be seen in hypertension.

Certain vascular malformations are another important cause of intracranial hemorrhage. Vascular malformations are classified as:

1. Arteriovenous malformations
2. Cavernous malformations (sometimes called cavernous angiomas, cavernous hemangiomas, or cavernomas)
3. Capillary telangiectasias (capillary angiomata)
4. Venous angiomas (venous malformations, deep venous anomalies).

Of these, only arteriovenous and cavernous malformations have a high likelihood of causing intracranial hemorrhage.

Arteriovenous malformations (AVMs) are congenital abnormalities in which there are abnormal direct communications between arteries and veins, often forming a tangle of abnormal blood vessels visible as flow voids on MRI scan, but best seen on conventional angiography (see Figures 11.25, 11.26). Size can range from a few centimeters to half the brain. Aside from sudden severe symptoms from intracranial hemorrhage, patients also commonly present with seizures, or with migrainelike headaches in the absence of hemorrhage. Hemorrhage is usually intraparenchymal, but it can extend to the intraventricular or subarachnoid space as well. The risk of rebleeding is about 1% to 4% per year, much lower than an aneurysmal hemorrhage (discussed earlier). Treatments for AVM, which depend on clinical status, size, and location of the lesions, include neurosurgical removal, intravascular embolization, and stereotactic radiosurgery (see KCC 16.4).

Cavernous malformations are abnormally dilated vascular cavities lined by only one layer of vascular endothelium. They are not visible on conventional angiography, but with the advent of MRI the diagnosis of cavernous malformations has increased dramatically. They have a characteristic MRI appearance, with a central T1 or T2, surrounded by a dark rim on T2-weighted sequences because of the presence of hemosiderin (see Table 4.4). Some patients have multiple cavernous malformations, and a familial autosomal dominant form of this disorder exists. Patients often present with seizures. Risk of hemorrhage is between 0.1% and 2.7% per lesion per year, but the risk of hemorrhage increases after an initial bleed. Although still evolving, clinical criteria for operating on cavernous angiomas often include clinically significant hemorrhage or seizures, and favorable operative location.

Capillary telangiectasias are small regions of abnormally dilated capillaries that rarely give rise to intracranial hemorrhage. Venous angiomas are dilated veins visible on MRI scans as a single flow void extending to the brain surface. They are usually an incidental finding on MRI and are not known to cause any clinical symptoms themselves, but they can sometimes be seen in association with cavernous malformations.

Extracranial Hemorrhage

Head trauma can also cause hemorrhage in the inner ear, called hemotympanum; hemorrhage in subarachnoid tissues, resulting in Battle's sign; or subconjunctival hemorrhage (see Table 3.9). Scalp hemorrhage can cause profuse bleeding. Hemorrhage in the loose space between the external peristeum and galea aponeurotica (see Figures 5.1) can produce a "goose egg," or subgaleal hemorrhage. In newborns, bleeding during delivery can occur between the skull and external peristeum (periosteum), called a cephalohematoma, which can occasionally be quite large.

Hydrocephalus (meaning "water in the head") is caused by excess CSF in the intracranial cavity. This condition can result from (1) excess CSF production, (2) obstruction of flow at any point in the ventricles or subarachnoid space, or (3) decrease in reabsorption via the arachnoid granulations.

Excess CSF production is quite rare as a cause of hydrocephalus. It is seen only in certain tumors, such as choroid plexus papilloma. Obstruction of CSF flow is a common cause of hydrocephalus and can be produced by obstruction of the ventricular system by tumors, intraparenchymal hemorrhage, other masses, and congenital malformations. This can occur anywhere along the path of CSF flow (see Figures 5.10, 5.11), but especially at narrow points such as the foramen of Monro, the cerebral aqueduct, or the fourth ventricle. Obstruction can also occur outside the ventricles in the subarachnoid space as a result of debris or adhesions from prior hemorrhage, infection, or inflammation.

Decreased CSF reabsorption can cause hydrocephalus when the arachnoid granulations are damaged or clogged. Decreased reabsorption at the arachnoid granulations is difficult to distinguish clinically from obstruction of CSF flow in the subarachnoid space, and often has similar causes (i.e., prior hemorrhage, infection, inflammation, etc.). For this reason, in clinical practice, hydrocephalus is often divided into two categories:

1. Communicating hydrocephalus is caused by impaired CSF reabsorption in the arachnoid granulations, obstruction of flow in the subarachnoid space, or (rarely) by excess CSF production.

2. Noncommunicating hydrocephalus is caused by obstruction of flow within the ventricular system.

The main symptoms and signs of hydrocephalus are similar to those of any other cause of elevated intracranial pressure (see KCC 8.2, 8.3) and can be acute or chronic, depending on how quickly the hydrocephalus develops. These symptoms and signs include headache, nausea, vomiting, cognitive impairment, decreased level of consciousness, papilledema, decreased vision, and sixth-nerve palsies. In addition, ventricular dilation in hydrocephalus may compress descending white matter pathways from the frontal lobes, leading to frontal lobe-like abnormalities including an unsteady magnetic gait (the patient cannot bare the floor) and incontinence. In neonatal hydrocephalus when the cranial sutures have not yet fused, the skull expands to reduce elevated intracranial pressure, resulting in increased head circumference. A bulging anterior fontanelle is also an important sign of elevated intracranial pressure in infants.

It is important to recognize the eye movement abnormalities associated with hydrocephalus. In mild or slowly developing cases, only a sixth-nerve palsy may be seen, which causes incomplete or slow abduction of the eye in the horizontal direction. Interestingly, hydrocephalus may affect the sixth nerve of one or both eyes. When hydrocephalus is more severe, inward deviation of one or both eyes may be present at rest. Also, in more severe or rapidly developing cases, dilation of the suprapineal recess (see Figure 5.11D) of the posterior third ventricle can push downward onto the collicular plate of the midbrain, producing Parnaud's syndrome. This syndrome is described in greater detail in Chapter 13 (see KCC 13.9); however, the important abnormality to be aware of for now is limited vertical gaze, especially in the upward direction. Therefore, particularly in children with acute hydrocephalus, the ominous "setting sun" sign, consisting of bilateral deviation of the eyes downward and inward, may be seen. These abnormalities often reverse after treatment.

Treatment of hydrocephalus usually involves a procedure that allows cerebrospinal fluid to bypass the obstruction and drain from the ventricles. In an
KEY CLINICAL CONCEPT

BRAIN TUMORS

There are two broad categories of brain tumors. Primary CNS tumors arise from abnormal proliferation of cells originating in the nervous system. Metastatic tumors arise from neoplasms originating elsewhere in the body that spread to the brain. Common brain tumors in adults are shown in Table 5.6. The two most common brain tumors are glioblastoma and brain metastases, of which the more common varies from series to series depending on the methodology used to select patients. In some series, particularly those based on postmortem pathology, metastatic tumors are 5 to 8 times more common than all primary CNS tumors combined. The next most common brain tumor is meningioma, followed by astrocytoma, pituitary adenoma, schwannoma, and ependymoma.

In adults, about 70% of tumors are supratentorial and 30% are infratentorial, while in pediatric patients the reverse is true, with about 70% of tumors located in the posterior fossa and 30% supratentorial. The most common brain tumors in children are astrocytoma and medulloblastoma, followed by ependymoma. Since pediatric brain tumors are often in the posterior fossa, they tend to cause hydrocephalus (see KCC 5.7) through compression and obstruction of the fourth ventricle or aqueduct of Sylvius.

Symptoms of brain tumors depend on the location, size, and rate of growth of the tumor. Headache and other signs of elevated intracranial pressure (see Table 5.3) are common at presentation. Some tumors may present with seizures, or with focal symptoms and signs depending on the location of the tumor. The tumors most commonly associated with seizures are oligodendrogliomas and meningiomas.

Brain tumors are considered benign if they do not infiltrate or disseminate widely through the nervous system and malignant if they have the potential to spread. Unlike systemic malignancies, however, malignant brain tumors only rarely undergo metastasis spread outside of the central nervous system. In addition, so-called benign brain tumors may be incurable, and ultimately fatal if they grow in vital areas of the brain where surgical excision is not possible.

Treatments for brain tumors depend on the histological type, location, and size of the tumor. Surgical removal of as much tumor as possible without causing serious deficits is usually pursued. Recent data suggest that the extent of surgical resection should be greater than 90% to have a positive effect on outcome. Next, depending on the lesion, radiation therapy and/or chemotherapy may be beneficial. Steroids are often used to reduce edema and swelling. Small, benign-looking tumors may simply be followed with serial MRI scans, depending on the clinical situation, especially in elderly patients. Gliomas are subdivided into several different types (see Table 5.6). Gliomas arising from astrocytes are called astrocytomas. Gliomas are usually classified by the World Health Organization grading system, in which the most malignant is grade IV, or glioblastoma multiforme. Unfortunately, glioblastoma is relatively common and usually leads to death within 1 year despite maximal resection, radiation, and chemotherapy.

Meningiomas arise from the arachnoid villi cells and occur in order of decreasing frequency, over the lateral convexities, in the falx, and along the basal regions of the cranial. They grow quite slowly and appear on CT and MRI scans as homogeneously enhancing areas that arise from the meningeal layers. In female patients, meningiomas are associated with breast cancer. Meningiomas are treated by local excision. Five percent of meningiomas behave in an atypical or malignant fashion.

Pituitary adenomas can cause endocrine disturbances or compress the optic chiasm, usually resulting in a bitemporal visual field defect (see Figure 11.32C). Other lesions can arise in this area as well (including meningiomas, craniopharyngiomas, hypothalamic gliomas, and others). Pituitary adenomas are discussed further in Chapter 17 (see KCC 17.1). Treatment with dopaminergic agonists often shrinks pituitary adenomas. If this is ineffective, transphenoidal resection is performed (see KCC 17.1). Schwannomas, which are most common on CN VIII, are discussed in Chapter 12 (see KCC 12.5).

Lymphomas of the central nervous system have been on the rise in recent years, only in part attributable to the increase in human immunodeficiency virus (HIV). This neoplasm arises from B lymphocytes and commonly involves regions adjacent to the ventricles. It can often be controlled for several years with chemotherapy and radiation therapy and currently has a median survival rate of close to four years.

Pineal region tumors are relatively uncommon (less than 1% of CNS neoplasms) and include pineocytoma (pineocytoma and pineoblastoma), germinoma, and rarely teratoma or glioma. Tumors in this region may obstruct the cerebral aqueduct, causing hydrocephalus (see KCC 5.7), or may compress the dorsal midbrain, causing Parinaud's syndrome (see KCC 13.9). Brain metastases can occur with numerous tumor types. The most common are carcinomas of the lung, breast, kidneys, and gastrointestinal tract, and melanoma. Some brain metastases have a tendency to hemorrhage, including melanoma, renal cell carcinoma, thyroid carcinoma, and choriocarcinoma. Although lung cancer metastases do not often hemorrhage, the most common tumor-causing brain hemorrhage is lung cancer, simply because the incidence of lung cancer and metastases to the brain is so
high. When solitary (or even two to three circumscribed) brain metastases occur, outcome is improved by complete surgical excision, when possible. Multiple or unresetable brain metastases are treated with radiation therapy. In pediatric patients, the most common brain tumors are posterior fossa astrocytoma, medulloblastoma, and ependymoma. Cerebellar astrocytoma is a type of grade I/IV astrocytoma that can often be cured by surgical resection. Medulloblastoma and ependymoma of the posterior fossa have worse prognoses, although long-term survivors do occur following a combination of surgery, radiation, and chemotherapy. Medulloblastoma occurs before age 10 about 90% of the time, while it is less common for cerebellar astrocytoma to occur after age 10.

Paraneoplastic syndromes are relatively rare neurologic disorders caused by remote effects of cancer in the body, thought to result from autoimmune mechanisms. Examples of paraneoplastic syndromes include limbic or brainstem encephalitis, cerebellar Purkinje cell loss, spinal cord anterior horn cell loss, neuropathy, impaired neuromuscular transmission (Lambert-Eaton syndrome), and opsoclonus myoclonus, which is characterized by irregular jerking movements of the eyes and limbs. Tumors that most often cause paraneoplastic syndromes include small cell lung carcinoma, breast cancer, and ovarian cancer.

### TABLE 5.7 Cerebrospinal Fluid Profiles in Normal Adults and in Those with Infectious Meningitis

<table>
<thead>
<tr>
<th>CONDITION</th>
<th>WHITE BLOOD CELLS (per mm³)</th>
<th>PROTEIN (mg/dl)</th>
<th>GLUCOSE (mg/dl)</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (adults)</td>
<td>&lt;10, lymphocytes only</td>
<td>15-45</td>
<td>50-120</td>
<td>If traumatic lumbar puncture,* expect 1 additional white blood cell for every ~700 red blood cells.</td>
</tr>
<tr>
<td>Acute bacterial meningitis</td>
<td>100-500, usually polymorphonuclear neutrophils</td>
<td>100-1000</td>
<td>Reduced, &lt;60</td>
<td>In patients with hypoglycemia, CSF glucose is abnormal if &lt;50% of serum glucose.</td>
</tr>
<tr>
<td>Viral meningitis or &quot;aseptic&quot; meningitis (see Table 5.9)</td>
<td>10-200, usually lymphocytes</td>
<td>50-100</td>
<td>Normal</td>
<td>Glucose is occasionally reduced in herpes, mumps, and lymphocytic choriomeningitis virus.</td>
</tr>
<tr>
<td>Herpes meningitis or encephalitis</td>
<td>0-500, usually lymphocytes</td>
<td>50-100</td>
<td>Normal or reduced, &lt;50</td>
<td>Red blood cells or xanthochromy may be present.</td>
</tr>
<tr>
<td>Tuberculous meningitis or cryptococcal meningitis</td>
<td>10-200, usually lymphocytes</td>
<td>100-200</td>
<td>Reduced, &lt;50</td>
<td></td>
</tr>
</tbody>
</table>

*See also KCC 5.10 for discussion of lumbar puncture technique and interpretation of red blood cell count in CSP.

Like all other parts of the body, the nervous system can be affected by a variety of infectious pathogens, including bacteria, viruses, parasites, fungi, and yeasts. In this section, we will briefly review the diagnosis and treatment of common infections of the nervous system.

### Bacterial Infections

**Infections Caused by Cocci and Bacilli.** Important bacterial infections of the nervous system caused by cocci and bacilli include bacterial meningitis, brain abscess, and epidural abscess. Bacteria most often gain access to the nervous system through the bloodstream, and they frequently originate from an infection elsewhere in the body, such as the respiratory tract or heart valves (endocarditis). In addition, infections can spread by direct extension from the oronasal passages. Finally, trauma or surgery can introduce bacteria into the nervous system from the skin.

**Infectious meningitis** is an infection of the cerebrospinal fluid in the subarachnoid space. It can be caused by bacteria, viruses, fungi, or parasites. Except for in elderly, very young, or immunocompromised patients, infectious meningitis is usually heralded by marked signs and symptoms of meningitis (see Table 5.5). These meningial signs can also be seen in subarachnoid hemorrhage, carcinomatous meningitis, and chemical meningitis. Common features of meningial irritation include headache, lethargy, sensitivity to light (photophobia) and noise (phonophobia), fever, and nuchal rigidity. In nuchal rigidity the neck muscles contract involuntarily resulting in resistance to active or passive neck flexion, accompanied by neck pain.

Depending on the cause of meningial irritation, onset of symptoms may be gradual, over weeks to months in the case of some fungal or parasitic infections, or symptoms may progress rapidly, within hours in the case of many bacterial infections. Diagnosis is made by clinical evaluation, and by sampling of cerebrospinal fluid by lumbar puncture (see KCC 5.10; Table 5.7). A head CT should usually be performed before lumbar puncture is considered because removal of CSF in the presence of a mass lesion can occasionally precipitate herniation. However, antibacterial therapy should not be de-
TABLE 5.8 Bacterial Meningitis: Common Pathogens and Treatment Based on Age

<table>
<thead>
<tr>
<th>Pathogens</th>
<th>BIRTH-1 MONTH</th>
<th>1-3 MONTHS</th>
<th>3 MONTHS-7 YEARS</th>
<th>7 YEARS-ADULT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemophilus influenzae</td>
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<tr>
<td>Neisseria meningitidis</td>
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<tr>
<td>Streptococcus pneumonia</td>
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<tr>
<td>Treatment*</td>
<td>Ampicillin &amp; ceftriaxone</td>
<td>Ampicillin &amp; ceftriaxone</td>
<td>Ceftriaxone</td>
<td>Ceftriaxone</td>
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(1) There is some evidence that treatment of adult patients with N. meningitidis or H. influenzae should be started intrathecally with ceftriaxone.

(2) Close household contacts of patients with N. meningitidis or H. influenzae meningitis should be treated prophylactically with oral penicillin.

(3) Patients who are elderly or immunocompromised, or who have had head trauma or neurosurgery, are also susceptible to E. coli, Bordetella, Pneumococcus, Staph. aureus, Strep. epidermidis, and others. Therefore, additional antibiotics are often used in these populations.

(4) If herpes simplex meningitis is suspected, acyclovir should be added.

mass effect or progressive deterioration, should be treated with stereotactic needle aspiration (see KCC 16.4), as well as antibiotics. Another important cause of brain abscess other than bacteria is the parasite Toxoplasma gondii, discussed along with HIV later in this section.

Epidural abscess can occasionally occur, especially in the spinal canal, and requires prompt diagnosis and treatment. Common presenting features include back pain, fever, elevated peripheral white blood cell count, headache, and signs of nerve root or spinal cord compression. An emergency MRI scan should be performed when epidural abscess is suspected so that treatment can be initiated before spinal cord compression, paraplegia, and urinary and fecal incontinence occur. Epidural abscess is treated with surgical drainage and antibiotics (ceftriaxone and cefotaxime). Early cases without progressive deterioration may be treatable with antibiotics alone.

Common organisms are Staphylococcus aureus, streptococci, Gram-negative bacilli, and anaerobes. Subdural empyema is a collection of pus in the subdural space, usually resulting from direct extension from an infection of the nasal sinuses or inner ear. This condition is treated by urgent surgical drainage and antibiotics (ceftriaxone plus metronidazole).

In recent years, with the resurgence of tuberculosis in several urban centers in the United States, tuberculous meningitis has become more common as well. Headache, lethargy, and meningeval signs (see Table 5.5) usually appear over the course of several weeks. There is often an inflammatory response in the basal cisterns of the brain, which can affect the circle of Willis vessels, resulting in infarcts. If untreated, coma, hydrocephalus, and death ensue. Tuberculous involvement of the epidural space and vertebral bones can also occur, called Pott’s disease. Populations at risk are intravenous drug abusers, patients with HIV, and people from areas where tuberculosis is endemic.

The meningeval involvement results from reactivation of previous tuberculosis infection, and signs of pulmonary tuberculosis are often not present at the time of presentation. Cerebrospinal fluid shows an elevated white blood cell count with lymphocyte predominance (see Table 5.7), elevated protein, and low glucose. Early on, there may be a polymorphonuclear predominance. The Mycobacterium tuberculosis organisms that cause this infection are often not visible microscopically in the CSF. The diagnosis can be confirmed by culture, which takes several weeks, or more recently, by polymerase chain reaction (PCR). Tuberculous meningitis is treated with a combination of isoniazid, rifampin, ethambutol, and pyrazinamide.

As we will see in the sections that follow, lymphocyte-predominant meningitis, or "aseptic meningitis," can have numerous other causes in addition to tuberculosis (Table 5.9), but it is most commonly viral in origin.

Infections Caused by Spirochetes. The two most important spirochetal infections of the nervous system are neurosyphilis and Lyme disease. Neurosyphilis was fairly common in the pre-penicillin era and has had a resurgence in recent years, possibly related to HIV. Syphilis, formerly called venereal disease, is caused by the spirochete Treponema pallidum. It is transmitted sexually and has various stages that occur at different times after primary infection. In primary syphilis, painless skin lesions called chancre occur at the site of infection, about 1 month after exposure. In secondary syphilis, more diffuse skin lesions appear within approximately 6 months, characteristically including the palms and soles. In tertiary syphilis, neurologic manifestations are often present.

Meningeval involvement can cause aseptic meningitis (see Table 5.9), sometimes with associated cranial nerve palsies, especially involving the optic, facial, and vestibulocochlear nerves. Later stages of neurologic involvement can occur following a latency of about 4 to 15 years. These are classified as meningoencephalitis, general paresis, and tabs dorsalis. In meningoencephalitis, chronic meningeval involvement causes an arthritis, typically involving medium-sized vessels, that results in diffuse white matter in- fects. If untreated, this condition eventually leads to general paresis, in which the accumulation of lesions causes dementia, behavioral changes, delusions of grandeur, psychosis, and diffuse upper motor neuron-type weakness. In another variant that often coexists with general paresis, patients with tabs dorsalis have involvement of the spinal cord dorsal roots, especially in the lumboosacral region, resulting in degeneration of the dorsal columns. Therefore, these patients have sensory loss in the lower extremities, sensory ataxia (see KCC 13.2), and optic atrophy.

Diagnosis of neurosyphilis is based on blood tests for treponemal antibodies (FTA-ABS or MHA-TP), together with cerebrospinal fluid showing lymphocyte-predominant meningitis. So-called nontreponemal blood tests (RPR or VDRL) may be positive or negative in neurosyphilis, but cerebrospinal fluid VDRL is usually positive. Neurosyphilis is treated with intravenous penicillin G, and serial lumbar punctures should be performed to monitor the response to therapy.

Lyme disease is caused by the spirochete Borrelia burgdorferi, carried by Ixodes species of deer tick, which are endemic to certain areas of the United States, Europe, and Australia. The disease is named for the town of Lyme, Connecticut, where the disorder was first described. Primary infection is often heralded by a characteristic raised rash, called erythema chronicum migrans.

Note: See also Table 5.7.
Chronic meningitis, which gradually shifts its location and enlarges over days to weeks. In some cases, neurologic manifestations occur. These usually appear after a delay of several weeks and include a lymphocytic-predominant meningitis (see Table 5.5) or mild meningoencephalitis, characterized by meningeal signs and emotional changes, with impaired memory and concentration.

Other features that may be present include cranial neuropathies (especially of the facial nerve), peripheral neuropathies, and, rarely, spinal cord involvement. Non-neurolologic manifestations include arthritides and cardiac conduction abnormalities. Lyme disease is diagnosed by typical clinical features, lumbar puncture, and serological testing. Untreated cases can eventually show white matter abnormalities on MRI scan. Lyme disease with neurologic involvement is treated with intravenous ceftriaxone.

**Viral Infections**

Viral meningitis tends to be less fulminant than bacterial meningitis, and recovery usually occurs spontaneously within 1 to 2 weeks. Patients present with headache, fever, lethargy, nuchal rigidity, and other signs of meningitis (see Table 5.5). Common causes include enteroviruses such as echovirus, coxsackievirus, and mumps virus. Often the causative agent is not identified. There is no specific treatment for most viral infections of the nervous system, except for herpes and HIV.

Cerebrospinal fluid in viral meningitis shows an elevated white blood cell count with a lymphocytic predominance, normal or mildly elevated protein, and normal glucose. In the early stages, a polymorphonuclear predominance may be present. The differential diagnosis of lymphocytic, or lymphocyte-predominant meningitis of the kind seen with viral meningitis is broad and occasionally making the diagnosis difficult (see Table 5.9, Table 5.7). Viral meningitis and other types of lymphocyte-predominant meningitis are sometimes called aseptic meningitis to distinguish them from bacterial meningitis. We have already discussed several other conditions characterized by lymphocyte-predominant meningitis, including tuberculous meningitis, neurosyphilis, and CNS Lyme disease.

When viral infections involve the brain parenchyma, they are called viral encephalitis. Unlike typical cases of viral meningitis, the clinical manifestations of viral encephalitis are often quite severe. The meninges are often also involved, resulting in meningoencephalitis. The most common cause of viral encephalitis is herpes simplex virus type 1 (type 2 also occasionally causes encephalitis). As discussed in Chapter 14, the herpes simplex virus has a tropism for limbic cortex. Patients often present with bizarre psychotic behavior, confusion, lethargy, headache, fever, meningitis signs, and seizures. Focal signs such as amaurosis, hemiparesis, memory loss, and aphasia may be present as well. Herpes simplex encephalitis causes necrosis of the hippocampus, entorhinal cortex, and other regions of the brain. It can be fatal. CSF polymerase chain reaction (PCR) can be useful in identifying herpes simplex virus in cerebrospinal fluid.

However, there are a variety of causes of viral encephalitis, but unfortunately none of these have a specific treatment. Prognosis depends on the causative agent. In addition, postinfectious encephalitis can occur, usually several days after a viral infection, with diffuse autoimmune demyelination of the central nervous system. Prognosis is variable. Measles is occasionally associated with a delayed, slowly progressive fatal encephalitis called subacute sclerosing panencephalitis. Fortunately, the incidence of this disorder has dropped markedly since the introduction of the measles vaccine and commercial measles vaccine.

**Herpes zoster**, or shingles, is an infection caused by the same virus as chickenpox (varicella-zoster virus). The primary symptom is a painful rash forming to nerve root distributions that will be discussed further in Chapter 83. Viral infections of the nervous system are also a common cause of transverse myelitis (see Chapter 7.2). Important viral causes of myelitis include enteroviruses (such as coxsackie and polio), varicella-zoster virus, HIV, or less commonly, Epstein-Barr virus, cytomegalovirus, herpes simplex, rubella, Japanese B virus, or HTLV-1.

**HIV-Associated Disorders of the Nervous System**

Human immunodeficiency virus (HIV) can increase susceptibility to numerous infectious disorders of the nervous system, including viral, bacterial, fungal, and parasitic infections. HIV itself can cause an aseptic meningitis at the time of seroconversion. This condition is sometimes associated with cranial neuropathies, especially involving the facial nerve (see Chapter 12). AIDS dementia complex is the most common neurologic manifestation of HIV, with increased frequency late in the course of the illness. Treatment with the antiretroviral agent azidothymidine (AZT), often used in combination therapy (e.g., AZT + 3TC + protease inhibitors = highly active antiretroviral therapy, or HAART), can cause some improvement in AIDS-related dementia.

In addition to having an effect on the brain, the HIV virus has been associated with involvement of the spinal cord, peripheral nerves, and muscles (myelopathy, neuropathy, and myopathy, respectively). Other viral infections in patients with HIV include encephalitis caused by herpes simplex virus, varicella-zoster virus, or cytomegalovirus. Cytomegalovirus can also cause retinitis, which responds to ganciclovir and a polycyclic substance that often involves the cauda equina (see Chapter 8). Progressive multifocal leukoencephalopathy (PML) may occur in patients with HIV or other immunodeficiency states. This disorder is caused by a papovavirus called JC virus and results in gradual demyelination of the brain, usually leading to death within 3 to 6 months. Survival time has improved to about 11 months for patients on HAART. MRI shows 12 bright white matter abnormalities, especially in the posterior regions of the brain.

Important bacterial infections of the nervous system in patients with HIV include tuberculous meningitis and neurosyphilis (discussed earlier). There is some evidence that neurosyphilis may have a more rapid and atypical course in patients with HIV. In the category of fungal infections, cryptococcal meningitis is common. It should be suspected in all HIV-positive patients with chronic headache and is diagnosed by lumbar puncture (see Chapter 5.10). Cerebrospinal fluid may show an elevated white blood cell count with lymphocytic predominance (see Table 5.7), but it is occasionally normal. The presence of cryptococcal antigen in the CSF should therefore be checked. The organisms can also sometimes be identified by India ink stain. Cryptococcal meningitis is treated with intravenous amphotericin B followed by oral fluconazole. Milder cases may be treated with fluconazole alone. Severe cases can cause progressive obtundation, neuropathies, seizures, hydrocephalus, and death.

A common parasitic infection of the nervous system in patients with HIV is toxoplasmosis. Central nervous system toxoplasmosis is caused by matrination of infection with the parasite Toxoplasma gondii. Initial exposure is from cysts in cat feces or undercooked meat and is usually asymptomatic. In pa-
tients with AIDS or other causes of immunosuppression, the Toxoplasma in-
fection becomes reactivated and spreads to the central nervous system, form-
ing brain abscesses visible on MRI scans as ring-enhancing lesions: a nonenh-
cancing center (dark on T1) surrounded by a ring of enhancement. Common
presenting features are seizures, headache, fever, lymphocytic predominant
meningitis, and focal signs, depending on the location of the lesions. Serolog-
cal tests for toxoplasmosis are unreliable because much of the general popu-
lation has been exposed (30% in the United States, 80% in France). Toxoplas-
mosis is the most common cause of intracranial mass lesions in patients
with HIV. Therefore, when typical-appearing lesions are found on MRI scan in
these patients, they are usually treated empirically with pyrimethamine and
sulfadiazine (for approximately 2 weeks, and a follow-up MRI scan is then
performed. If there is improvement, therapy is continued. If not, a brain
biopsy is recommended to establish the diagnosis.

Patients with AIDS are at increased risk for primary central nervous
system lymphoma (see KCC 5.9). This B cell lymphoma can appear rad-
ologically similar to toxoplasmosis, and it is the second most common cause
of intracranial mass lesions in patients with HIV. The condition is diagnosed
by brain biopsy, or by cerebrospinal fluid PCR for Epstein-Barr virus. Treat-
ment with steroids and radiation therapy may be of some benefit, although
the prognosis is much worse than for primary central nervous system ly-
phoma without HIV. Kaposi’s sarcoma has only very rarely been reported to
metastasize to the central nervous system.

Parasitic Infections
Parasitic infections that can involve the nervous system include cysticercosis,
toxoplasmosis, malaria, African sleeping sickness (caused by the parasite Try-
panosoma brucei), amebiasis, rickettsial illnesses, and schistosomiasis. In
this section we will discuss cysticercosis. Toxoplasmosis was discussed earlier in
the section on HIV. The other disorders, which are relatively uncommon in North America, are reviewed in the references at the end of this chapter.

Cysticercosis is caused by ingestion of the eggs of the pork tapeworm
Taenia solium, found predominantly in Latin America and in certain regions
of Africa, Asia, and Europe. The organism migrates through the bloodstream
to the whole body, forming multiple small cysts in the muscles, eyes, and
central nervous system. Seizures are a common result. Other common features
are headache, nausea, vomiting, lymphocytic meningitis, and focal deficits,
depending on cyst location. The spinal cord can also occasionally be
involved. Obstruction of the ventricular system by cysts can cause hydro-
cephalus. CT scans in active infection typically show multiple small, 1 to 2 cm
cysts in the brain parenchyma, with surrounding edema. The organisms
eventually die, leaving numerous 1 to 3 mm calcifications scattered through-
out the brain (“brain sand”).

Cysticercosis is diagnosed by history in appropriate populations, by typ-
ical radiologic appearance, and by antibody tests of the serum and cerebro-
spinal fluid. Sometimes eosinophilia, parasites in the stool, and soft tis-
sue calcifications on X-rays may be present as well. In questionable cases,
biopsy may be necessary. The condition is treated with albendazole.

Fungal Infections
Fungal infections of the central nervous system are uncommon in immuno-
competent hosts, but can occur occasionally. Cryptococcal meningitis was
discussed earlier in the section on HIV. Aspergillosis (caused by the fungus
Aspergillus) and candidiasis (caused by Candida) can involve the brain
parenchyma and are usually accompanied by an intense inflammatory re-
response. Other fungi that can infect the brain parenchyma or meninges in-
clude Histoplasma, Coccioides, and Blastomyces. Aspergillosis can also occasionally
spread from the nasal passages to the orbital apex, causing an orbital
apex syndrome (see KCC 13.7). An important fungal infection to be aware of is
Mucormycosis, which occurs predominantly in diabetics in the rhinocerebral form
and also involves the orbital apex. Rhinocerebral mucormycosis causes oph-
thalmo-neurologic, facial numbness, visual loss, and facial weakness, with a typi-
cal violet coloration of the tips of the eyelids. Most fungal infections can be
diagnosed only by biopsy, which should be pursued aggressively because an
early treatment is essential. Mucormycosis is treated with amphotericin B.
Steroids can exacerbate fungal infections and should be avoided when a fun-
gal infection is suspected.

Prion-Related Illnesses
In recent years, a novel protein-based infectious agent called the prion has
been identified in certain neurologic disorders. Prions are unique in their
ability to transmit illnesses from one animal to another, despite the fact that
they apparently do not contain DNA or RNA. Pathologically, diffuse degener-
ation of the brain and spinal cord occurs, with multiple vacuoles resulting in
a spongiform appearance. Human prion-related illnesses include Creutzfeldt-Jakob disease, Gerstmann-Sträussler-Scheinker disease, kuru, and
familial Creutzfeldt-Jakob disease. These disorders are all relatively rare. The
most common, Creutzfeldt-Jakob disease, has an incidence of approximately one
new case per million individuals per year.

Typical presenting features of Creutzfeldt-Jakob disease are rapidly pro-
gressive dementia, an exaggerated startle response, myoclonus, visual disor-
ter, and ataxia. EEG often shows periodic sharp wave complexes. Un-
fortunately, there is currently no treatment. Progressive neurologic
deterioration and death usually occur within 6 to 12 months. Prion-related
illnesses can occur in an inherited pattern, or they can be transmitted by ex-
posure to infected tissues with an incubation period of 2 to 25 years (prions
were formerly misnamed "slow viruses"). A recent cluster of atypical cases
of Creutzfeldt-Jakob disease may have been caused by ingestion of cattle
infected with bovine spongiform encephalopathy in Britain.

Lumbar puncture is an important procedure that provides direct ac-
cess to the subarachnoid space of the lumbar cistern (Figure 5.22). It can be
used to obtain samples of CSF, measure CSF pressure, to remove CSF in cases of
subarachnoid hemorrhage, or to inject contrast material for diagnostic CT or
MRI studies.

The lumbar puncture procedure is performed with sterile technique
under local anesthesia (see Figure 5.22). A hollow spinal needle is intro-
duced through the skin with a stylus occluding the lumen to prevent the in-
trusion of skin cells into CSF during needle insertion. The needle passes
through subcutaneous tissues, ligaments of the spinal column, dura, and
arachnoid, to finally enter the subarachnoid space of the lumbar cistern.

Note that the lumbar cistern is normally in direct communication with
the CSF in the ventricles and CSF flowing over the surface of the brain (see
Figures 5.10, 5.12). The procedure may be done in the lying or seated posi-
tion. A manometer tube is used to measure CSF pressure. Pressure measure-
ments are more reliable in the lying position (see Figure 5.22A) because in

KEY CLINICAL CONCEPT
LUMBAR PUNCTURE
Figure 5.22 Lumbar Puncture
(A) Position of patient and landmarks for needle insertion. (B) Location of needle relative to structures of the lumbar cistern. Switch between measurement of CSF pressure or collection of CSF samples can be selected with a three-way stopcock, as shown.

the seated position the entire column of CSF in the spinal canal adds to the pressure measured in the lumbar cistern. Normal CSF pressure in adults is less than 20 cm H₂O (see KCC 5.3).

Note that the bottom portion of the spinal cord, or conus medullaris, ends at about the L1 or L2 level of the vertebral bodies, and the nerve roots continue downward into the lumbar cistern, forming the cauda equina, meaning "horse's tail" (see Figure 5.22B). To avoid hitting the spinal cord, the spinal needle is generally inserted at a space between the L1 or L5 vertebral bodies. As the tip of the needle enters the subarachnoid space, the nerve roots are usually harmlessly displaced. The posterior iliac crest serves as a landmark to determine the approximate level of the L5-L5 interspace.

The opening CSF pressure should be measured and recorded (see Figure 5.22B). CSF samples are then collected and sent for numerous studies, including cell count, protein, glucose, and microbiological testing. The CSF samples are collected in different tubes, which should be numbered sequentially, since the order in which CSF is taken can affect cell count, as we will discuss shortly. CSF profiles under normal conditions and in several infectious disorders are listed in Table 5.7, and causes of lymphocytic-predominant meningitis are listed in Table 5.9.

Normally, red blood cells are not present in the CSF. Red blood cells in the CSF can indicate subarachnoid hemorrhage (see KCC 5.6), hemorrhagic herpes encephalitis (see KCC 5.9), or they may simply have been introduced by damage to blood vessels by the spinal needle at the time of lumbar puncture, referred to as a traumatic tap. A traumatic tap can often be distinguished from pathological subarachnoid blood by the following guidelines: (1) The number of red blood cells usually decreases from the first to last tubes of CSF collected in a traumatic tap, but not in subarachnoid hemorrhage. (2) If the CSF is centrifuged, the supernatant may have a yellowish, or xanthochromic, appearance as a result of red blood cell lysis if hemorrhage occurred several hours previously, but no xanthochromia should be present in a traumatic tap if the CSF is centrifuged immediately after collection. A traumatic tap may also confound the analysis of CSF white blood cell count because white blood cells are introduced as well. In this case the ratio of red blood cells to white blood cells, and the white blood cell differential count, should be the same in the CSF as in the patient's peripheral blood smear. As a general guideline, in a traumatic tap one white blood cell is introduced into the CSF for every 700 red blood cells. Large amounts of hemorrhage in the CSF from any cause can also sometimes result in reduced CSF glucose or elevated protein.

In addition to diagnosing infection or hemorrhage, lumbar puncture can be useful for obtaining cytological specimens for the diagnosis of neoplastic, or carcinomatous, meningitis, and it can be useful for immunologic testing such as detection of oligoclonal bands in suspected multiple sclerosis (see KCC 6.6)."
CLINICAL CASES

CASE 5.1 AN ELDERLY MAN WITH HEADACHES AND UNSTEADY GAIT

CHIEF COMPLAINT
An 82-year-old man came to his physician with right-sided headaches and difficulty walking.

HISTORY
The patient was in a motor vehicle accident 3 months ago. He did not hit his head or lose consciousness, but the car was "demolished." He was examined in the emergency room and no abnormalities were found, so he was sent home. Ever since, he has complained of generalized fatigue and right-sided headaches, especially over the past 2 weeks. The headaches are worse at night, often keeping him awake. He has also recently stumbled several times while walking because of left leg weakness.

PHYSICAL EXAMINATION
General appearance: A thin elderly man in no acute distress.
Head: No evidence of trauma.
Neck: Supple with no bruits.
Lungs: Clear.
Heart: Regular rate with no murmurs, gallops, or rubs.
Abdomen: Normal bowel sounds; soft, nontender.
Extremities: Normal.
Neurologic exam:
Mental status: Alert and oriented × 3. Speech fluent, with good naming and repetition. Able to count down from 100 by sevens (a test of attention and calculation skills).
Cranial nerves (see Table 2.6): Pupil equal round and reactive to light (CN II, III). Extraocular movements intact (CN III, IV, VI). Visual fields (CN II) full, but with extinction on the left to double simultaneous stimulation. Facial sensation intact (CN V). Face symmetrical (CN VII), Normal gag (CN IX, X). Normal stereomastoid strength (CN XI). Tongue midline (CN XII).
Motor: Poor drift of left arm (see KCC 6.4). Mild left hemiparesis (4/5 strength throughout left arm and leg). Normal strength on the right side.
Sensory: Intact except for left extension on double simultaneous stimulation.

REFERRAL

Gait: Takes short steps, but with good speed. Able to perform tandem gait.
Coordination: Not tested.

LOCALIZATION AND DIFFERENTIAL DIAGNOSIS
1. On the basis of the symptoms and signs shown in bold above, what is the general location of the patient's lesion? Is it intracranial or extracranial? Is it on the left side or the right side?
2. Given the recent history of a motor vehicle accident in this elderly man and the fact that the headaches are worse at night, what is the most likely diagnosis? What are some other possibilities?

Discussion
1. The key symptoms and signs in this case are:
   a. Left hemiparesis, and left Babinski's sign
   b. Visual and tactile extinction on the left
   c. Right-sided headaches
   d. Generalized fatigue

   The patient has mild left arm and leg weakness with a left Babinski's sign, suggesting an upper motor neuron lesion (see Table 5.3) in the corticospinal system anywhere from the right motor cortex to the left cervical spine (see Figure 2.16). The visual and tactile extinction in this patient are forms of left hemineglect (see KCC 19.9), which is most commonly seen in right parietal lesions but can also be seen in right frontal or subcortical lesions. These findings are compatible with a right intracranial rather than a left spinal cord localization. Generalized fatigue is a nonspecific complaint, but in association with right-sided headaches it suggests a possible right intracranial mass lesion (see KCC 5.1-5.3). The most likely clinical localization is a right hemisphere cortical and/or subcortical lesion affecting corticospinal and attentional pathways.

2. This is an elderly patient with 3 months of headaches and generalized fatigue following a motor vehicle accident, who more recently developed a left hemiparesis. Chronic vague symptoms of this type, with stepwise worsening in an elderly patient following minor head injury are very suggestive of chronic subdural hematoma (see KCC 5.6). As a result of his multiple falls, there may be some more recent blood in the hematoma as well. Another possible but less likely diagnosis would be several small right-sided intracranial hemorrhages over the past few months, caused by hypertension, tumor, vascular malformation, anisocoria, angioptysis, coagulation disorder, or trauma (contusions). In addition, it is possible that the car accident was a coincidence, or it may even have been an effect of the lesion rather than its cause. This would be the case if the patient had a preexisting right hemisphere lesion such as a tumor, infarct, demyelination, or infection that impaired driving skills.

Neuroimaging
The patient's physician decided to order a head CT (Figure 5.23).
1. How old is the blood in the hematoma seen on the head CT (see Figure 5.19 and Chapter 4)?
2. Cover the labels on Figure 5.23 and identify as many structures as possible on the CT scan.
3. Between what meningeal layers is the hemorrhage located, and what is the name of this kind of hematoma?

Discussion
1. The fluid collection is hypoechoic relative to the brain, but more dense than CSF. It generally takes about 2 to 3 weeks for a hematoma to become hypoechoic in appearance.
2. See labels on Figure 5.23.
3. A large, right-sided fluid collection is seen located between the brain and the skull.

Clinical Course
The patient was admitted to the hospital and taken to the operating room for drainage of the hematoma. Two burr holes were drilled through the skull, one in the frontal area and a second in the parietal area. The dura was opened through the burr holes, releasing "crankcase oil-colored" (dark purple) fluid under a large amount of pressure. There was no evidence of any acute blood. The subdural space was irrigated with saline until there was no further oil-colored fluid.

The patient's hemiparesis showed immediate improvement after surgery. Follow-up exam in the physician's office 3 weeks later showed 5/5 strength, intact vision, intact somatic sensation, no hemineglect, and bone downgoing bilaterally. The patient had no further complaints of headaches or generalized fatigue.
CASE 5.1  AN ELDERLY MAN WITH HEADACHES AND UNSTEADY GAIT

Figure 5.23  Head CT Showing Chronic Subdural Hematoma
A hypodense right chronic subdural hematoma is present. Compare to Figure 4.12.

CASE 5.2  ALTERED MENTAL STATUS FOLLOWING HEAD INJURY

CHIEF COMPLAINT
A 67-year-old man was found at the bottom of a flight of stairs, lethargic and smelling of alcohol.

HISTORY
Little information could be obtained from the patient. He was discovered at the base of a staircase intoxicated and with a posterior scalp laceration and was therefore brought to the emergency room.

INITIAL PHYSICAL EXAMINATION
General appearance: An unkempt man lying on a stretcher.
Hx: Scale 3 on right occipital area; normal tympanic membranes (see Table 3.9).
Neck: In cervical stabilization collar put on by emergency personnel.
Lungs: Clear.
Heart: Regular rate with no murmurs, gallops, or rubs.
Abdomen: Normal bowel sounds; soft, nontender.
Extremities: No edema, normal pulses.
Rectal: Normal tone, hem-negative.
Neurologic exam:
MENTAL STATUS: Lethargic but arousable, with garbled speech. Stated his full name but did not know his location or the date. Did not recall what happened to him, saying "I'm all right." Followed simple commands.

SPEECH EXAM:
unable to move all four extremities.

LOCALIZATION AND DIFFERENTIAL DIAGNOSIS
1. Dysfunction of what regions of the nervous system could produce the mild to moderately depressed level of consciousness seen in this patient?
2. In broad terms, what are the two most likely causes of this patient's altered mental status?

CASE 5.2 (CONTINUED)

CLINICAL COURSE IN THE EMERGENCY ROOM
The initial impression of the emergency room personnel was that the patient was intoxicated with alcohol and perhaps had a mild concussion, both of which should improve with observation over the next few hours. The patient was sent for X-rays of the cervical spine and chest. His blood alcohol level came back at 325 mg/dl (>100 mg/dl can cause intoxication, although chronic users can develop tolerance). While at the radiology department, he became uncooperative and combative, moving too much for the X-rays to be done. He then became increasingly somnolent and developed irregular respirations, requiring emergency intubation and mechanical ventilation. A second, rapid but more detailed neurologic exam was done, and the patient was taken for an emergency head CT scan.

FOLLOW-UP PHYSICAL EXAMINATION
Vital signs: P = 95, BP = 184/90.
The remainder of the general exam was unchanged.
Neurologic exam:
MENTAL STATUS: Unresponsive except for movement to painful stimuli.
Cranial nerves: Pupils 3 mm, constricting to 2 mm bilaterally. Oculocephalic maneuvers (see Chapter 3) were not done because of the cervical collar. Corneal reflex present on the left, but absent on the right.

SYMPATHETIC AND MOTOR: Movements of left arm and leg in response to painful stimulus. Right arm and leg did not move in response to pain.
PLANTAR REFLEXES: No response on the right, upgoing on the left.
COORDINATION AND GAIT: Not tested.

LOCALIZATION AND DIFFERENTIAL DIAGNOSIS
1. The neurologic exam was incomplete, but it suggests depressed consciousness together with right hemiplegia (unilateral paralysis) and/or right sensory loss. Decreased function in which structures could cause this picture? What is the most likely cause of this patient's sudden deterioration?
2. In what location(s) might we expect to see hemorrhage on CT scan in a patient with acute head trauma? (see KCC 5.5, 5.8? For each location, identify the inner and outer layers that confine the space (see Figure 5.1), and state whether it is an actual space or a potential space. To answer this question, complete the following table:

<table>
<thead>
<tr>
<th>Locations of Hemorrhage Associated with Head Trauma</th>
<th>LOCATION</th>
<th>POTENTIAL OR ACTUAL SPACE</th>
<th>BOUNDED BY</th>
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<tbody>
<tr>
<td>Intraventricular hemorrhage</td>
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<td>Contusion with intracerebral or intraparenchymal hemorrhage</td>
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<td>Subarachnoid hemorrhage</td>
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<td>Subdural hematoma</td>
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<td>Epidural hematoma</td>
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<td>Subgaleal hematoma</td>
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</table>
Discussion

1. The key symptoms and signs in this case are:
   - Unresponsiveness except to painful stimuli
   - Absent right corneal reflex, and no right arm or leg movement to pain with plantar response absent on the right and upgoing on the left

Depressed consciousness can be caused by dysfunction of brainstem-diencephalic activating systems or of bilateral cerebral cortices (see Figure 2.23). Absent right face, arm, and leg movements in response to pain could be explained by impaired function in the motor pathways that begin in the left motor cortex (see Figures 2.13, 2.16), and/or by right body sensory loss (see Figure 2.19). The absent right plantar response is also compatible with corticospinal dysfunction because reflexes are sometimes depressed rather than increased in acute upper motor neuron lesions (see Table 3.3).

Although unilateral arm and leg paralysis can be caused by lesions above or below the foramen magnum, the presence of hemiplegia, together with impaired consciousness, strongly suggests pathology within the cranial vault. Intracranial lesions of the left brainstem or left cerebral hemisphere can cause right hemiplegia. There is some evidence of right brain dysfunction as well, with an upgoing toe in the left foot, suggesting either that the lesion is so large that it compromises structures across the midline, or that a second lesion is present.

In summary, one possible localization is the upper brainstem, with involvement of the pontomesencephalic reticular formation and of the left more than the right corticospinal and corticobulbar tracts. Because of the cervical collars, eye movements could not be tested easily, and such testing might have helped further with localization (see neurosurgery.com video 38). Another possibility is a large intracranial lesion affecting the left motor cortex or descending white matter pathways, and also compressing the upper brainstem-diencephalic junction through mass effect and transtentorial herniation (see KCC 5.4).

The external evidence of head trauma (scalp laceration) is most suggestive of a rapidly expanding lesion in the left cranial cavity, which could impinge on the left hemisphere corticospinal system in both the cortex and the white matter. It could also impair consciousness through midline shift, distorting the reticular formation, and through elevated intracranial pressure. The most likely causes of an expanding lesion following trauma would be epidural hematoma, acute subdural hematoma, cerebral contusion, or cerebral edema (see KCC 5.5, 5.6). Although less likely, additional possibilities for the deterioration seen in this patient would include intracranial hemorrhage in a preexisting lesion such as a tumor, vascular malformation, or aneurysm; ischemic infarction of the left cerebral hemisphere or brainstem; hydrocephalus; or delayed absorption of an ingested toxin (although the last two possibilities should not be confused with hemiplegia).

2. See Table 5.10 and Figure 5.1.

Neuroimaging

In patients of this kind, there are several serious pitfalls in making the diagnosis of intracranial pathology. First, alcohol intoxication obscures the clinical picture, making it difficult to recognize mental status changes from other causes. Second, the restless agitation and combativeness present in this patient are frequently seen as a sign of acute worsening of intracranial hypertension or hydrocephalus (KCC 5.3, 5.7) but can easily be mistaken for an assaultive, intoxicated personality. Therefore, intoxicated patients require extra vigilance, and if a clear trend toward neurologic improvement is not seen, an urgent CT scan of the head is warranted. Our patient had an emergent head CT (Figure 5.24A-C) and was then rushed immediately to the operating room. The images in Figure 5.24A-C were taken just before surgery; those in Figure 5.24D-I were taken 1 year later.

1. How old is the hemorrhage in Figure 5.24A-C?
2. What kind of hemorrhages are present in this patient? (Hint: All the hemorrhages listed in Table 5.10 can be seen except for epidural hematoma.)

Discussion

1. All of the hemorrhage appears quite hyperdense, and on radiological grounds it is less than about 1 week old (see Chapter 4). On the basis of the clinical story, the blood is probably only a few hours old.

2. A thin crescent-shaped hematoma on the left side extends over a large region, consistent with an acute subdural hematoma (see KCC 5.6). In addition, some blood can be seen to extend down into the sulci (see Figure 5.24C). Recall that the pia follows the brain surface down into the sulci, while the arachnoid does not (see Figure 5.1). The blood in the sulci must therefore be in the subarachnoid space, representing subarachnoid hemorrhage. Large, confluent areas of hemorrhage are present in the left temporoparietal and inferior frontal poles, consistent with cerebral contusion (see Figure 5.24A,B). Note that on the right posterior temporal and occipital lobes, one can draw an imaginary “line of force” from the right posterior temporal injury straight through to the left frontotemporal contusion. This is a classic coup-contrecoup injury, in which a blow to one side of the head is accompanied by deceleration injury on the opposite side of the brain as it bangs against the inner surface of the skull. The frontal and temporal poles are especially susceptible to contusion where they abut the bony ridges of the anterior and middle cranial fossae (see Figure 5.21). A small amount of intraventricular blood can be seen layering on the right occipital horn (see Figure 5.24B), which can be better appreciated by comparison to the follow-up study (see Figure 5.24C).

Finally, there is an abnormal bright band of hyperdensity between the cerebellum and medial temporal occipital lobes (see Figure 5.24A). Recall that the dark form a fold extending into the cranial vault between these structures called the tentorium cerebelli (see Figure 5.6). This is therefore an acute subdural hematoma of the tentorium cerebelli, which can be seen on other images (not shown) to be a direct extension of the subdural hematoma on the
left cerebral convexity. Also not shown are the CT image bone windows that revealed a nondisplaced right occipital skull fracture.

Severe mass effect produced by hemorrhage and edema can also be seen on this scan. The **midline shift at the level of the pineal calcification** is a good indicator of how much the reticular formation is distorted at the midbrain–diencephalic junction. Our patient has approximately 11 mm of rightward pineal shift (see Figure 5.24B). More than 10 mm of shift is usually associated with profound coma. The midbrain appears elongated in the anterior to posterior dimension, and somewhat flattened from side to side (see Figure 5.24A). The left uncus and medial temporal lobe can be seen to extend across the region normally delineated by the territorial edge, and to press up against the midbrain. This is consistent with early left uncus transtentorial herniation (see K.C. 5.4). Marked mass effect is also demonstrated by the near-complete effacement of the basal cisterns (see Figure 5.24A) compared with after recovery (see Figure 5.24D). The left lateral ventricle and sulci are nearly completely obliterated (see Figure 5.24A–C). The right ventricle, in contrast, is somewhat dilated because of partial obstruction of CSF flow and consequent mild hydrocephalus. The left hemisphere appears swollen and somewhat hypodense (see Figure 5.24B,C), consistent with diffuse cerebral edema.

**Clinical Course**

Emergency measures were instituted to lower intracranial pressure (see K.C. 5.3), including intravenous administration of the hyperosmolar agent mannitol, and adjustment of the ventilator settings for hyperventilation, as the patient was taken directly to the operating room. During surgery an incision was made in the left scalp, and a large bone flap (see K.C. 5.1) was removed, exposing the underlying dura, which appeared tense and blue. The dura was opened, revealing a large, freshly cutted subdural hematoma, which was then evacuated. There were also significant subarachnoid blood, swelling, and contusions of the left temporal and frontal poles. To further decompress the intracranial cavity, the severely contused portions of the anterior left temporal lobe, as well as the anterior inferior left frontal lobe, were removed, and a large left frontal intraparenchymal hematoma was evacuated. The dura was closed with sutures, and the bone flap was replaced before the scalp was closed.

In the intensive care unit, 3 hours after surgery, the patient remained intubated but was awake, with full extraocular movements and equal and reactive pupils. He would squeeze the examiner's hand or wiggle his toes bilaterally on verbal command, with greater strength on the left side. His left plantar reflex was downgoing, and right plantar silent. After a prolonged recovery period in the hospital and at a rehabilitation facility, the patient returned home, was able to function fully independently, and soon found his way back to the neighborhood bar. Follow-up head CT scan done 1 year later during another episode of intoxication (see Figure 5.24D–F) showed complete resolution of all hemorrhage and mass effect, with residual hypodensities present in the region of the left temporal and frontal poles representing gliotic scar and tissue loss (hydrocephalus ex vacuo). This was somewhat unusual in showing such dramatic recovery despite the severe appearance of the patient's postoperative CT scan with multiple contusions, acute subdural blood, and marked distortion of the brainstem. He was fortunate to have had his acute deterioration occur in a place where emergency neurosurgery could be undertaken without delay, but unfortunate to have a continued addiction to alcohol.
CASE 5.2 (CONTINUED)

(C) Septum pellucidum
Choroid plexus
Central sulcus
Body of lateral ventricle
Superior sagittal sinus
Subdural hematoma
Subarachnoid hemorrhage
Dura
Subdural hematoma
Aneurysm
Cerebrospinal fluid (CSF)
Pia
Pons cerebri

 Laud

(E) Encephalomalacia
Sylvian fissure
Pineal calcification
Internal capsule
Thalamus
Calculated choroid plexus

(F) Fronto horn
Central sulcus
Cerebrospinal fluid (CSF)
Gliotic scar
Site of Burr hole
Pons cerebri
Superior sagittal sinus

(Case 5.2 continued...)

(Midbrain
Temporal horn
Temporal lobe
Cerebellum
Tentorium cerebelli
Posterior cerebral artery

(Case 5.2 continued...)}
CASE 5.3 DELAYED UNRESPONSIVENESS AFTER HEAD INJURY

CHIEF COMPLAINT
A 51-year-old man was found to be progressively unresponsive the morning after a head injury.

HISTORY
The night before admission, the patient fell down a flight of cement stairs at 12:00 am, following a domestic altercation. He struck his left temporal area and lost consciousness for about 15 minutes. By the time the police and ambulance arrived, however, he was fully awake, smelled of alcohol, and refused medical treatment. He was arrested on domestic violence charges and spent the night in prison. In the morning, the guards came to summon him for a court appearance and found him difficult to arouse, thrashing about incoherently. He had vomited and defecated in the cell overnight. An ambulance was called, and he was brought to the emergency room for evaluation.

PHYSICAL EXAMINATION
General appearance: Disheveled-appearing man lying on a stretcher.
Head: Left forehead abrasion. No Battle's sign, raccoon eyes, CSF otorrhea, or rhinorrhea. Tympanic membranes normal (see Table 3.9).
Neck: In cervical stabilization collar put on by emergency personnel.
Lungs: Clear.
Rectal: Normal tone, home negative.
Neurologic exam: Unresponsive to commands. Not talking. Occasionally thrashed on stretcher in agitated, semipurposeful fashion.

CRANIAL NERVES: Left pupil 5 mm, fixed (no response to light). Right pupil 2 mm, constricting to 1 mm, without lateralization. Oculocephalic maneuvers not done because of cervical collar. Gag reflex present. Sensory and motor: Left arm and left leg moved spontaneously. Withdrawn left arm and leg purposefully from painful stimulation. Right arm and leg did not move, even in response to pain.

COORDINATION AND GAIT: Not tested.

Shortly after arriving in the emergency room the patient developed respiratory distress and was therefore intubated. He subsequently stopped moving his left side as well and became completely unresponsive.

LOCALIZATION AND DIFFERENTIAL DIAGNOSIS
1. For each of the symptoms and signs appearing in bold above, review the neuroanatomical pathways involved (see Figures 2.16, 2.23; Tables 2.5, 3.3). In what single brain region do these pathways intersect? Which part of the brain is affected? (see KCC 5.4) What cause of compression of this brain region? On which side would you expect to find the cause of the compression?
2. Given the history of acute head injury, with delayed and progressive unresponsiveness over the course of several hours, what is the most likely diagnosis? What are some other possible diagnoses?

Discussion
1. The key symptoms and signs in this case are:
   - Agitation and decreased level of consciousness
   - Left pupil fixed and dilated
   - Right hemiplegia, right hyperreflexia, and right Babinski's sign
   - Impairment of consciousness could be caused by lesions affecting the brainstem-diencephalic reticular activating systems either directly or through compression and distortion from nearby lesions; see Figure 2.23)
   - By lesions affecting the cerebral hemispheres bilaterally, pupillary constriction is mediated by parasympathetic fibers that travel with the oculomotor nerves (CN III) arising from the midbrain (see Figures 2.9, 2.22; Table 2.3). Therefore, a fixed, dilated left pupil could be caused by a lesion involving the left midbrain, CN III as it exits the brainstem and travels toward the eye, or possibly

the pupillary constrictor muscle directly. The combination of right-sided weakness and increased reflexes suggests an upper motor neuron lesion (see Table 3.3) somewhere in the corticospinal pathway beginning in the left motor cortex and ending in the right spinal cord (see Figure 2.16). These are pathways systems intersect in the midbrain, producing the triad of coma, a

blown pupil, and hemiplegia seen in uncal herniation (see KCC 5.4; Figure 5.18). The dilated pupil on the left suggests that the lesion is on the left side of the interpeduncular cistern, compressing the left midbrain.

The most likely clinical localization is left uncal herniation compressing the left midbrain.

2. The patient suffered a significant blow to the left temporal area. Recall that fracture of the temporal bone can lacerate the middle meningeal artery resulting in epidural hematoma (see Figure 5.7; KCC 5.6). In addition, as can sometimes be seen with epidural hematomas, the patient initially regained consciousness during a fluid interval lasting several hours, and only later lapsed back into unconsciousness, probably because of progressin expansion of the hematoma. Recall that epidural hematoma are arterial in origin and therefore can cause rapid deterioration due to expansion. We have already seen in Case 5.2 that acute subdural hematoma, brain contusion, and edema can also sometimes cause progressive deterioration, so these diagnoses should be considered here as well. Finally, it is possible but less likely that during the night the patient had a cerebral infarct perhaps due to posttraumatic vertebrobasilar artery dissection (see KCC 10.6), or that he had an intracerebral hemorrhage caused by something not directly related to the head injury, such as hypertension, brain tumor, or vascular malformation (see KCC 5.6).

Neuroimaging
Because of the change in this patient's clinical status, an urgent head CT was done (Figure 5.25).
1. How recent is the hemorrhage seen on the CT scan (see Chapter 4)?
2. On the basis of its appearance, what kind of hemorrhage is this, and where is it located (see KCC 5.6)?
3. Identify the fracture on the bone windows (see Figure 5.25D). What bone does it involve?
4. Describe the mass effect (see KCC 5.2) caused by the hematoma and any herniation (see KCC 5.4) that can be identified on the CT.

Discussion
1. The hemorrhage is hyperdense and therefore occurred within the past week (see Chapter 4).
2. A large, lens-shaped fluid collection is seen along the inner surface of the left temporal and parietal bones. Note that this hematoma has a biconvex shape and is limited anteriorly by the coronal suture line (see Figure 5.25C), where the pericranial layer of dura forms a tight insertion. These features are characteristic of an epidural hematoma formed by high-pressure arterial blood dissecting between the dura and bone (see KCC 5.6).
3. A fracture of the left parietal bone can be seen (see Figure 5.25D). On higher cuts (not shown), the fracture was seen to extend into the left parietal bone as well.
4. There is extensive midline shift caused by the hematoma, with displacement of the entire brain to the right, compressing the left lateral ventricle (see Figure 5.25A,B). The left anterior cerebral temporal lobe, including the uncus, extends over the tentorial edge and compresses the left side of the midbrain (see Figure
5.25A), constituting left transtentorial herniation (see KCC 5.4). In addition, the cingulate gyrus is forced under the falx (see Figure 5.2b2), causing subfalcine herniation (see Figure 5.58).

Clinical Course
Because of his rapid decline, the patient was taken immediately from the CT scanner to the operating room. Emergency measures to lower intracranial pressure (see KCC 5.3; Table 5.3), including hyperventilation and intravenous mannitol, were initiated en route. In the operating room, an incision was made from just above the left ear up to the crest of the head, revealing a large linear fracture in the temporal and parietal bones. A craniotomy was performed (see KCC 5.11), and a large fresh clot of blood was evacuated from the epidural space. Several tears in the middle meningeal artery were identified (see Figure 5.7), so the artery was coagulated down to the skull base. The patient had a prolonged hospital course postoperatively, but he gradually regained consciousness and the ability to ambulate and use his right hand. A follow-up CT scan performed a week and a half after the injury showed remarkable recovery of the normal intracranial anatomy following removal of the hematoma. This case demonstrates the importance of being able to recognize the neuroanatomical features of uncal herniation so that therapeutic measures can be instituted promptly, while recovery is still possible.

CASE 5.4 HEADACHE AND PROGRESSIVE LEFT-SIDED WEAKNESS

MINICASE
A 52-year-old lumber executive developed mild difficulty running, initially confusing his left big toe, which progressed to constant left leg weakness over the course of 6 months. He also complained of headaches. Examination was normal except for decreased left nasociliary fold and 4/5 weakness in the left tripeps and left leg.

LOCALIZATION AND DIFFERENTIAL DIAGNOSIS
1. On the basis of the limited information provided, is the lesion intracranial or extracranial (see Figures 2.13, 2.17)? Which side is the lesion on?
2. What is the most likely diagnosis? What are some other possibilities?

Discussion
1. The key symptoms and signs in this case are:
   - Headaches
   - Left hemiparesis

   Weakness affecting the left face, arm, and leg together is caused by lesions of the corticobulbar (face) and corticospinal (arm and leg) pathways originating in the right motor cortex (see Figures 2.13, 2.17). The lesion must be at or above the level of the pons, since the facial nerve (CN VII) nucleus is in the pons and exits the brainstem at the pontomedullary junction (see Figure 2.22; Table 2.5); lesions below this point would not cause face weakness. The presence of headaches further supports an intracranial localization.

   The most likely clinical localization is right intracranial lesion affecting corticobulbar and corticospinal tracts at or above the level of the pons.

   Headache can have many causes (see KCC 5.3). New-onset headaches for a man in his 50s, together with a progressive neurologic deficit over a 6-month period, suggests brain tumor (see KCC 5.8), most commonly glioblastoma multiforme or metastasis. Other, less likely possibilities include infection, demyelination, multiple small hemorrhages or infarcts, or vascular.

Clinical Course
An MRI scan was consistent with the primary brain tumor called glioblastoma multiforme (see KCC 5.8) involving mainly the right hemisphere. The diagnosis was confirmed by biopsy. The patient was treated with surgical resection as much tumor as possible, followed by radiation therapy. Nevertheless, about 1 year after his first symptoms he developed gradually worsening headaches, lethargy, and left-sided weakness. MRI revealed recurrent tumor. He was treated with high-dose steroids (dexamethasone) and intravenous mannitol (see KCC 5.3) but continued to worsen. On the day before he died, at 3:00 P.M., he was described as sleepy but arousable and "oriented x 3." Pupils were 4 mm and briskly reactive bilaterally. He was hemiplegic on the left. At 10:00 P.M. the same day, he was unresponsive even to deep pain. His right pupil was 7 mm and unreactive, left pupil 4 mm. A little later the pupils were 7 mm bilaterally and fixed. The dexamethasone and mannitol were increased further with no improvement. Given his unreattendable condition, the family requested no resuscitation measures, and the patient stopped breathing the next day.

1. Impaired function in what brainstem region could explain the progressive hemiplegia, lapse in consciousness, and pupillary abnormalities seen just before death in this patient?
2. What herniation syndrome causes compression of this brain region?

Discussion
1. The midbrain (see Figures 2.16, 2.22A, 2.23; Tables 2.5, 3.3).
2. This patient had a long-standing left hemiparesis caused by a right hemispheric mass lesion, so it is difficult to invoke a herniation syndrome to explain the hemiplegia. However, impaired consciousness with a dilated, unreactive pupil is characteristic of the midbrain compression seen with uncal transtentorial herniation (see KCC 5.6). Elevated intracranial pressure (see KCC 5.3) may also have contributed to the impaired level of consciousness. Thus, when the patient became unresponsive with a dilated, unreactive right pupil, he was probably undergoing right transtentorial herniation caused by the enlarging right hemisphere mass. Eventually, the midbrain was compromised bilaterally, as evidenced by the fact that the left pupil became dilated and unreactive as well.

Pathology
The patient's family requested an autopsy to confirm the cause of death (Figure 5.26). The brain weighed 1200 g (normal weight is 1250-1400 g) and appeared swollen and edematous. On surface examination, prominent grooves were seen on the inferior medial surfaces of the temporal lobes, especially on the right side, located 1.0 cm from the uncus tip on the right and 0.4 cm from the uncus tip on the left (see Figure 5.26A), consistent with bilateral uncinal herniation, more severe on the right side. The midbrain appeared crowded at this level and deformed from right to left seen (see Figure 5.30B). The right CN III appeared flattened for about 1.0 cm of its extent in the area adjacent to the right uncus (see Figure 5.30A).

Coronal sections (see Figure 5.26C,D) revealed a necrotic mass centered near the leg region of the motor strip in the right hemisphere, with mild pallor and dramatic enlargement of the right hemisphere, white matter consistent with edema. The gyriform appearance flattened from being pressed against the inner surface of the skull, and the sulci were effaced. The right uncus could again be seen to have a prominent groove caused by the tentorial edge, and...
CASE 5.3 DELAYED UNRESPONSIVENESS AFTER HEAD INJURY

Figure 5.25  Head CT Showing Epidural Hematoma
(A-C) Left epidural hematoma causing left uncal transtentorial herniation. Axial images progressing from inferior to superior. (D) Bone windows demonstrating left temporal bone fracture.
the midbrain–diencephalic junction appeared deformed and compressed (see Figure 5.26C). The right cingulate gyrus was shifted 1.0 cm from right to left of midline, consistent with subcalvarial herniation. A brownish area was present in the right medial occipital lobe involving gray and white matter surrounding the calcarine fissure (see Figure 5.26D). This is consistent with an ischemic infarct in the territory of the right posterior cerebral artery, with subsequent petechial hemorrhage. Recall that the posterior cerebral artery passes through the tentorial notch and can therefore sometimes be compressed during transtentorial herniation, causing infarcts (see Figures 5.6, 10.5; KCC 5.4).

Transverse section through the midbrain (see Figure 5.26B) showed it to be markedly elongated in the anterior to posterior dimension, and distorted by compression from right to left. There was an irregular area of dark brown pigmentation in the center of the midbrain. This finding is called a Duret-Bernard hemorrhage and can be seen with severe compression of the midbrain and other brainstem areas during transtentorial herniation.

CASE 5.5 SUDDEN COMA AND BILATERAL POSTURING DURING INTRAVENOUS ANTICOAGULATION

MINICASE
A 51-year-old woman presented to the emergency room 2 hours of left face and arm weakness. On examination at 8:00 a.m., she was fully alert, with mild left face and arm weakness completely sparing the left leg. She had a history of atrial fibrillation, which can cause blood clots to form in the cardiac atria as a result of stasis (see KCC 10.4). For this reason she was taking the oral anticoagulant warfarin (Coumadin). However, blood tests in the emergency room showed that she was not adequately anticoagulated on her current dosage. It was felt that she most likely had an embolus from the heart to the right side of the brain. A head CT within 3 hours of onset was unremarkable. This finding was consistent with the diagnosis, since it can take from 6 to 24 hours for an acute stroke to become visible on CT (see Chapter 4). She was therefore admitted to the hospital and started on the intravenous anticoagulant heparin because this approach can achieve a therapeutic range of anticoagulation more quickly than oral medications can. The patient remained stable throughout the day, but at 10:00 p.m. she was suddenly found to be unarousable. Exam was notable for fixed, midsize pupils, no extraocular movements, and bilateral extensor (decerebrate) posturing of both arms and legs. She was eminently intubated because of shallow respirations.

LOCALIZATION AND DIFFERENTIAL DIAGNOSIS
1. On the basis of the findings shown in bold above, where is the lesion located (see Figures 2.16, 2.22, 2.23, 3.5; Table 2.5)?
2. What is the most likely diagnosis?

Discussion

1. This patient has had a massive hemorrhage in the region of initial infarct, an occasional tragic complication of anticoagulation therapy. The hemorrhage is centered deep in the right hemisphere but is so large that essentially the whole brain is compressed. The blood has extended into the ventricular system, and several pockets of blood with CSF–blood levels can be seen (see Figure 5.27A). The cortical sulci and gyri are completely effaced by mass effect, the left ventricle appears dilated from obstructive hydrocephalus, and there is substantial midline shift. On the basis of the large volume of the blood and the patient's poor level of neurologic function, her prognosis is quite poor.

2. See labels on Figure 5.27.

3. Note that before the hemorrhage, there was a large amount of CSF-filled space surrounding the cor ticomedialular junction and caudal medulla at the level of the foramen magnum (Figure 5.27A, B). The cerebellar tonsils can be seen to extend into the cisterna magna at a distance somewhat removed from the medulla. After the hemorrhage, the cerebellar tonsils have been forced downward and inward, compressing the caudal medulla and extending downward through the foramen magnum (Figure 5.27E, F). Thus, tonsillar herniation has occurred. In this patient, tonsillar herniation has resulted from a massive supratentorial lesion that produced downward central herniation of the entire brainstem, a situation sometimes referred to as a pressure cone. At the level of the midbrain in this patient, there was also complete effacement of the basal cisterns and bilateral midbrain compression due to bilateral uncal transtentorial herniation (Figure 5.27C, G).

Clinical Course
In view of the patient's grim prognosis, the family decided not to pursue heroic measures, and the patient died the next day.
CASE 5.4 HEADACHE AND PROGRESSIVE LEFT-SIDED WEAKNESS

Figure 5.26 Pathologic Specimens Showing Hemiations and PCA Hemorrhagic Infarcts (A) Inferior surface view showing effects of uncal transtentorial hemiation on CN III. Hemiation is more severe on the right side. (B) Transverse section revealing distortion of the midbrain and Duret-Bernard hemorrhages. (C) Coronal section showing evidence of uncal and sublaminar herniation. Neuronal tumor mass can be seen in the right hemisphere. (D) Coronal sections through occipital lobes with posterior cerebral artery (PCA) territory hemorrhagic infarct caused by compression of the PCA in the tentorial notch.
**CASE 5.5 SUDDEN COMA AND BILATERAL POSTURING DURING INTRAVENOUS ANTICOAGULATION**

Figure 5.27 CT Scan Images Showing Intracranial Hemorrhage: Axial CT images progressing from inferior to superior. Baseline scans (A, C, E, G) compared with scans showing catastrophic intracranial hemorrhage with tonsillar and bilateral uncal herniation (B, D, F, H).

- **A (Baseline scan)**
  - Medulla
  - Foramen magnum

- **B (After hemorrhage)**
  - Medulla
  - Foramen magnum

- **C (Baseline scan)**
  - Cistern magna
  - Medulla
  - Cerebellar tonsils

- **D (After hemorrhage)**
  - Cerebellar tonsils
  - Intraventricular hemorrhage

**CASE 5.5 (CONTINUED)**

- **Baseline scan**
- **Vertebral arteries**
- **Medulla**
- **Cerebellar tonsils**
- **Cistern magna**
CASE 5.6 SEVERE HEAD INJURY

MINICASE
An 80-year-old man was found lying on the rocks under a 6-foot-high wall near the shoreline. He was conscious and speaking for a brief time before lapsing into a coma. On initial examination he had a right scalp abrasion; 6 mm right pupil and 5 mm left pupil, both nonreactive to light; no corneal reflexes; flaccid (decorticate) posturing of the upper extremities to pain (see Figure 3.5A); and ongoing plantar responses bilaterally.

Neuroimaging
The patient was brought to the emergency room, where an emergency head CT was done, shown in Figure 5.28.
1. What kind of hemorrhage is present (see KCC 5.6)?
2. Severe hemorrhage of what kind can be seen (see KCC 5.4; Figure 5.18)?

Discussion
1. A large, crescent-shaped, hyperdense fluid collection is seen between the right hemisphere and the skull, consistent with acute subdural hematoma. Note that some areas of decreased density are present toward the top of the hematoma, likely representing CSF (darker areas) and nonclotted blood or blood mixed with CSF (gray areas). Small amounts of blood can also be seen extending into the sulci, consistent with subarachnoid hemorrhage. There is also a small amount of blood in the right lateral ventricle (see Figure 5.28A).
2. Marked subdural hematoma is present, with extension of a substantial amount of the right hemisphere under the falx. In addition to the findings already described, lower images on the CT demonstrated right transtentorial herniation and a right frontotemporal fracture.

Clinical Course
The patient was taken immediately to the operating room, and the subdural hematoma was evacuated. Unfortunately, he did not improve postoperatively. A follow-up CT scan was done the next day (see Figure 5.28B).

The subdural hematoma is no longer present, and there is no longer subfalcine herniation or midline shift. However, there are now two strips of hypodensity located on either side of the falx. These represent ischemic infarctions in the territory of the anterior cerebral arteries bilaterally (see Figure 3.6). Some spots of hemorrhage are located within these infarcts, suggesting hypoperfusion causing infarction, followed by reperfusion with hemorrhage into necrotic areas. The anterior cerebral arteries (see Figure 2.26C) probably were trapped under the falx by the severe degree of subfalcine herniation, leading to infarction and, later, reperfusion injury once the herniation was relieved.

The patient continued to decline medically and neurologically over the following days, and eventually died 8 days after admission.

CASE 5.7 A CHILD WITH HEADACHES, NAUSEA, AND DIPLOPIA

CHIEF COMPLAINT
An 11-year-old girl was brought to the pediatrician's office because of worsening headaches, nausea, and diplopia during the past week.

HISTORY
The patient was healthy until 1 week ago, when she developed persistent bifrontal headaches and nausea. Both symptoms gradually worsened, and for the past 2 days she has had multiple episodes of vomiting. Four or 5 days ago she also noticed horizontal diplopia when looking to the left. She denied any other symptoms. Her birth and developmental history were unremarkable, according to the parents. At the time of her appointment she was a sixth-grade honor student.

PHYSICAL EXAMINATION
Vital signs: T = 98.8°F, P = 76, BP = 120/68, R = 16.
Heart circumference: 54 cm (75th percentile for age).
Neck: Supple with no bruits.
Lungs: Clear.
Heart: Regular rate with no murmurs, gallops, or rubs.
Abdomen: Normal bowel sounds; soft, nontender.
Extremities: Normal.
Neurologic exam:
Mental Status: Alert and oriented x 3. Normal language and praxis.
 Cranial Nerves: Pupils 5 mm, constricting to 3 mm with light bilaterally. Ophthalmoscopic exam: Bilateral papilledema (see Figure 5.17). Extraocular movements: Left eye did not fully abduct on left lateral gaze. Otherwise, intact horizontal and vertical eye movements, and intact convergence.

Discussion
1. The key symptoms and signs in this case are:
   - Headaches, nausea, and papilledema
   - Horizontal diplopia and incomplete abduction of the left eye when looking to the left
2. Dysfunction of the left abducens nerve (CN VI) or the left lateral rectus muscle could cause incomplete abduction of the left eye on left lateral gaze, and horizontal diplopia (see KCC 13.4).
3. In this patient we have some signs of elevated intracranial pressure (see KCC 5.3). Interestingly, the abducens palsy produced by mildly elevated intracranial pressure can be unilateral (on either side), and may become bilateral with more severe pressure elevations.
4. The progressively worsening signs of elevated intracranial pressure in this patient could be caused by a mass lesion such as a brain tumor (see KCC 5.8), hydrocephalus (see KCC 5.7), or pseudotumor cerebri (see KCC 5.1). Other, less likely possibilities include a slowly developing intracranial infection (see KCC 5.9) or perhaps a coagulation disorder causing sagittal sinus thrombosis (see Chapter 10).
**CASE 5.6 SEVERE HEAD INJURY**

Figure 5.28 CT Scan Images Showing Subfalcial Herniation and Anterior Cerebral Artery Infarcts
(A) Subfalcial herniation caused by acute right subdural hematoma. (B) Follow-up scan 1 day later (following surgical removal of the hematoma), showing bilateral anterior cerebral artery infarcts.

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**Neuroimaging**

On the basis of the patient's symptoms and signs, the pediatrician decided to admit him to the hospital and ordered an MRI scan to be performed the same day (Figure 5.29).

1. Are these T1-, T2-, or proton density-weighted images (see Figure 4.6)? Are they horizontal, coronal, or sagittal (see Figure 2.5)?
2. Cover the labels in Figure 5.29A and B and identify as many structures as possible. In particular, review the pathway of CSF flow (see Figures 5.10, 5.11) from synthesis to reabsorption by identifying the following: choroid plexus, occipital and frontal horns of the lateral ventricles, region of foramen of Monro, third ventricle, cerebral aqueduct of Sylvius, fourth ventricle, cisterna magna, foramen magnum, and finally, superior sagittal sinus.
3. Gadolinium was given intravenously for the image shown in Figure 5.29B, but not for that in Figure 5.29B. Describe the location of the mass lesion. Does the mass enhance with gadolinium?
4. What is the cause of the elevated intracranial pressure (see KCC 5.3) in this patient? Which ventricles appear dilated, and why?

**Discussion**

1. The TR (repetition time) and TE (echo time) are both relatively short, so these are T1-weighted images (see Chapter 4). Recall that in T1-weighted images CSF appears dark, and white matter appears relatively bright compared to gray matter, thus resembling a true brain section. Figure 5.29A is a sagittal section near the midline; Figures 5.29B and C are horizontal images.
2. See labels on Figure 5.29A,B. Compare to Figures 4.13 and 4.15.
3. An approximately 2-cm-diameter roundish mass lesion can be seen in the posterior third ventricle, located between the thalami (see Figure 5.29B) and extending slightly into the third ventricle (see Figure 5.29A). The mass appears bright in Figure 5.29B but dark in Figure 5.29A, demonstrating enhancement with gadolinium. Recall that enhancement (see Chapter 4) suggests increased vascularity, or breakdown of the blood-brain barrier that can be seen with inflammation, tissue damage, or tumors.
4. This patient has elevated intracranial pressure caused by hydrocephalus (see KCC 5.7). The mass lesion is located in the posterior third ventricle and blocks the foramen of Monro, preventing CSF outflow into the fourth ventricle (see Figures 5.10, 5.11). The lateral ventricles and the third ventricle are therefore dilated, but the fourth ventricle is not. In the sagittal view (see Figure 5.29A) the corpus callosum appears somewhat thinned out and ballooned upward from the dilated ventricles. Note also that there are some regions of decreased density in the white matter adjacent to the frontal and occipital horns (see Figure 5.29B). This represents transependymal absorption of CSF from the ventricles into the white matter and is a sign that hydrocephalus has developed relatively recently and is severe. In addition, if the patient had hydrocephalus in infancy before closure of the cranial sutures, she may have had an enlarged head circumference; however, this patient’s head circumference was normal, again suggesting the hydrocephalus had developed recently.

**Clinical Course**

The patient was taken to the operating room the day after admission for placement of a right ventriculoperitoneal shunt (see KCC 5.7). A small incision was made in the scalp over the right frontal area. A second small incision was made in the abdominal skin and extended down to the peritoneum. The shunt tubing was passed under the skin through the subcutaneous tissues extending from the scalp incision down to the abdomen. A hole was
CASE 5.7 A CHILD WITH HEADACHES, NAUSEA, AND DIPLOPIA

Figure 5.29 MRI Scan Images Showing Pineal Tumor and Recovery
(A) Sagittal image. (B) Axial image with intravenous gadolinium, showing pineal tumor obstructing the (opening of the) aqueduct and causing noncommunicating hydrocephalus. (C) Follow-up axial images with gadolinium 8 months after treatment.

---

CASE 5.7 (CONTINUED)

(C)

Fornix of Monro
Region of third ventricle
Frontal horn
Thalami
Pineal tumor

Drilled through the skull, the dura was opened, and a catheter was passed through the right frontal lobe into the right lateral ventricle at a depth of approximately 6 cm from the surface. There was good flow of clear CSF under markedly elevated pressure. The catheter was connected to the shunt tubing through the scalp incision. Good flow was observed from the distal end of the tubing at the abdominal incision before it was inserted into the peritoneal cavity, and both incisions were closed with sutures. The shunt system contains a one-way flow valve to prevent fluid from traveling in the wrong direction. Postoperatively the patient's headaches and nausea resolved immediately, and her sixth-nerve paresis resolved more slowly but recovered completely by 2 months after surgery.

One week after admission, she was taken back to the operating room for a biopsy of the mass lesion. Because of its location, deep within the brain adjacent to the midbrain, open surgical resection or biopsy was not feasible. Therefore, a stereotactic needle biopsy (see KCC 16.4) was performed.

The results of the biopsy in our patient showed that she had a primitive neuroectodermal tumor (PNET; see Table 5.5) of the pineal region, also called a pineoblastoma. This is an uncommon brain tumor, which often responds well to treatment but can eventually be fatal. The patient was treated with radiation and chemotherapy and returned to school several months later. A follow-up MRI scan 8 months after initial presentation showed nearly complete disappearance of the tumor with therapy (see Figure 5.29C). The hydrocephalus had also completely resolved. At 3-year follow-up, she continued to do well, with no further growth of the tumor.

Related Case. An MRI scan from another patient with hydrocephalus from obstruction at the foramen of Monro is shown in Figure 5.30. This patient was a 42-year-old...
Figure 5.30 MRI Scan Images Showing Cysticercosis Obstructing Iver and Causing Noncommunicating Hydrocephalus. T1-weighted images. (A-C) Axial images. (D) Sagittal image. (E) Coronal image.
CASE 5.7 RELATED CASE (CONTINUED)

Portuguese-speaking man brought to the emergency room by his girlfriend after he became increasingly difficult to arouse, as well as agitated and confused over the course of 1 day. He had a past history of seizures. A CT scan showed multiple small calcifications consistent with CNS cysticercosis (see KCC 5.9). Note the presence of a cyst obstructing the 3rd visible on the MRI scan in the horizontal (see Figures 5.30A-C), sagittal (see Figure 5.30D), and coronal (see Figure 5.30E) views. He was treated by ventriculoperitoneal shunting (see KCC 5.7) and appropriate antiparasitic medication and made a full recovery.

CASE 5.8 HEADACHES AND PROGRESSIVE VISUAL LOSS

MINICASE
A 51-year-old man came to an ophthalmology appointment complaining of 8 months of progressive visual loss and headaches. He was found to have bilateral mild papilledema, with some pallor of the optic disc, visual fields with enlarged blind spots, and concentric loss of the peripheral visual fields in both eyes (he could see only the center of the visual field with either eye; see Figure 11.16A). The remainder of his neurologic exam was normal.

LOCALIZATION AND DIFFERENTIAL DIAGNOSIS
1. Headaches, papilledema, and visual loss of this kind are seen in what syndrome?
2. What is the appropriate test to perform next?

Discussion
1. Headaches with papilledema are worrisome signs of elevated intracranial pressure (see KCC 5.5). Concomitant visual loss can be caused by certain ophthalmologic conditions, but also by chronic or intermittent elevated intracranial pressure (see Table 5.3). Elevated intracranial pressure compresses the optic nerve, causing damage especially to the more superficial fibers nearest the nerve sheath, thus leading to concentric visual loss. Elevated intracranial pressure in this patient present over several months would most likely be caused by hydrocephalus (see KCC 5.7) or a mass lesion (see KCC 5.2), but it could also be caused by pseudotumor cerebri, sagittal sinus thrombosis, or other disorders.

2. The best test to perform next would be an MRI scan.

Neuroimaging
The attending ophthalmologist ordered an MRI scan (Figure 5.31).
1. Cover the labels on Figure 5.31 and identify the plane of section, image type (T1, T2, or proton density-weighted), and the labeled structures for each image (see Figures 2.5, 4.6). Again, review the pathway of CSF flow through the ventricles (see Figures 5.10, 5.11).
2. Which ventricles are dilated, and what does this suggest about the site of the obstruction?

Discussion
1. All images have relatively short TR and TE and are therefore T1-weighted (see Chapter 4). Figure 5.31A is coronal, 5.31B axial, and 5.31C sagittal.
2. The lateral ventricles are markedly dilated, while the third and fourth ventricles are not, suggesting obstruction bilaterally at the foramina of Monro. In fact, a small mass lesion can be identified in the anterior third ventricle, just underneath the fornix, obstructing the foramina of Monro in Figure 5.31A. This is the typical location and appearance of a colloid cyst of the third ventricle, a benign tumor that causes symptoms primarily through intermittent and sometimes fatal hydrocephalus (see KCC 5.7). Note the prominent dilation of the lateral ventricles bilaterally (see Figure 5.31).

Clinical Course
The patient was admitted to the hospital for surgery. An incision was made in the right scalp, and a large bone flap was carefully removed, exposing the dura over the right hemisphere and a portion of the superior sagittal sinus in the midline. The dura was opened in a longitudinal fashion to the right of the midline. A large bridging vein (see Figure 5.1) was encountered entering the superior sagittal sinus from the right side, and care was taken not to disrupt it. The dura was folded back, revealing the right cerebral cortex and the falx cerebri in the midline. The cortex was gently retracted laterally off the falx along the medial surface of the hemisphere, allowing the surgeon to peer down onto the top surface of the corpus callosum. The pericallosal vessels (see Figure 4.16) were carefully moved to either side, and a 2 cm longitudinal incision was made in the corpus callosum, providing access to both lateral ventricles, with the septum pellucidum visible in the midline. An operating microscope was used for the remainder of the procedure. The colloid cyst was easily visible through the right foramen of Monro and was gently aspirated, with care taken to avoid damaging the fornix. At the end of the procedure, all visible colloid cyst was removed, and excellent flow of irrigant
**CASE 5.8 HEADACHES AND PROGRESSIVE VISUAL LOSS**

Figure 5.31 MRI Scan Images Showing Colloid Cyst Causing Obstructive Hydrocephalus. Colloid cysts of the third ventricle obstructing foramina of Monro and causing noncommunicating obstructive hydrocephalus. T1-weighted images with TR = 450, TE = 11. Coronal (A), axial (B), and sagittal (C) views. The coronal scan (A) was performed with intravenous gadolinium.

![MRI Scan Images](image)

Body of lateral ventricle
- Meso under fornix
- Third ventricle
- Frontal horn
- Septum pellucidum
- Lateral ventricle

Postoperatively, the patient did quite well, with no further headaches and no further worsening or perhaps even some mild improvement in his vision over the following months. An MRI done 1 week after surgery showed marked improvement in the hydrocephalus. The hole made in the corpus callosum caused no functional deficits because of its relatively small size (see KCC 19.8).

**CASE 5.9 AN ELDERLY MAN WITH PROGRESSIVE GAIT DIFFICULTY, COGNITIVE IMPAIRMENT, AND INCONTINENCE**

**MINICASE**

A 76-year-old man was admitted to the hospital because of progressive gait unsteadiness, memory difficulty, and incontinence. His gait unsteadiness developed over the course of about 1 year, beginning with a shuffling stride and difficulty rising from a chair. This unsteadiness progressed until he required a cane, and eventually assistance from another person, in order to ambulate. Urinary incontinence began 4 months prior to admission, and his family noted the onset of memory problems around the same time. Examination on admission was notable for recall of only one of three objects at 5 minutes, and an unsteady, shuffling gait, the patient barely lifting his feet off the floor.

**Neuroimaging**

A head CT was performed (Figure 5.32).

1. [Cover the labels on Figure 5.32 and identify as many structures as possible on each image. Describe the appearance of the ventricles. Is this appearance due to generalized brain atrophy or to hydrocephalus (see KCC 5.7)?]
2. [What syndrome fits the clinical history, exam, and CT scan of this patient?]
Discussion

1. See the labels on Figure 5.32 for specific structures. The lateral ventricles, third ventricle, and even fourth ventricle appear enlarged. Note that in patients with brain atrophy, both the sulci and the ventricles are proportionately increased in size. In hydrocephalus, however, the ventricles are increased out of proportion to the amount of sulcal prominence. In our patient the sulci are slightly prominent, while the ventricles are markedly enlarged, making this hydrocephalus (see KCC 5.7). This diagnosis can be best appreciated if you look near the top of the brain (see Figure 5.32D), where the sulci are not especially prominent in this patient. Patients with generalized brain atrophy usually have enlarged sulci in this area.

2. This patient has the clinical trial of shuffling "magnetic gait," incontinence, and mental decline, together with a head CT strongly supporting the diagnosis of normal-pressure hydrocephalus (see KCC 5.7).

Clinical Course

The patient was evaluated before and after CSF removal by lumbar puncture (see KCC 5.10). Two large-volume lumbar punctures were performed—one on hospital day 1, and one on hospital day 12—with 45 cc and 33 cc of CSF removed, respectively. Locomotion was evaluated before and after each lumbar puncture (see table), as well as on the intervening days (not shown). After each lumbar puncture, the patient showed dramatic improvement in the speed and stability of his gait, as well as in his ability to stand up from a lying position. The improvement lasted several days after each lumbar puncture, but then his condition gradually worsened again. It is not known why a single removal of 30 to 40 cc of CSF by lumbar puncture should have an effect persisting longer than the time it takes to replace this volume of CSF (a few hours). It has been suggested that this extended effect may result from a small tear in the dura created by the lumbar puncture that continues to leak for a period of time.

Because of the patient's excellent but temporary response to lumbar puncture, and the clinical setting consistent with normal-pressure hydrocephalus, a right ventriculoperitoneal shunt was placed (see KCC 5.7). The result was lasting improvement. When the patient was seen in the office 7 months later, his gait was more stable, he lifted his feet higher off the floor, and he walked 15 feet in 9 seconds. He no longer had urinary incontinence. His memory and attention remained mildly impaired, however. For example, he recalled only three of six objects after 5 minutes.

<table>
<thead>
<tr>
<th>Effects of CSF Removal via Lumbar Puncture (LP) on Locomotion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Day 1, 24 hours post-LP   Day 12, 4 hours post-LP</td>
</tr>
<tr>
<td>pre-LP     post-LP    pre-LP    post-LP    pre-LP    post-LP</td>
</tr>
<tr>
<td>Time to walk 15 feet (average of 3 trials)</td>
</tr>
<tr>
<td>Number of steps to walk 15 feet (average of 3 trials)</td>
</tr>
<tr>
<td>Number of steps to turn 180° (average of 3 trials)</td>
</tr>
<tr>
<td>Time from lying to standing (s)</td>
</tr>
<tr>
<td>Subjective evaluation</td>
</tr>
</tbody>
</table>

CASE 5.9 AN ELDERLY MAN WITH PROGRESSIVE GAIT DIFFICULTY, COGNITIVE IMPAIRMENT, AND INCONTINENCE

Figure 5.32 Head CT Showing Dilated Ventricles Typical of Normal-Pressure Hydrocephalus (A-D) Axial images progressing from the inferior to superior direction.
CASE 5.10 A YOUNG MAN WITH HEADACHE, FEVER, CONFUSION, AND STIFF NECK

CHIEF COMPLAINT
A 28-year-old man was brought to the emergency room with 1 day of worsening headache, fever, confusion, and stiff neck.

HISTORY
Previously healthy, the patient awoke on the day of admission at about 4:00 a.m. with chills and body aches. By noon, he was breathing quickly and had nausea and vomiting, but then he felt better and took a nap. He awoke at 3:00 p.m. with a midfrontal headache, photophobia, and stiff neck with a temperature of 102°F. He took some acetaminophen and went to a party that evening. However, by 9:00 p.m., he appeared confused, talking about “rattling” and “skirt party pick me up.” His girlfriend then brought him to the emergency room by taxi cab.

The patient had no known recent exposure to anyone ill and no HIV risk factors. He had visited a friend in Mississippi the previous week but had not recently traveled abroad, and he had not had any recent insect bites or rash. He had no pets. He worked as an air force pilot. He was not taking any medications and had no known drug allergies.

PHYSICAL EXAM
General appearance: Acute ill-appearing young man lying on a stretcher.
Vital signs: 
- T: 101.7°F
- P: 110
- BP: 136/84
- R: 24
Head: Normal tympanic membranes bilaterally. Dry oral mucous. No oral thrush.
Lungs: Clear.
Heart: Regular rate with no murmurs, gallops, or rubs.
Abdomen: Normal bowel sounds; soft, nontender.
Extremities: Normal.
Skin: Nonblanching, purplish 2 to 3 mm petechiae scattered on arms, legs, and chest.

Neurologic exam:
- Motor: Normal tone. Power 5+ throughout, with intermittent cooperation.
- Sensory: Intact light touch, pinch.
- Reflexes: 
  - 2 2 2
  - 2 2 2

Coordination: Normal finger-nose-finger testing.
Gait: Not tested.

LOCALIZATION AND DIFFERENTIAL DIAGNOSIS
1. Irritation of what structure(s) is suggested by the signs and symptoms seen in this patient? What is the most likely diagnosis?
2. What are the most likely pathogens, given this patient’s age and history? What are some other possibilities?
3. What diagnostic test should be done, and what treatment should be started without delay?

Discussion
1. Headache, fever, photophobia, and nuchal rigidity are strongly suggestive of meningeval irritation (see Table 5.5). The lethargy and confusion suggest a process causing diffuse cerebral dysfunction as well (encephalopathy; see KCQ 19.15). The acute progressive time course of this patient's presentation strongly suggests acute bacterial meningitis, or possibly viral meningitis.
2. Acute bacterial meningitis in immunocompetent adults is usually caused by Streptococcus pneumoniae or Neisseria meningitidis, but it can also be caused by Listeria meningitidis (see Table 5.8). The purplish skin lesions are suggestive of N. meningitidis, although they can also be seen in rickettsial infections. Viral meningitis, including herpes encephalitis, should also be considered. Postinfectious meningitis or other less common forms of meningitis are also possible.
3. Patients with acute infectious meningitis can deteriorate within a matter of hours or even minutes, so rapid evaluation and treatment are essential. A head CT and lumbar puncture (see KCC 5.10) should be performed to narrow the diagnosis and help determine the most appropriate therapy (see Tables 5.7, 5.8). However, antimicrobial treatment should not be delayed if any reason a lumbar puncture cannot be performed immediately.

Initial Clinical Course

The patient was started on intravenous ceftriaxone and ampicillin. A head CT was normal, and lumbar puncture was performed successfully about 20 minutes (see table). Blood toxicity screen was negative, and other routine blood tests were unremarkable. Chest X-ray was normal.

Results of Lumbar Puncture

<table>
<thead>
<tr>
<th>Tube number</th>
<th>Red blood cells (per mm³)</th>
<th>White blood cells (per mm³)</th>
<th>Percent PMNs¹</th>
<th>Percent lymphocytes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>230</td>
<td>3280</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>220</td>
<td>2030</td>
<td>99</td>
<td>1</td>
</tr>
</tbody>
</table>

¹PMNs = polymorphonuclear leukocytes.
Protein: 716 mg/dL; Glucose: <20 mg/dL.

1. From what space is CSF removed to perform lumbar puncture, and what two meningeal layers is it bounded by (see Figure 5.22B)? What landmark is used to enter the lumbar cistern at the appropriate level (see Figure 5.22A)?

2. What do the results of the CSF analysis in this patient suggest (compare Table 5.7)?

Discussion

1. In lumbar puncture, CSF is removed from the subarachnoid space of the lumbar cistern, bounded by the pia and the arachnoid (see Figures 5.1, 5.22B). The iliac crest is used as a landmark to enter the lumbar cistern at the L4-L5 interspace, well below the conus medullaris of the spinal cord (see KCC 5.10; Figure 5.22).

2. The CSF in this patient shows a very high protein level, low glucose level, and very high white blood cell count, consisting mostly of polymorphonuclear cells, consistent with acute bacterial meningitis (see Table 5.7).

The CSF cultures grew no organisms. However, blood cultures performed prior to the administration of antibiotics grew Neisseria meningitidis. By 1 day after admission the patient's fever had stopped and his mental status cleared. He was treated with a course of intravenous antibiotics and made an excellent recovery and was discharged 7 days later with no sequelae.

Additional Cases

Related cases can be found in other chapters for the following topics: herniation (Case 10.10); intracranial hemorrhage (Cases 10.1, 10.13, 14.9, 19.3, 19.4); aneurysm (Case 13.1); arteriovenous malformation (AVM) (Case 11.5); hydrocephalus (Case 15.3); brain tumors (Cases 7.4, 11.3, 11.4, 12.2, 12.3, 12.5-12.7, 13.9, 15.2, 17.1, 19.2, 18.4, 18.5, 19.7); and infectious disorders of the nervous system (Cases 8.4, 16.1, 18.3, 19.10). Other relevant cases can be found using the Case Index.

Brief Anatomical Study Guide

1. In this chapter, we have discussed the anatomy of the meninges (see Figure 5.1), including the pia, arachnoid, and dura, as well as the major dural infoldings (see Figures 5.5, 5.6).

2. The cranial cavity is composed of anterior, middle, and posterior fossae, which contain specific brain structures (see Figures 5.2-5.4).

3. The blood-brain barrier is formed by brain capillary endothelial cells sealed together by tight junctions (see Figures 5.13B, 5.14).

4. To gain a three-dimensional understanding of the ventricular system and its spatial relationships to adjacent structures, review Figures 5.10 and 5.11, and the Neurological Atlas MRI images in Figures 4.13-4.15. Several C-shaped structures follow the course of the lateral ventricles, including the caudate nucleus, corpus callosum, and fornix (see Figure 4.15). We will now discuss the spatial relationships of these structures—both as a review of the anatomy of the ventricular system and to prepare you for the next section, "A Scuba Expedition through the Brain."

5. The caudate nucleus and thalamus bulge inward from the lateral walls of the lateral ventricles (see Figures 4.13, 4.14). The caudate nucleus forms a C-shaped structure that lies along the wall of the C-shaped lateral ventricle in all planes of section (see Figures 4.14, 16.4).

6. The septum pellucidum is a thin membrane that separates the two lateral ventricles in the midline. The septum pellucidum hangs from the corpus callosum, another C-shaped structure, which forms the roof of most parts of the lateral ventricles (see Figures 4.14, 4.15).

7. Dangling from the bottom of the septum pellucidum, the fornix (see Figure 18.13) again forms a C-shaped structure that parallels the curve of the lateral ventricles. The fornix is composed of a pair of archlike bundles of myelinated axons that connect structures in the temporal lobes to the hypothalamus and basal forebrain (see Figure 18.9).

8. The hippocampal formation, a structure involved in memory and other limbic functions (see Chapter 18) lies on the floor and the medial wall of the temporal horn of the lateral ventricles (see Figure 4.14).

9. The interventricular foramina of Monro are bounded by the fornix medially and superiorly, by the thalamus laterally, and by the anterior commissure (a white matter tract connecting structures in the two temporal lobes) inferiorly (see Figures 16.4, 18.9A).

10. The third ventricle is bounded laterally by the thalamus and hypothalamus; superiorly by the fornix; inferiorly by the hypothalamus; anteriorly by the anterior commissure, fornix, lamina terminals, and hypothalamus; and posteriorly by the posterior commissure, pineal region, and hypothalamus (see Figures 4.15, 5.10).

11. The cerebral aqueduct (of Sylvius), a thin canal of cerebrospinal fluid, is located entirely within the midbrain gray matter (see Figure 5.10).
A Scuba Expedition through the Brain

Imagine your colleague has lost his memory just before the neuroanatomy final exam. Fortunately, a mutual friend owns a miniature ray and specialized electronic apparatus that, when plugged directly into the hippocampus, can immediately retrieve any lost memories. To help your friend, you bravely don your scuba gear and allow yourself to be miniaturized and injected via lumbar puncture into your friend’s lumbar cistern (see Figure 5.22), taking along a set of your friend’s MRI scans as a map (see Figures 4.13-4.15). Your mission: Find the hippocampus.

Looking around as you swim in the cerebrospinal fluid, you see many wispy spiderweb-like strands extending inward from the (2. ______) space (Figure 5.3), bounded externally by the (3. ______) and internally by the (4. ______). As you swim upward, you notice long ropelike strings descending all around you in the lumbar cistern that for some reason remind you of a horse’s tail. This is the (5. ______), consisting of spinal (6. ______) roots. Soon you see a thick, gleaming, pinkish white structure, the (7. ______). It has sensory roots entering its (8. ______) surface, and motor roots exiting its (9. ______) surface.

As you swim up the spinal canal in the subarachnoid space, eventually you come to a large ring-shaped hole leading into the cranial cavity. This entryway is the (10. ______), bringing you into the cisterna (11. ______). Above you is a pinkish gray structure with lots of bumps on it that seems to be furiously calculating coordination and other operations. It is the (12. ______). You peek around to the sides at the lateral foramina of (13. ______), but then you decide to swim straight up along the dorsal surface of the medulla and under the cerebellum to enter the midline foramen of (14. ______). Suddenly, you feel a rush of clear cerebrospinal fluid against your face as it flows out into the subarachnoid space, and you need to kick a little harder with your flippers. You have entered a large cavity called the (15. ______) ventricle. You let yourself sink to the ventral floor of the fourth ventricle and take a few steps forward. Bumper your flippers, the floor of the fourth ventricle is formed initially by the (16. ______), and then, as you progress farther rostrally, by the (17. ______).

Looking upward, you direct your headlight toward a large structure forming the roof of the cavern. This is the (18. ______). You decide to swim farther rostrally to enter a narrow tunnel called the (19. ______). To pass through this tunnel you have to wriggle your shoulders against the walls, which are part of the (20. ______), and you continue to swim for-ward against the CSF current. Finally, you pop out of the top end of the tunnel and find yourself sinking down toward the floor of another cavity, called the (21. ______) ventricle. As you sink downward, you look to the left and to the right, and you see walls made up first by the (22. ______) and later by the (23. ______). You decide not to let yourself sink to the bottom, which is also formed by the (23. ______), but instead you look up at the roof and see two parallel gleaming white arches running from back to front, making up the roof of the third ventricle. This is the (24. ______). You kick with your flippers and swim up toward the front of the third ventricle, where you see two holes, called the foramina of (25. ______). You choose the foramen on the right and climb up onto the threshold of the hole and find yourself standing on the (26. ______) commissure, with your left (medial) hand leaning up against the (27. ______) and your right (lateral) hand leaning up against the (28. ______). You swim forward and upward and find that you have entered another very large cavity, the right (29. ______) ventricle. As you continue to swim forward in this cavity, you are entering the (30. ______) horn of the lateral ventricle. Looking upward, you see a whitish “hand body” forming the roof, the (31. ______).

You soon reach a dead end, also formed by the (31. ______) as it curves downward around the most anterior portions of the lateral ventricle. You turn around 180° and start swimming back caudally toward the other portions of the lateral ventricle. You then pass the foramen of (32. ______) again and have to kick a little harder to avoid being sucked back down into the (33. ______) ventricle. You have now entered the (34. ______) of the right lateral ventricle. On your right side is a translucent membrane forming the medial wall of the ventricle, called the (35. ______). It extends downward from the (36. ______), which also forms the roof of the lateral ventricle, to the (37. ______) on the medial floor. As you shine your powerful searchlight through this membrane, you can barely make out another, nearly identical cavity on the other side of the brain, the left (38. ______) ventricle. Looking laterally (to your left), you see a large gray matter structure bulging inward into the ventricle and forming its lateral wall. Checking your map (Figures 4.13-4.15), you realize this is the (39. ______) nucleus. As you swim farther back, another gray matter structure called the (40. ______) bulges inward from the lateral wall. Suddenly you notice that the floor has become ensheathed in a pulsatile tangle of blood vessels that seems to be secreting a clear fluid. This is the (41. ______), which you had noticed all along the way inside the ventricles but had so far managed to avoid. Carefully you disentangle your flipper and soon enter another part of the ventricle, called the (42. ______).

From here you seem to have three choices of where to swim next. You could turn around and swim forward into the (43. ______) of the lateral ventricle, or you could swim downward into the (44. ______) horn, but instead you choose to continue swimming toward the back of the brain and enter the (45. ______) horn. However, you soon meet another dead end when you find yourself well within the (46. ______) lobe. So you turn around and start walking forward, but then—WHOAA! Suddenly you are sliding down a steep slope into the (47. ______) horn. You stand up, brush yourself off, and lean your left hand against the medial wall. You look around and decide you must be deep within the (48. ______) lobe. Then you look down at your feet and at your left hand, and what do you know, you’re finally standing right on top of the (49. ______). Congratulations! You have succeeded in reaching your goal, and in preserving many valuable memories.

Answers are found on page 210.
Lumbar Puncture


Scuba Expedition through the Brain—Answers

1. arachnoid
2. subarachnoid
3. arachnoid
4. pia
5. cauda equina
6. nerve
7. spinal cord
8. dorsal (or posterior)
9. ventral (or anterior)
10. foramen magnum
11. magna
12. cerebellum
13. Luschka
14. Magendie
15. fourth
16. medulla
17. pons
18. cerebellum
19. cerebral aqueduct (of Sylvius)
20. midbrain (or mesencephalon)
21. third
22. thalamus
23. hypothalamus
24. fornix
25. Monro
26. anterior
27. fornix
28. thalamus
29. lateral
30. anterior (or frontal)
31. corpus callosum
32. Monro
33. third
34. body
35. septum pellucidum
36. corpus callosum
37. fornix
38. lateral
39. caudate
40. thalamus
41. choroid plexus
42. atrium (or trigonum)
43. body
44. temporal (or inferior)
45. occipital (or posterior)
46. occipital
47. temporal (or inferior)
48. temporal
49. hippocampus


Movement is crucial to our normal functioning, and damage to the motor systems can be profoundly disabling. In this chapter, we will learn of a 74-year-old woman who awoke one morning and suddenly developed slurred speech and paralysis of the entire right side of her body, including her right face, arm, and leg. Her reflexes were brisk on the right side, and she also had a Babinski’s sign on the right, but her sensory exam was normal. She was unable to walk or stand without assistance. To diagnose and treat patients with such symptoms, we must learn about the pathways in the brain and spinal cord that control movement of the body.
ANATOMICAL AND CLINICAL REVIEW

In this chapter and the next we will focus on the three most important motor and sensory "long tracts" in the nervous system. Familiarity with these three pathways is essential and suffices for full neuroanatomical localization in many clinical cases. These three fundamental pathways and their functions are listed in Table 6.1.

Each of these pathways crosses over, or decussates, to the contralateral side at a specific point in its course. Knowledge of the crossover points is very helpful for localizing lesions. A second clue to localizing lesions often comes from an understanding of the topographical representation of different body parts in these pathways. In these two chapters (6 and 7), we will trace the routes of the main motor and sensory pathways through all levels of the nervous system and review their overall organization and functions, with special emphasis on the spinal cord. We will also briefly discuss other systems that involve the spinal cord, such as the autonomic nervous system, sphincter control mechanisms, and motor pathways other than the corticospinal tract.

Motor Cortex, Sensory Cortex, and Somatotopic Organization

The primary motor cortex and primary somatosensory cortex are shown in Figure 6.1. Recall from Chapter 2 that these areas are located on either side of the central, or Rolandic, sulcus, which divides the frontal lobe from the parietal lobe. The primary motor cortex (Brodmann’s area 4) is in the precentral gyrus, while the primary somatosensory cortex (Brodmann’s areas 3, 1, and 2) is in the postcentral gyrus (see Figure 6.1). Lesions in these areas cause motor or sensory deficits, respectively, in the contralateral body.

Several important areas of motor association cortex lie just anterior to the primary motor cortex, including the supplementary motor area and premotor cortex (see Figure 6.3). These regions are involved in higher-order motor planning and projection to the primary motor cortex. Similarly, somatosensory association cortex in the parietal lobe receives inputs from primary somatosensory cortex and is important in higher-order sensory processing. Unlike lesions in the primary cortices, lesions in secondary association cortex do not produce severe deficits in basic movement or sensation. Instead, lesions of the association cortex cause deficits in higher-order sensory analysis or motor planning, discussed further in Chapter 19. Interestingly, there are reciprocal connections between primary and association cortex, sensory and motor areas, as shown in Figure 6.1A.

Functional mapping and lesion studies have demonstrated that the primary motor and somatosensory cortices are somatotopically organized (Figure 6.2). That is, adjacent regions on cortex correspond to adjacent areas on the body surface. The cortical maps are classically depicted by a motor homunculus and a sensory homunculus (homunculus means "little man" in Latin). Since the original description of these homunculi, additional work in both humans and other animals has shown that the somatotopic maps are not as clear-cut and consistent as originally depicted, especially when studied at high spatial resolution. Multiple fractionated representations exist, more so for motor than for sensory maps. Nevertheless, the homunculi remain a useful concept for understanding the broad strokes of cortical representation, and they are widely used for clinical localization.

As we will see in the sections that follow, somatotopic organization is not confined to the cortex. Rather, some motor and sensory pathways maintain a rough somatotopic organization along their entire length, which can be traced from one level to the next in the nervous system.
Basic Anatomy of the Spinal Cord

The spinal cord contains a butterfly-shaped central gray matter surrounded by ascending and descending white matter columns, or fasciculi (Figure 6.3A). Sensory neurons in the dorsal root ganglia have axons that bifurcate. One branch conveys sensory information from the periphery, and the other carries this information through the dorsal nerve root filaments into the dorsal aspect of the spinal cord. The central gray matter has a dorsal (posterior) horn that is involved mainly in sensory processing, an intermediate zone that contains interneurons and certain specialized nuclei (Table 6.2), and a ventral (anterior) horn that contains motor neurons. Motor neurons send their axons out of the spinal cord via the ventral nerve root filaments. The spinal gray matter can also be divided into nuclei or, using a different nomenclature, into laminae named by B. Reid (see Figure 6.3B); Table 6.2), with different functions that we will discuss in this chapter and in Chapter 7. The spinal cord while matter consists of dorsal (posterior) columns, lateral columns, and ventral (anterior) columns (see Figure 6.3A).

The spinal cord does not appear the same at all levels (Figure 6.4). The white matter is thickest in the cervical levels (see Figure 6.4C), where most ascending fibers have already entered the cord and most descending fibers have not yet terminated on their targets, while the sacral cord is mostly gray matter (see Figure 6.4F). In addition, the spinal cord has two enlargements (see Figure 6.4A). The cervical enlargement and the lumbar enlargement give rise to the nerve plexuses for the arms and legs. The spinal cord has more gray matter at the cervical and lumbar levels (see Figure 6.4C, E, and F) than at the thoracic levels.

<table>
<thead>
<tr>
<th>TABLE 6.2: Nuclei and Laminae of the Spinal Cord</th>
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<tbody>
<tr>
<td>REGION</td>
</tr>
<tr>
<td>--------</td>
</tr>
<tr>
<td>Dorsal horn</td>
</tr>
<tr>
<td>Dorsal horn</td>
</tr>
<tr>
<td>Dorsal horn</td>
</tr>
<tr>
<td>Dorsal horn</td>
</tr>
<tr>
<td>Dorsal horn</td>
</tr>
<tr>
<td>Intermediate zone</td>
</tr>
<tr>
<td>Ventral horn</td>
</tr>
<tr>
<td>Ventral horn</td>
</tr>
<tr>
<td>Gray matter surrounding central canals</td>
</tr>
</tbody>
</table>
Spinal Cord Blood Supply

The blood supply to the spinal cord arises from branches of the vertebral arteries and spinal radicular arteries (Figure 6.5). The vertebral arteries give rise to the anterior spinal artery that runs along the ventral surface of the spinal cord (see Figure 2.26C). In addition, two posterior spinal arteries arise from the vertebral or posterior inferior cerebellar arteries and supply the dorsal surface of the cord. The anterior and posterior spinal arteries are variable in prominence at different spinal levels and form a spinal arterial plexus that surrounds the spinal cord (see Figure 6.5). Thirty-one segmental arterial branches enter the spinal canal along its length; most of the branches arise from the aorta and supply the meninges. Only six to ten of these reach the spinal cord as radicular arteries, arising at variable levels (see Figure 6.4D), particularly in the ventral horns, where lower motor neurons for the arms and legs reside. In the thoracic cord, a lateral horn is present (see Figure 6.4D) that contains the intermediolateral cell column.


Figure 6.5 Spinal Cord Arterial Supply. (A) Vertebral and radicular arteries give rise to anterior and posterior spinal arteries forming the spinal arterial plexus. (B) Spinal cord cross section showing regions supplied by the anterior and posterior spinal arteries.
6.5A). There is usually a prominent radicular artery arising from the left side, anywhere from T6 to L3, but usually between T9 and T12. This is called the great radicular artery of Adamkiewicz, and provides the major blood supply to the lumbar and sacral cord.

The mid-lumbar region, at approximately T4 to T8, lies between the lumbar and vertebral arterial supplies and is a vulnerable zone of relatively decreased perfusion. This region is most susceptible to infarction during thoracic surgery or other conditions causing decreased aortic pressure. The anterior spinal artery supplies approximately the anterior two-thirds of the cord, including the anterior horns and anterior and lateral white matter columns (see Figure 6.3B). The posterior spinal arteries supply the posterior columns and part of the posterior horns. Venous return from the spinal cord occurs via a plexus of veins draining initially into the epidural space before reaching systemic circulation. The epidural veins, called Batson’s plexus (see Figure 8.2), do not contain valves, so elevated intra-abdominal pressure can cause reflux of blood carrying metastatic cells (such as prostate cancer) or pelvic infections into the epidural space.

General Organization of the Motor Systems

Given the extraordinarily refined movements that can be carried out by a musician, gymnast, or surgeon, it should come as no surprise that motor systems form an elaborate network of multiple, hierarchically organized feedback loops. A summary of motor system pathways is shown in Figure 6.6. Only the most important loops are depicted, and sensory inputs have been omitted. Recall that the cerebellum and basal ganglia participate in important feedback loops in which they project back to the cerebral cortex via the thalamus and do not themselves project to lower motor neurons (see Figure 2.17). The roles of the cerebellum and basal ganglia in motor control will be discussed further in Chapters 15 and 16. Within the cerebral cortex itself, there are numerous important circuits for motor control. For example, circuits involving association cortex regions such as the supplementary motor area, premotor cortex, and parietal association cortex are crucial to the planning and formulation of movements (see Figure 6.3A). As we will discuss in Chapter 15, lesions of these regions of association cortex can lead to apraxia, in which there is a deficit in higher-order motor planning and execution despite normal strength (neuroexams.com Video 15). Although not shown in Figure 6.6, sensory inputs clearly also play an essential role in motor control and participate in motor circuits and feedback loops that range from the level of the spinal cord (see Figure 2.21) to the cerebral cortex (see Figure 6.1). Recall also that upper motor neurons carry motor system outputs to lower motor neurons located in the spinal cord and brainstorm, which in turn, project to muscles in the periphery. Descending upper motor neuron pathways arise from the cerebral cortex and brainstorm (see Figure 6.6). These descending motor pathways can be divided into lateral motor systems and medial motor systems based on their location in the spinal cord. Lateral motor systems travel in the lateral columns of the spinal cord and synapse on the more lateral groups of ventral horn motor neurons and interneurons (Figure 6.7). Medial motor systems travel in the anterior-medial spinal cord column to synapse on medial ventral horn motoneurons and interneurons.

The two lateral motor systems are the lateral corticospinal tract and the rubrospinal tract (Table 6.3). These pathways control the movement of the extremities (Figure 6.7). The lateral corticospinal

![Figure 6.6 General Organization of the Motor Systems](Image)

Table 6.3 Lateral and Medial Descending Motor Systems

<table>
<thead>
<tr>
<th>TRACT</th>
<th>SITE OF ORIGIN</th>
<th>SITE OF DECUSATION (WHERE RELEVANT)</th>
<th>LEVELS OF TERMINATION</th>
<th>FUNCTION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LATERAL MOTOR SYSTEMS</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Lateral corticospinal</td>
<td>Primary motor cortex, other frontal and parietal</td>
<td>Pyramidal decussation, at the cervical/medullary junction</td>
<td>Lateral cord (predominantly at cervical and lumbar enlargements)</td>
<td>Movement of contralateral limbs</td>
</tr>
<tr>
<td></td>
<td>areas</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rubrospinal</td>
<td>Red nucleus, magnocellular division</td>
<td>Ventral cervical decussation, in the midbrain</td>
<td>Cervical cord</td>
<td>Movement of contralateral limbs (function is uncertain in humans)</td>
</tr>
<tr>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>MEDIAL MOTOR SYSTEMS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior corticospinal</td>
<td>Primary motor cortex and supplementary motor area</td>
<td></td>
<td>Cervical and upper thoracic cord</td>
<td>Control of distal axial and girdle muscles</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vestibulospinal tracts  (VSTs)</td>
<td>Medial VST; medial and inferior vestibular nucleus; Lateral VST; lateral vestibular nuclei</td>
<td>Medial VST; Cervical and upper thoracic cord; Lateral VST; entire cord</td>
<td>Lateral VST: balance</td>
<td>Vestibulospinal control</td>
</tr>
<tr>
<td>Reticulospinal tracts</td>
<td>Ponsine and medullary reticular formation</td>
<td></td>
<td></td>
<td>Automatic posture and gait-related movements</td>
</tr>
<tr>
<td>Tectospinal tracts</td>
<td>Superior colliculus</td>
<td>Dorsal spinal decussation, in the midbrain</td>
<td>Cervical cord</td>
<td>Coordination of head and eye movements (uncertain in humans)</td>
</tr>
</tbody>
</table>

*Despite their names, both medial and lateral VSTs are medial motor systems.
tract in particular is essential for rapid, dextrous movements at individual digits or joints. Both of these pathways cross over from their site of origin and descend in the contralateral lateral spinal cord to control the contralateral extremities (see Table 6.3 and Figure 6.11A,B).

The four medial motor systems are the anterior corticospinal tract, the vestibulospinal tracts, the reticulospinal tracts, and the tectospinal tract (see Table 6.3). These pathways control the proximal axial and girdle muscles involved in postural tone, balance, orienting movements of the head and neck, and automatic gait-related movements (see Figure 6.7). The medial motor systems descend ipsilaterally or bilaterally. Some extend only to the upper few cervical segments (see Table 6.5 and Figure 6.11C–F).

The medial motor systems tend to terminate on interneurons that project to both sides of the spinal cord, controlling movements that involve multiple bilateral spinal segments. Thus, unilateral lesions of the medial motor systems produce no obvious deficits. In contrast, lesions of the lateral corticospinal tract produce dramatic deficits (see the next section). The rubrospinal tract (in humans is small and its clinical importance is uncertain, but it may participate in taking over functions after corticospinal injury. It may also play a role in flexor (decorticating) posturing of the upper extremities (see Figure 5.3A), which is typically seen with lesions above the level of the red nucleus, in which the rubrospinal tract is spared.

**Lateral Corticospinal Tract**

The corticospinal tract or, more specifically, the lateral corticospinal tract, is the most clinically important descending motor pathway in the nervous system. This pathway controls movement of the extremities, and lesions along its course produce characteristic deficits that often enable precise clinical localization. Let's follow the course of the corticospinal tract from cerebral cortex to spinal cord (Figure 6.8). Over half of the corticospinal tract fibers originate in the primary motor cortex (Brodman's area 4) of the precentral gyrus. The remainder arise from the premotor and supplementary motor areas (area 6), or from the parietal lobe (areas 1, 2, 5, and 7) (Figure 6.8A). The primary motor cortex neurons contributing to the corticospinal tract are located mostly in cortical layer 5 (see Figure 2.14A). Layer 5 pyramidal cell projections synapse directly onto motor neurons in the ventral horn of the spinal cord, as well as onto spinal interneurons. About 3% of corticospinal neurons are giant pyramidal cells called Betz cells, which are the largest neurons in the human nervous system.

Axons from the cerebral cortex enter the upper portions of the cerebral white matter, or corona radiata (see Figure 4.13I), and descend toward the internal capsule (see Figure 4.13C). In addition to the corticospinal tract, the cerebral white matter conveys bidirectional information between different cortical areas, and between cortex and deep structures such as the basal ganglia, thalamus, and brainstem (Figure 6.9B). These white matter pathways form a fanlike structure as they enter the internal capsule, which condenses down to fewer and fewer fibers as connections to different subcortical structures are made (see Figure 6.9A).

**Figure 6.8 Lateral Corticospinal Tract**. Upper motor neuron in primary motor cortex (precentral gyrus) sends an axon downward to cross over at the pyramidal decussation. The axon then continues downward in the contralateral spinal cord before synapsing with lower motor neuron in the anterior horn.
The internal capsule is best appreciated in horizontal brain sections (Figure 6.10A), in which the right and left internal capsules look like arrowheads or two letter Vs with their points facing inward. Note that the thalamus and caudate nucleus are always medial to the internal capsule, while the globus pallidus and putamen are always lateral to the internal capsule. There are three parts to the internal capsule: anterior limb, posterior limb, and genu. Note that the anterior limb of the internal capsule separates the head of the caudate from the globus pallidus and putamen, while the posterior limb separates the thalamus from the globus pallidus and putamen (see also Figures 16.2, 16.3). The genu (“knee” in Latin) is at the transition between the anterior and posterior limbs, at the level of the fornix of Monro. The corticospinal tract lies in the posterior limb of the internal capsule. The somatotopic map is preserved in the internal capsule, so motor fibers for the face are most anterior, and those for the arm and leg are progressively more posterior (see Figure 6.10A). Fibers projecting from the cortex to the brainstem, including motor fibers for the face, are called corticobulbar instead of corticospinal because they project from the cortex to the brainstem, or “bulb.” Despite the somatotopic arrangement, the fibers of the internal capsule are compact enough that lesions at this level generally produce weakness of the entire contralateral body (face, arm, and leg) (see KCC 6.3; see Figure 6.14A). However, occasionally capsular lesions can also produce more selective motor deficits. Additional details of the fibers carried by the internal capsule other than the corticobulbar and corticospinal tracts are shown in Figure 6.9B.

The internal capsule continues into the midbrain cerebral peduncles, meaning literally “feet of the brain” (see Figure 6.10B). The white matter is located in the ventral portion of the cerebral peduncles and is called the basis pedunculi. The middle one-third of the basis pedunculi contains corticobulbar and corticospinal fibers with the face, arm, and leg axons arranged from medial to lateral, respectively (see Figure 6.10B). The other portions of the basis pedunculi contain primarily corticoamine fibers (see Chapter 15).

The corticospinal tract fibers next descend through the ventral pons, where they form somewhat scattered fascicles (Figure 6.11A). These collect on the ventral surface of the medulla to form the medullary pyramid (see Figures 6.8, 6.11A). For this reason the corticospinal tract is sometimes referred to as the pyramidal tract (this terminology, though widely used, is somewhat imprecise since the pyramids include reticulospinal and other brainstem pathways in addition to the corticospinal tract). The transition from medulla to spinal cord is called the cervical medullary junction, which occurs at the level of the foramen magnum (see Figure 5.10). At this point about 85% of the pyramidal tract fibers cross over in the pyramidal decussation to enter the lateral white matter columns of the spinal cord, forming the lateral corticospinal tract (see Figures 6.8, 6.11A). A somatotopic representation is present in the lateral corticospinal tract, with fibers controlling the upper extremity located medial to those controlling the lower extremity (see Figure 6.10C). Finally, the axons of the lateral corticospinal tract enter the spinal cord central gray matter to synapse onto anterior horn cells (see Figures 6.7, 6.8, 6.11A). The remaining approximately 15% of corticospinal fibers continue into the spinal cord ipsilateral, without crossing, and enter the anterior white matter columns to form the anterior corticospinal tract (see Figures 6.9A, 6.11C).

In addition to the lateral corticospinal tract, the other lateral and medial descending motor systems (see Table 6.3) are shown in Figure 6.11 as well, including the rubrospinal, anterior corticospinal, tectospinal, reticulospinal, and vestibulospinal tracts.
Figure 6.11 Descending Motor Pathways

(A) Lateral corticospinal tract

(B) Rubrospinal tract

(C) Anterior corticospinal tract

(D) Vestibulospinal tracts

(See also Table 6.3.)
**Autonomic Nervous System**

In contrast to the somatic motor pathways described in the preceding discussion, the autonomic nervous system generally controls more automatic and visceral bodily functions. Autonomic efferents are different anatomically from somatic efferents (Figure 6.12). In somatic efferents, anterior horn cells or cranial nerve motor nuclei project directly from the central nervous system to skeletal muscle (Figure 6.12A). In autonomic efferents, there is a peripheral synapse located in a ganglion interposed between the central nervous system and the effector gland or smooth muscle (see Figure 6.12B,C). There are sensory inputs to the autonomic nervous system both centrally and in the periphery. However, the autonomic nervous system itself consists of only efferent pathways and is therefore discussed here with other motor systems.

The autonomic nervous system has two main divisions (Figure 6.13). The sympathetic, or thoracolumbar, division arises from T1 to L2 or L3 spinal levels and is involved mainly in such “fight-or-flight” functions as increasing heart rate and blood pressure, bronchodilation, and increasing pupil size. The parasympathetic, or craniosacral, division, in contrast, arises from cranial nerve nuclei and from S2 through S4 and is involved in “rest and digest” functions, such as increasing gastric secretion and peristalsis, slowing the heart rate, and decreasing pupil size. The enteric nervous system, a third autonomic division, consists of neural plexuses lying within the walls of the gut that is involved in controlling peristalsis and gastrointestinal secretions.

**Preganglionic neurons** of the sympathetic division are located in the intermediolateral cell columns in lamina VII of spinal cord levels T1 to L2 or L3 (see Figures 6.4D, 6.12B, 6.13). There are two sets of sympathetic ganglia. The paired paravertebral ganglia form a chain called the sympathetic trunk (or sympathetic chain) running all the way from cervical to sacral levels on each side of the spinal cord. The sympathetic trunk allows sympathetic ganglia, which exit only at thoracolumbar levels, to reach other parts of the body as well. For example, sympathetic trunks are provided to the head and neck by the upper thoracic spinal cord (T1–T3) intermediolateral cell columns via sympathetic chain ganglia named the superior, middle (often absent), and inferior (stellate) cervical ganglia (see Figure 13.10). The other sympathetic ganglia are paired prevertebral ganglia, which are located in the cephalic plexuses surrounding the aorta and include the celiac ganglion, superior mesenteric ganglion, and inferior mesenteric ganglion. Axons of preganglionic sympathetic neurons thus have a fairly short distance to travel, while axons of postganglionic neurons travel a long distance to reach effector organs (see Figures 6.12B, 6.13). In contrast, parasympathetic preganglionic fibers must travel a long distance to reach the terminal ganglia located within or near the effector organs (see Figures 6.12C, 6.13). Parasympathetic preganglionic fibers arise from cranial nerve parasympathetic nuclei (see Figures 12.5, 12.6) and from the sacral parasympathetic nuclei located in the lateral gray matter of S2, S3, and S4, in a similar location to the intermediolateral column (see Figure 6.12C).

The sympathetic and parasympathetic nervous systems also differ in terms of their neurotransmitters (see Chapter 2; Figures 6.12, 6.13). Sympathetic postganglionic neurons release predominantly norepinephrine onto end organs. Parasympathetic postganglionic neurons release predominantly acetylcholine, activating muscarinic cholinergic receptors on end organs. Sympathetic neurotransmission in both sympathetic and parasympathetic ganglia is mediated by acetylcholine (nicotinic receptors) released by preganglionic neurons (see Figures 6.12, 6.13). Noradrenergic (α1, α2, β1, β2) and cholinergic (M1, M2, M3) receptor subtypes mediate different actions of these transmitters on end organs (see the References). In addition, various peptides and other substances (such as ATP and adenosine) are released at autonomic synapses. One notable exception to the norepinephrine/sympathetic, acetylcholine/parasympathetic rule for postganglionic neurotransmitters is the sweat glands, which are innervated by sympathetic postganglionic neurons that release acetylcholine (see Figure 6.13).

Sympathetic and parasympathetic outflow are controlled both directly and indirectly by higher centers, including the hypothalamus (see Chapter 17), brainstem nuclei such as the nucleus solitarius (see Chapter 12), the amygdala, and several regions of limbic cortex (see Chapter 18). Autonomic responses are also regulated by afferent sensory information, including sig-

![Figure 6.12 Somatic and Autonomic Efferents](image)

- (A) Somatic effector arising from an anterior horn cell.
- (B) Sympathetic efferents arising from the intermediolateral nucleus.
- (C) Parasympathetic efferent arising from sacral parasympathetic nuclei.

*(For the interested reader, this point of relatively minor clinical significance can be remembered by noting that botulinum toxin, a blocker of cholinergic transmission, has recently been shown to be an effective treatment for hyperhidrosis (excessive sweating) when injected locally into the skin of the axilla.*
Sympathetic and Parasympathetic Divisions of the Autonomic Nervous System

- **Sympathetic division**
  - **Dilator pupil**
  - **Constrictor pupil**
  - **Inhibits salivation and lacrimation**
  - **Stimulates salivation and lacrimation**
  - **Oculomotor nerve (CN III)**
  - **Facial nerve (CN VII)**

- **Parasympathetic division**
  - **Cutaneous (CN V)**
  - **Glossopharyngeal nerve (CN IX)**
  - **Vagus nerve (CN X)**
  - **Ciliary (CN V1)**

**Cervical**
- Superior cervical ganglion
- Inferior cervical (sternal) ganglion
- Vagus nerve (CN X)

**Thoracic**
- Sympathetic plexus
- Hilaris lymphatic duct
- Stimulates secretion by sweat glands
- Stimulation of adrenal medulla

**Lumbar**
- Sympathetic trunk
- Inferior mesenteric ganglion
- Stimulation of sympathetic blood vessels

**Sacroiliac**
- Stimulation of parasympathetic ganglia

**TABLE 6.4 Signs of Upper Motor Neuron and Lower Motor Neuron Lesions**

<table>
<thead>
<tr>
<th>Sign</th>
<th>Upper Motor Neuron Lesions</th>
<th>Lower Motor Neuron Lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weakness</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Atrophy</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Fasciculations</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Reflexes</td>
<td>Increased</td>
<td>Decreased</td>
</tr>
<tr>
<td>Tone</td>
<td>Increased</td>
<td>Decreased</td>
</tr>
</tbody>
</table>

*Note: Values marked with an asterisk (*) indicate significant changes.*
### TABLE 6.5 Terms Commonly Used to Describe Weakness

<table>
<thead>
<tr>
<th>TERM</th>
<th>DEFINITION</th>
<th>EXAMPLE</th>
<th>CLINICAL SYMPTOMS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DENOTING SEVERITY</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paresis</td>
<td>Weakness (partial paralysis)</td>
<td>Hemiparesis</td>
<td>Weakness of one side of body (face, arm, and leg)</td>
</tr>
<tr>
<td>-plegia</td>
<td>No movement</td>
<td>Hemi-plegia</td>
<td>No movement of one side of body (face, arm, and leg)</td>
</tr>
<tr>
<td>Paralysis</td>
<td>No movement</td>
<td>Leg paralysis</td>
<td>No movement of the leg</td>
</tr>
<tr>
<td>Flail</td>
<td>Imprecise term for weakness or no movement</td>
<td>Facial palsy</td>
<td>Weakness or paralysis of face muscles</td>
</tr>
<tr>
<td><strong>DENOTING LOCATION</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemi-</td>
<td>One side of body</td>
<td>Hemi-plegia</td>
<td>No movement of one side of body (face, arm, and leg)</td>
</tr>
<tr>
<td>Para-</td>
<td>Both legs</td>
<td>Paraparesis</td>
<td>Weakness of both legs</td>
</tr>
<tr>
<td>Mono-</td>
<td>One limb</td>
<td>Monoparesis</td>
<td>Weakness of one limb (arm or leg)</td>
</tr>
<tr>
<td>Di-</td>
<td>Both sides of body</td>
<td>Diplegia</td>
<td>Symmetrical facial weakness</td>
</tr>
<tr>
<td>Quadri- or tetra-</td>
<td>All four limbs</td>
<td>Quadriplegia (tetraplegia)</td>
<td>Paralysis of all four limbs</td>
</tr>
</tbody>
</table>

### KEY CLINICAL CONCEPT

**TERMS USED TO DESCRIBE WEAKNESS**

- Weakness is one of the most important functional consequences of both upper and lower motor neuron lesions. Various terms are used in clinical practice to describe both the severity and distribution of weakness (Table 6.5). We will discuss localization of these different patterns of weakness in the next section.

### KEY CLINICAL CONCEPT

**WEAKNESS PATTERNS AND LOCALIZATION**

- Weakness can be caused by lesions or dysfunction at any level in the motor system, including the association and limbic cortices involved in volitional or motivational control of movement, the upper motor neurons of the corticospinal tract anywhere from cortex to spinal cord, the lower motor neurons anywhere from anterior horn to peripheral nerve, the neuromuscular junction, the muscles, and the mechanical functions of joints and tendons. The process of localizing lesions, as outlined in the sections that follow, involves choosing the correct motor system level, side, and specific neuroanatomical structures affected. In the illustrations in this section, lesions are shown in red and deficits are shown in purple.

### REVIEW EXERCISE

Cover the right two columns in Table 6.4. For each sign, state whether it is present, increased, or decreased with upper motor neuron lesions and with lower motor neuron lesions.

---

![Figure 6.14A Pure Hemiparesis](image)

**Side of lesion:** Contralateral to weakness (above the pyramidal decussation).

**Common causes:** Lacunar infarct of the internal capsule (lenticulostriate branches of the middle cerebral arterial system) or anterior choroidal arterial system (see Figures 10.7, 10.9; Table 10.3) or of the pons (median perforating branches of the basilar arterial system; see Figures 14.20C; Table 14.8). Infarct of the cerebral peduncle (see Figure 14.20A) is less common.

**Associated features:** Upper motor neuron signs (Table 6.4) are usually present. Dysarthria (see KCC 12.9) is common, giving rise to the name **dysarthria-pure motor hemiparesis.** Ataxia of the affected side may also occasionally be seen because of involvement of the cerebellar pathways, giving rise to the name **ataxia-hemiparesis** (see Table 10.3; KCC 15.2).

2. With Associated Somatosensory, Oculomotor, Visual, or Higher Cortical Deficits (Figure 6.14B)

- **Locations ruled out:** Unlikely to be centered on the medulla, for the reasons listed in the previous section.

- **Locations ruled in:** Entire primary motor cortex, including face, arm, and leg representations of the precentral gyrus, or corticospinal and corticobulbar tract fibers above the medulla (e.g., thalamocortical bundle; see Table 10.3). The lesion can usually be further localized on the basis of other associated deficits.

**Side of lesion:** Contralateral to weakness (above the pyramidal decussation).

**Associated features allowing further localization:** In addition to somatosensory, oculomotor, visual, or higher cortical deficits such as aphasia or neglect, there may be dysarthria or ataxia. Upper motor neuron signs are usually present as well.

**Common causes:** Numerous, including infarct, hemorrhage, tumor, trauma, herniation, post-traumatic state, and so on.

**Unilateral Arm and Leg Weakness or Paraparesis** (Figure 6.14C)

- **Other names:** Hemiparesis or hemiparesis sparing the face; brachiofacial plegia or paresis.

- **Locations ruled out:** Unlikely to be cortical because the lesion would have to involve the entire motor strip, in which case sensory involvement is hard to avoid. Similarly, to be muscle or peripheral nerve because in the case of coincidental involvement of only half of the body would be required. Not the spinal cord or medulla because in that case the face would be spared.

- **Locations ruled in:** Corticospinal and corticobulbar tract fibers below the cortex and above the medulla; posterior limb of the internal capsule, basis pontis, or middle third of the cerebral peduncle.

---

![Figure 6.14B Hemiparesis with Additional Deficits](image)

**Side of lesion:** Motor cortex or medulla (above the pyramidal decussation): contralateral to weakness. Cerebral spinal cord (below the pyramidal decussation): ipsilateral to weakness.
**Figure 6.14C Hemiparesis Sparring the Face**

**Associated features allowing further localization:** Upper motor neuron signs are usually present. Cortical lesions sparing the face are often in a watershed distribution, and they affect proximal more than distal muscles ("weak in the beard" syndrome; see KCC 10.2). Cortical lesions may be associated with aphasia (see KCC 19.6) or hemiglossectomy (see KCC 19.9). In medial medullary lesions there may be loss of vibration and joint position sense on the same side as the weakness, and tongue weakness on the opposite side (Figure 14.20D; Table 14.7). In lesions extending to the lateral medulla, the lateral medullary syndrome may be present (see KCC 14.3; Table 14.7). In lesions of the spinal cord, the Brown-Séquard syndrome may be present (see KCC 7.4). High cervical lesions may involve the spinal trigeminal nucleus and tract (see Figure 12.7), causing decreased facial sensation.

**Common causes:** Hemispheric infarct (anterior cerebral-middle cerebral watershed), medial or combined medial and lateral medullary infarct, multiple sclerosis, lateral trauma, or compression of the cervical spinal cord.

**Unilateral Face and Arm Weakness or Paralysis** (Figure 6.14D)

**Other names:** Facial (facial) paresis or plegia.

**Locations ruled out:** Unlikely to be a muscle or peripheral nerve because in that case coincidental involvement of the face and arm would be required. Uncommon (but not impossible) in lesions at the internal capsule or because the corticobulbar and corticospinal tracts are fairly compact, resulting in leg involvement with most lesions.

**Locations ruled in:** Face and arm areas of the primary motor cortex, over the lateral frontal convexity.

**Side of lesion:** Contralesional to weakness (above the pyramidal decussation).

**Associated features allowing further localization:** Upper motor neuron signs and dysarthria are usually present. In dominant-hemisphere lesions, Broca’s aphasia is common (see KCC 19.6). In nondominant-hemisphere lesions, hemiglossectomy may occasionally be present (see KCC 19.9). Sensory loss can occur if the lesion extends into the parietal lobe (see KCC 7.3).

**Common causes:** Middle cerebral artery superior division infarct is the classic cause (see Figures 10.4, 10.5). Tumor, abscess, or other lesions may also occur in this location.

**Unilateral Arm Weakness or Paralysis** (Figure 6.14E)

**Other names:** Brachial monoparesis or monoplegia; there are specific names for different weakness patterns associated with peripheral nerve injuries (see Table 8.1, KCC 9.1).

**Figure 6.14D Unilateral Face and Arm Weakness**

**Figure 6.14E Brachial Monoparesis**

**Locations ruled out:** Unlikely anywhere along the corticospinal tract (internal capsule, brainstem, spinal cord), because in that case one the face and/or lower extremity would also be involved. Rare cases of lower cranial nerve tumors may initially affect one arm.

**Locations ruled in:** Arm area of the primary motor cortex, or peripheral nerves supplying the arm.

**Side of lesion:** Motor cortex; contralateral to weakness. Peripheral nerves ipsilateral to weakness.

**Associated features allowing further localization:**
- **Motor cortex lesions:** There may be associated upper motor neuron signs, cortical sensory loss, aphasia (see KCC 19.6), or subtle involvement of the face or leg. Occasionally none of these are present. The weakness pattern may be incompatible with a lesion of peripheral nerves (see Table 8.1, KCC 9.1). For example, marked weakness of all finger, hand, and wrist muscles with no sensory loss and normal proximal strength does not occur with peripheral nerve lesions.
- **Peripheral nerve lesions:** There may be associated lower motor neuron signs. Weakness and sensory loss may be compatible with a known pattern for a peripheral nerve lesion (see Table 8.1, KCC 9.1).

**Common causes:**
- **Motor cortex lesion:** Infarct of a small cortical branch of the middle cerebral artery, or a small tumor, abscess, or the like.
- **Peripheral nerve lesion:** Compression injury, diabetic neuropathy, and so on (see KCC 8.3, 9.1).

**Unilateral Leg Weakness or Paralysis** (Figure 6.14F)

**Other names:** Crural monoparesis or monoplegia; there are specific names for weakness patterns associated with various peripheral nerve or spinal cord lesions (see KCC 7.4, KCC 9.1; Table 8.1).

**Locations ruled out:** Unlikely to be in the corticospinal tract above the upper thoracic cord (internal capsule, brainstem, spinal cord), because in that case the face and/or upper extremity would usually also be involved. Rarely, cervical cord tumors can initially cause leg weakness only.

**Locations ruled in:** Leg area of the primary motor cortex along the medial surface of the frontal lobe, lateral corticospinal tract below TI in the spinal cord, or peripheral nerves supplying the leg.

**Side of lesion:** Motor cortex: contralateral to weakness. Spinal cord or peripheral nerves: ipsilateral to weakness.

**Associated features allowing further localization:**
- **Motor cortex lesions:** There may be associated upper motor neuron signs, cortical sensory loss, frontal lobe signs such as a grasp reflex, or subtle involvement of the arm or face. Occasionally none of these are present. The weakness pattern may be incompatible with a lesion of peripheral nerves—for example, diffuse weakness of all muscles in one leg.
Spinal cord lesions: There may be associated upper motor neuron signs, a Brown-Séquard syndrome (see KCC 7.4), a sensory level, or some subtle spasticity of the contralateral leg. Sphincter function may be involved (see KCC 7.5). The weakness pattern may be incompatible with a lesion of peripheral nerves (see Table 8.1; KCC 9.1).

Peripheral nerve lesions: There may be associated lower motor neuron signs. Weakness and sensory loss may be compatible with a known pattern for a peripheral nerve lesion (see Chapters 8 and 9).

Common causes:
- Motor cortex lesion: Infract in the anterior cerebral artery territory, or a small tumor, abscess, or the like.
- Peripheral nerve lesion: Compression injury, diabetic neuropathy, and so on.

Unilateral Facial Weakness or Paralysis (Figure 6.14G.H)
Other names: Bell’s palsy (peripheral nerve); isolated facial weakness.

Locations ruled out: Unlike with lesions below the rostral medulla.

Locations ruled in: Common: peripheral facial nerve (CN VII). Uncommon: lesions in the face area of the primary motor cortex or in the genu of the internal capsule (usually lesions in these locations cause arm and leg involvement as well); facial nucleus and exiting nerve fascicles in the pons or rostral lateral medulla.

Side of lesion: Facial nerve or nucleus (ipsilateral to weakness). Motor cortex or internal capsule contralateral to weakness.

Associated features allowing further localization:
- Facial nerve or nucleus lesion (lower motor neuron; see Figure 6.14C). The forehead and orbicularis oculi are not spared (see Figure 12.13, lesion B). With facial nerve lesions (e.g., Bell’s palsy), there may be hyperacusis, decreased taste, and pain behind the ear on the affected side (see KCC 12.3). In facial nucleus lesions, the forehead is usually intact, and there are usually deficits associated with damage to nearby nuclei and pathways, such as CN VI, CN VII, or the corticospinal tract (see Figures 12.11, 14.2C; Table 14.8). In rostral lateral medullary lesions, a lateral medullary syndrome will be present.
- Associated features include the forehead to be spared (upper motor neuron pattern) in facial weakness caused by medullary lesions.

Motor cortex or capsular gama lesions (upper motor neuron; Figure 6.14H): The forehead is relatively spared (see Figure 12.13, lesion A). Dyssynergia and unilateral tongue weakness are common. There may be subtle arm involvement. In cortical lesions, sensory loss or aphasia may be present.

Common causes: Facial nerve: Bell’s palsy, trauma, surgery. Motor cortex, capsular genu, pons, or medulla: infarct.

To summarize, only cases of isolated facial weakness of a lower motor neuron pattern, possibly with some hypesthesia, loss of taste, or retroauricular pain, can be localized with certainty to the peripheral facial nerve. The presence of sensory loss or any other cranial nerve or motor abnormalities requires evaluation for a central nervous system lesion.

Note that facial weakness may be difficult to detect in cases in which it occurs bilaterally, called facial diplegia, since the weakness is symmetrical. Causes include motor neuron disease (see KCC 6.7), bilateral peripheral nerve lesions (such as in Guillain-Barré syndrome or in bilateral Bell’s palsy), or bilateral white matter abnormalities caused by ischemia or demyelination (such as in pseudobulbar palsy).

Bilateral Arm Weakness or Paralysis (Figure 6.14J)
Other names: Paraplegia, quadriplegia.

Locations ruled out: Unlikely to be in the corticospinal tracts because in that case the face and/or legs would also be involved.

Locations ruled in: Medial fibers of both lateral corticospinal tracts (see Figure 6.13C); bilateral cervical spine ventral horn cells; peripheral nerve or muscle disorders affecting both arms.

Associated features allowing further localization: A central cord syndrome or anterior cord syndrome may be present (see KCC 7.4).


Bilateral Leg Weakness or Paralysis (Figure 6.14H)
Other names: Paraparesis or paraplegia.

Locations ruled out: Unlikely to be in the corticospinal tracts above the upper thoracic cord (ventral horn cells, spinal cervical cord) because in that case the face and/or upper extremities would also be involved. Rarely, cervical cord tumors can initially cause bilateral leg weakness without arm involvement.

Locations ruled in: Bilateral leg areas of the primary motor cortex along the medial surface of the frontal lobes; lateral corticospinal tracts below T1 in the spinal cord; cauda equina syndrome or other peripheral nerve or muscle disorders affecting both legs.

Associated features allowing further localization:
- Bilateral medial frontal lesions: Upper motor neuron signs may be present. There may also be frontal lobe dysfunction (see KCC 19.11), including confusion, apraxia, grasp reflexes, and incontinence.
- Spinal cord lesions: Upper motor neuron signs (see Table 6.4), spinbinder dysfunction, and autonomic dysfunction may be present.
A sensory level (see Figure 8.4) or loss of specific reflexes (see Tables 3.6, 3.7) may help determine the segmental level of the lesion.

**Bilateral peripheral nerve or muscle disorders:** Cauda equina syndrome is associated with sphincter and erectile dysfunction, sensory loss in lumbar or sacral dermatomes, and lower motor neuron signs (see KCC 8.4). Distal symmetrical polyneuropathies (see KCC 8.1) tend to preferentially affect distal muscles, and may have associated distal "glove-stocking" sensory loss and lower motor neuron signs. Neuromuscular disorders and myopathies often (but not always) affect proximal more than distal muscles.

**Common causes:** Bilateral medial frontal lesions: parasagittal meningioma (see KCC 5.8), bilateral anterior cerebral artery infarcts (see Figure 10.5), or cerebral palsy (bilateral periventricular leukomalacia). Spinal cord lesions: Numerous, including tumor, trauma, myelitis (see KCC 7.2; Figure 7.10).

**Bilateral peripheral nerve or muscle disorders:** Cauda equina syndrome: tumor, trauma, disc herniation. Other peripheral nerve or muscle disorders (see KCC 8.1, 8.2, 9.1): The lower extremities are often clinically affected before the arm in Guillain–Barré syndrome, Lambert–Eaton syndrome, numerous muscle disorders, and distal symmetrical polyneuropathies (caused by diabetes and other toxins, metabolic, congenital, and inflammatory conditions).

**Bilateral Arm and Leg Weakness or Paralysis** (Figure 6.14K)

**Other names:** Quadriparesis, quadriplegia, tetraparesis, tetraplegia.

**Locations ruled out:** Unlikely to be below the motor cortex and above the medulla because the face would then be involved. Unlikely to be in the spinal cord below C5 because the arms would then be partly spared.

**Locations ruled in:** Bilateral arm and leg areas of the motor cortex; bilateral lesions of the corticospinal tracts from the lower medulla to C5. Peripheral nerve motor neuron or muscle disorders severe enough to affect all four limbs usually also affect the face, although in some cases face involvement may be relatively mild.

**Associated features allowing further localization:**

- **Bilateral motor cortex lesions:** Cortical lesions sparing the face are often in a watershed distribution, and affect proximal more than distal muscles ("man in the barrel" syndrome; see KCC 10.2; Figure 10.10). Upper motor neuron signs are usually present, and there may be associated aphasia, neglect, or other cognitive disturbances (see Chapter 19).
- **Bilateral upper cervical cord lesions:** Upper motor neuron signs (see Table 6.4) are usually present. There may be a sensory level (see Figure 8.6), sphincter dysfunction (see KCC 7.5), or autonomic dysfunction (gastric paralytic, bladder atony, loss of erectile function, orthostatic hypotension). High cervical lesions may cause respiratory weakness and may involve the spinal trigeminal nucleus (see Figure 12.7), causing decreased facial sensation.
- **Lower medullary lesions:** Upper motor neuron signs are usually present. There may be occipital headache (see KCC 5.1), tongue weakness (Figure 14.20B; Table 14.7), sensory loss, bleeds (see KCC 14.3), respiratory weakness, autonomic dysfunction, sphincter dysfunction (see KCC 7.5), or abnormal eye movements.

**Peripheral nerve or muscle disorders:** Lower motor neuron signs may be present in nerve disorders.

**Common causes:**
- **Motor cortex lesions:** Bilateral watershed infarcts (anterior cerebral–middle cerebral watershed) (see KCC 10.2).
- **Upper cervical cord and lower medullary lesions:** Tumor, infarct, trauma, multiple sclerosis.

**Peripheral nerve or muscle disorders:** Numerous (see KCC 8.1, 8.2, 9.1).

**Generalized Weakness or Paralysis**

**Locations ruled out:** Small focal or unilateral lesions do not produce generalized weakness. Lesions of the lower medulla or spinal cord spare the face or upper extremities.

**Locations ruled in:** Bilateral lesions of the entire motor cortex or bilateral lesions of the corticospinal and corticobulbar tracts anywhere from the corona radiata to pons; diffuse disorders involving all lower motor neurons, peripheral axons, neuromuscular junctions, or muscles.

**Associated features allowing further localization:** Bilateral cerebral or corticospinal lesions may be associated with upper motor neuron signs. Lesions of the peripheral nerves may be associated with lower motor neuron signs. Sensory loss, eye movement abnormalities, pupillary abnormalities, autonomic disturbances, or impaired consciousness may be present, and these features help determine the location and nature of the lesion. Respiratory depression is common with severe generalized weakness.

**Common causes:** Global cerebral ataxia, pontine infarct or hemorrhage (locked-in syndrome, see KCC 14.1), advanced amyotrophic lateral sclerosis (see KCC 6.7), Guillain–Barré syndrome, myasthenia, botulism (see KCC 8.1), and numerous other diffuse neurologic infectious, inflammatory, traumatic, toxic, or metabolic disturbances.

**General Comment**

For patterns of weakness not described here, consider two or multiple lesions, unusual lesions, anatomical variants, or non-neurologic weakness as the cause. See also Chapters 8 and 9 for additional details about weakness caused by specific peripheral nerve lesions, and Chapters 12–14 for weakness of extracranial muscles, jaw, neck, or tongue or of other specific muscles innervated by the cranial nerves.

**68** Sometimes patients have no obvious weakness or upper motor neuron signs, yet clinical suspicion warrants additional probing for more subtle deficits. The following tests can help detect mild corticospinal damage. See Chapter 3 and neuroexam.com for a review of the basic motor exam.

**Pronator drift:** Patient holds arms extended, palms up, and closes eyes. Slight inward drifting rotation (permanence) of one forearm, or even a slight curling of the fingertips on one side, is abnormal (see neuroexam.com Video 51).

**Finger extensors:** Patient holds fingers extended and resists while examiner tries to flex them (see neuroexam.com Video 54). This is an excellent test because corticospinal damage generally spares flexors relative to extensors, and finger extensors are relatively weak muscles with large cortical representation.

**Fine movements:** Patient rapidly taps index finger and thumb together; taps each finger to the thumb in sequence; rapidly pronates and supinates the hand either by holding it up and "screwing in a lightbulb" or by alternately slipping the palm and dorsum of the hand against the
moves a coin from the palm to the fingers using one hand; taps the foot rapidly on the floor or bed (see neuroexam.com Videos 52, 53, 60, 63). The dominant hand or foot is normally only slightly faster at these tasks.

**Isolated finger movements:** Patient holds fingertips abducted and extended and then moves one finger at a time.

**Spastic catch:** Feel for a subtle "catch" on one side only when holding the patient's hand in a handshake position and then rapidly supinating the patient's forearm (see neuroexam.com Video 49).

**Subtle decreased nasolabial fold:** Observe patient's face carefully in different settings, including rest, spontaneous smiling (see neuroexam.com Video 68), and grimacing during exam, not just during voluntary smile.

**Careful gait testing:** Look for slight circumduction of one leg (the leg swings out in a circular arc with each step), or decreased arm swing. Also have the patient hop on each foot and walk on the toes (see neuroexam.com Videos 68, 69).

**Forced gait:** Patient walks on the outside of the feet. Observe the hands carefully for subtle dystonic posturing on one side.

**Silent plantar:** If a normal flexor plantar response is present on the other side, a silent plantar response may represent a subtle Babinski's sign.

**Quantitative testing:** Under special circumstances, quantitative testing of motor power and speed may be helpful.

### TABLE 6.6 Localization of Common Gait Disorders

<table>
<thead>
<tr>
<th>NAME</th>
<th>LOCALIZATION</th>
<th>DESCRIPTION OF GAIT ABNORMALITIES</th>
<th>COMMON CAUSES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spastic gait (see KCC 6.1)</td>
<td>Unilateral or bilateral corticospinal tracts</td>
<td>Unilateral or bilateral. Still-legged, circumduction, sometimes with scissors effect of the legs and toe-walking (from increased tone in calf muscles). Decreased arm swing, unsteady, falling toward side of greater spasticity.</td>
<td>Cortical, subcortical, or brainstem areas affecting upper motor neuron pathways; cerebellar palsy; degenerative conditions; multiple sclerosis; spinal cord lesions.</td>
</tr>
<tr>
<td>Ataxic gait (see KCC 15.2)</td>
<td>Cerebellar vermis or other midline cerebellar structures</td>
<td>Wide-based, unsteady, staggering side to side, and falling toward side of worse pathology. Subtle deficit can be detected with tandem (heel-to-toe), or &quot;drunk walk&quot; gait testing.</td>
<td>Toxins such as alcohol; tumors of cerebellar vermis; infarcts or ischemia of cerebellar pathways; cerebellar degeneration.</td>
</tr>
<tr>
<td>Vertiginous gait (see KCC 12.6)</td>
<td>Vestibular nuclei, vestibular nerve, or semicircular canals</td>
<td>Looks similar to atonic gait, wide based and unsteady. Patients sway and fall when attempting to stand with feet together and eyes closed (Romberg sign).</td>
<td>Tumors such as alcohol; infections or ischemia of vestibular nuclei; benign positional vertigo; Menière's disease.</td>
</tr>
<tr>
<td>Frontal gait (see KCC 5.7, 19.11)</td>
<td>Frontal lobes or subfrontal subcortical white matter</td>
<td>Slow, shuffling, narrow or wide based, &quot;magnetic&quot; (barely raising feet off floor), unsteady. Sometimes resembles Parkinsonism. Patients may perform cyclic movements on their back much better than they can walk, giving rise to the term &quot;gait apraxia&quot; in this condition.</td>
<td>Hydrocephalus; frontal lobe strokes; subarachnoid hemorrhage; bilateral anterior cerebral artery infarction; diffuse subcortical white matter disease.</td>
</tr>
<tr>
<td>Parkinsonian gait (see KCC 16.1, 16.2)</td>
<td>Substantia nigra or other regions of basal ganglia</td>
<td>Slow, shuffling, narrow based. Difficulty initiating walking. Often stooped forward, with decreased arm swing, and &quot;on block turning.&quot; Unsteady, with &quot;resumption,&quot; taking several rapid steps to regain balance when pushed backward.</td>
<td>Parkinson's disease; other parkinsonian syndromes, such as progressive supranuclear palsy; use of neuroleptic drugs.</td>
</tr>
</tbody>
</table>

### TABLE 6.6 (continued)

<table>
<thead>
<tr>
<th>NAME</th>
<th>LOCALIZATION</th>
<th>DESCRIPTION OF GAIT ABNORMALITIES</th>
<th>COMMON CAUSES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dykesmotic gait (see KCC 16.1, 16.3)</td>
<td>Subcortical nucleus, or other regions of basal ganglia</td>
<td>Unilateral or bilateral dislocation (dorsiflexing, plantarflexing, or flexing) movements occur during walking and may be accompanied by some unsteadiness.</td>
<td>Huntington's disease; infarct of subcortical nucleus or striatum; side effect of levodopa; other familial or drug-induced dyskinesia.</td>
</tr>
<tr>
<td>Tabetic gait (see KCC 7.4)</td>
<td>Posterior columns or sensory nerve fibers</td>
<td>High-stepping, foot-flapping gait, with particular difficulty walking in the dark or on uneven surfaces. Patients sway and fall in attempts to stand with feet together and eyes closed (Romberg sign).</td>
<td>Posterior cord syndrome; severe sensory neuropathy.</td>
</tr>
<tr>
<td>Paretic gait (see KCC 8.5, 9.1)</td>
<td>Nerve roots, peripheral nerves, neuramnacular junction, or muscles</td>
<td>Exact appearance depends on location of lesions. With proximal hip weakness there may be a waddling, Trendelenburg gait. Severe hip weakness may cause sudden knee buckling. Post drop can cause a high-stepping, slapping gait, with frequent tripping.</td>
<td>Numerous peripheral nerve and muscle disorders.</td>
</tr>
<tr>
<td>Painful (antalgic) gait</td>
<td>Peripheral nerve or orthopedic injury</td>
<td>Pain may be obvious based on patient's report or facial expression. Tends to avoid putting pressure on affected limb.</td>
<td>Hemiated disc; peripheral neuropathy; muscle strain; contusions; fractures.</td>
</tr>
<tr>
<td>Orthopedic gait disorder</td>
<td>Bones, joints, tendons, ligaments, and muscles</td>
<td>Depends on nature and location of the disorder. Peripheral nerve injury or spinal cord-related deficits may be present as well.</td>
<td>Arthritis; fractures; dislocations; contractures; soft tissue injuries.</td>
</tr>
<tr>
<td>Functional gait disorder</td>
<td>Psychologically based</td>
<td>Can be hard to diagnose. Sometimes patients say they have poor balance, yet spontaneously perform highly destabilizing walking movements while walking, without ever falling.</td>
<td>Conversion disorder; factitious disorder.</td>
</tr>
</tbody>
</table>
plagues of demyelination and inflammatory response can appear and disappear in multiple locations in the central nervous system over time, eventually forming sclerotic glial scars. Demyelination causes slowed conduction velocity, dispersion, or loss of coherence of action potentials, and ultimately conduction block. Because dispersion increases with temperature, some patients have worse symptoms when they are warm. In addition to demyelination, recent studies have shown that some axons may be destroyed as well in multiple sclerosis plaques.

Prevalence is about 0.1% in the United States, with a higher worldwide prevalence in whites from northern climates, and 1.2% females-to-male ratio. Lifetime risk of developing MS is 3% to 5% if a first-degree relative is affected. Peak age of onset is 20 to 40 years. Onset before 10 or after 60 years is rare but not unheard of.

The classic clinical definition of multiple sclerosis is two or more deficits separated in neuroanatomical space and time. In practice, the diagnosis is based on the presence of typical clinical features, together with MRI evidence of white matter lesions, slowed conduction velocity on evoked potentials, and the presence of oligodendral bands in cerebrospinal fluid obtained by lumbar puncture (see KCC 5.10). Oligodendral bands are abnormal discrete bands seen on CSF gel electrophoresis. They result from the synthesis of large amounts of relatively homogeneous myelin basic protein by individual plasma cells in the cerebrospinal fluid (CSF). Oligodendral bands are present in over 85% of patients with clinically definite multiple sclerosis, but they can be seen in about 8% of patients with other disorders as well. CSF with more than 50 white blood cells or with oligoclonal bands is unusual for multiple sclerosis. MRI findings suggestive of multiple sclerosis include multiple 12-brain abnormalities, representing demyelinating plaques located in the white matter. The plaques tend to extend into the white matter from periventricular locations (resulting in "Dawson’s fingers"), and they occur in both supratentorial and infratentorial structures. Acute plaques may expand with gadolinium. The clinical features described here need not all be present to make the diagnosis of multiple sclerosis. In unusual or atypical cases of suspected multiple sclerosis it is essential to test for other inflammatory, infectious, neoplastic, hereditary, and degenerative conditions that can have similar clinical features.

Multiple sclerosis can affect numerous systems (Table 6.7). When patients first present with obvious symptoms, more subtle previous episodes can often be elicited in retrospect. About 50% of patients have a single episode of optic neuritis (see KCC 11.4) or transverse myelitis (see Table 7.4) subsequently develop multiple sclerosis. The course of multiple sclerosis can be relapsing-remitting, progressive, or a mixture of these. Median survival from time of onset is 25 to 35 years and is continuing to increase with modern interventions. Current therapies include immunomodulators such as high-dose steroids, azathioprine, cyclophosphamide, interferon beta, and copolymer-1, which are not curative but can speed recovery from exacerbations and slightly delay progression. In addition, multidisciplinary treatment of symptoms such as spasticity, pain, impaired bowel, bladder, and sexual function, and psychologic manifestations can improve quality of life and prolong survival.

Several relatively uncommon disorders can selectively affect upper motor neurons, lower motor neurons, or both, producing motor deficits without sensory abnormalities or other findings. Most of these disorders are degenerative conditions referred to collectively as motor neuron disease. The classic example of motor neuron disease is amyotrophic lateral sclerosis, also known as ALS or Lou Gehrig’s disease. ALS is characterized by gradually progressive degeneration of both upper motor neurons and lower motor neurons, leading eventually to respiratory failure and death. ALS has an incidence of 2 to 3 per 100,000 and is slightly more common in men, by a factor of about 1.5. Usual age of onset is in the 50s and 60s, although early-onset cases can be seen. Most cases occur sporadically, but there are also inherited forms that can have autosomal dominant, recessive, or X-linked transmission. Initial symptoms include muscle weakness, which often begins in the hands and feet and then spreads to involve adjacent muscle groups. Painful muscle cramping and fasciculations are also common. Some patients present initially with predominantly bulbar complaints, such as dysarthria and dysphagia, or with respiratory symptoms. On neurologic examination, patients with ALS have weakness, with upper motor neuron findings such as increased tone and brisk reflexes, as well as lower motor neuron findings such as atrophy and fasciculations (see Table 6.4). Sometimes a brech appears in the tongue muscles. A head drop is often present because of weakness of the neck muscles. Some patients have uncontrollable bouts of laughter or crying without the usual accompanying emotions, a finding known as pseudobulbar affect (see KCC 12.8). Sensory exam and mental status are typically normal. The extraocular muscles tend to be relatively spared. As the disease progresses, some patients can communicate only through eye movements. Electromyography (see KCC 9.2) shows evidence of muscle denervation in two or more extremities.

Unfortunately, there is no cure for this tragic disorder at present, and median survival from onset is 23 to 52 months. Riluzole, a blocker of glutamate release, has been shown to prolong survival by seven to nine months, and experimental trials with other agents are under way. Education of the patient and family about this disorder, and implementation of a comprehensive program of medical and psychosocial services, are imperative.

In evaluating patients with suspected ALS, it is important to test for other disorders that can rarely cause similar clinical findings. These include lead toxicity, dysproteinemia, thyroid dysfunction, vitamin B12 deficiency, vasculitis, paraneoplastic syndromes (see KCC 5.8), hessamardine A deficiency, multifocal motor neuropathy with conduction block, and other disorders. Cervical spine compression can occasionally produce a mixture of upper motor neuron signs (corticospinal compression) and lower motor neuron signs in the upper extremities (causing root compression). A cervical MRI is helpful to rule this out.

Some motor neuron disorders affect primarily upper motor neurons or primarily lower motor neurons. Primary lateral sclerosis is an example of an upper motor neuron disease, while spinocerebellar atrophy affects lower motor neurons. Spinocerebellar atrophy occurs in infancy in some forms of spinal muscular atrophy, known as Werdnig-Hoffmann disease and usually leads to death by the second year of life. Much progress has been made recently in understanding the molecular basis of motor neuron disorders, offering some hope that we will have effective treatments for these devastating disorders in the near future.
CLINICAL CASES

CASE 6.1 SUDDEN ONSET OF RIGHT HAND WEAKNESS

CHIEF COMPLAINT
A 64-year-old man developed right hand weakness following cardiac arrest.

HISTORY
The patient had a history of hypertension and cigarette use but was otherwise healthy until the day of admission, when he suddenly collapsed in church. Family members at the scene administered immediate CPR, and when the ambulance arrived the patient received electrical defibrillation and promptly regained a normal cardiac rhythm. He was admitted to the cardiac intensive care unit and was found to have episodes of rapid atrial fibrillation. Several days after admission he was noted to have weakness of the right hand, and a neurology consult was requested.

PHYSICAL EXAMINATION
Vital signs: T = 98°F, P = 100, BP = 120/80.
Neck: Supple with no bruits.
Lungs: Clear.
Heart: Irregular rhythm, with a soft systolic murmur.
Abdomen: Normal bowel sounds; soft, nontender.
Extremities: Normal.
Neurologic exam:
MENTAL STATUS: Alert and oriented x 3. Language fluent, with intact naming, repetition, and reading. Able to recall 3/5 objects after 5 minutes.

CRANIAL NERVES: Normal, including no facial weakness.
MOTOR: Power 5/5 throughout, except for right hand and wrist. Right wrist flexion, extension, and hand grasp 3/5. Right finger extension, abduction, adduction, and thumb opposition 0/5.
REFLEXES: 2`

COORDINATION AND GAIT: Not tested.
SENSORY: Intact light touch, pinprick, joint position, and vibration sense. No extinction on double simultaneous stimulation.

LOCALIZATION AND DIFFERENTIAL DIAGNOSIS
1. On the basis of the symptoms and signs shown in bold above, where is the lesion?
2. Given the relatively acute onset of the deficits and the presence of atrial fibrillation, what is the most likely diagnosis? What are some other possibilities?

Discussion
1. The key symptom and sign in this case is:
   • Isolated right-sided weakness of wrist flexion and extension, finger flexion, extension, abduction, and adduction, and thumb opposition
2. Given the presence of cardiac disease including atrial fibrillation, and the relatively acute onset of deficits, the most likely diagnosis is an embolic infarct (see KCC 10.4). An infarct of the left precentral gyrus would be caused by occlusion of a small cortical branch of the left middle cerebral artery, superior division (see Figures 10.5, 10.6). Some other, much less likely causes of a lesion in this cortex in this setting include a small cortical hemorrhage, brain abscess, or tumor.

CASE 6.2 SUDDEN ONSET OF LEFT FOOT WEAKNESS

CHIEF COMPLAINT
An 81-year-old woman presented to the emergency room because of left foot weakness.

HISTORY
The patient was previously healthy except for a history of hypertension and diabetes. On the morning of admission, as she got out of bed she noticed difficulty when she first put her left foot on the floor. As she tried to walk, she felt that she was dragging her left foot. Nevertheless, she continued her usual morning activities, using a chair for support. Later in the morning, when the gait difficulty persisted, she called her children, who brought her to the emergency room. She had no other complaints except for a mild right frontal headache.

PHYSICAL EXAMINATION
Vital signs: Not recorded on admission.
Neck: Supple with no bruits.
Lungs: Clear.
Heart: Regular rate, with soft systolic murmur.
Abdomen: Benign, with normal bowel sounds
EXTREMES: Normal.
Neurologic exam:
MENTAL STATUS: Alert and oriented x 3. Speech fluent, with intact naming and comprehension.

CRANIAL NERVES: Normal, including no facial weakness.
MOTOR: No pronator drift. Normal tone. Power 5/5 throughout, except for left foot and leg; Left iliofemoral and hamstrings 4/5, left ankle dorsiflexion and extensor hallucis longus 4/5.
REFLEXES: 2`

COORDINATION AND GAIT: Normal except for slowing of heel-to-toe walking with left leg.
Gait: Not tested.
Sensory: Intact light touch, temperature, joint position, and vibration sense.

LOCALIZATION AND DIFFERENTIAL DIAGNOSIS
1. On the basis of the symptoms and signs shown in bold above, where is the lesion?
2. Given the sudden onset of symptoms in an elderly patient with diabetes and hypertension, what is the most likely diagnosis? What are some other possibilities?

Discussion
1. The key symptoms and signs in this case are:
   • Isolated left-sided weakness and slowness of the iliofemoral, hamstrings, ankle dorsiflexors, and extensor hallucis longus
   • Right frontal headache
2. Isolated leg weakness can be caused by a lesion in the primary motor cortex, spinal cord, or peripheral nerves (see KCC 6.3; Figure 16.4E). There are no upper or lower motor neuron signs to help localization. However, weakness in both a femoral and sciatic nerve distribution with no sensory loss (see Table 8.1; KCC 8.2, 9.1) makes a peripheral nerve or spinal cord lesion less likely. In addition, the right frontal headache suggests a cranial localization (see KCC 5.1).
The most likely clinical localization is right precentral gyrus, primary motor cortex, leg area.

2. Given the presence of diabetes and hypertension and the relatively acute onset of deficits, the most likely diagnosis is an embolic infarct (see KCC 10.4). An infarct of the right precentral gyrus leg area would be caused by occlusion of a cortical branch of the right anterior cerebral artery (see Figure 10.5). Some other, less likely causes of a cortical lesion in this setting include a small hemorrhage, brain abscess, or tumor. A spinal cord lesion or motor neuron disease is unlikely but still possible.

**Clinical Course and Neuroimaging**

A head MRI (Figure 6.16) showed increased T2 signal representing an infarct in right primary motor cortex leg area. The strength in the patient's right foot gradually improved to the 4+/5 to 5/5 range by the time she was discharged home. A variety of tests were done (see KCC 10.4) but showed no obvious cause for the stroke. She was therefore entered into an experimental trial for strokes of unknown cause comparing treatment with aspirin to Cocomadil.

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**CASE 6.1SUDDEN ONSET OF RIGHT HAND WEAKNESS**

Figure 6.15 Infarct in Left Precentral Gyrus Hand Area (A-C) Head CT with sequentially higher horizontal slices. The infarct in the left precentral gyrus hand area is visible in (B) and (C). (Compare to the normal CT in the Neuroradiological Atlas, Figure 4.12.)
CASE 6.2 SUDDEN ONSET OF LEFT FOOT WEAKNESS

Figure 6.16 Infarct in Right Precentral Gyrus Leg Area 
(A–C) Sequentially higher axial (horizontal) T2-weighted MRI images. The infarct is in the right precentral gyrus leg area is visible in (B) and (C). (Compare to normal MRIs in Neuroradiological Atlas Figures 4.68 and 4.14.)

(C) Infarct is in precentral gyrus

CASE 6.3 SUDDEN ONSET OF RIGHT FACE WEAKNESS

CHIEF COMPLAINT
A 62-year-old man came to the emergency room with right facial weakness.

HISTORY
The patient awoke in the morning with a "funny feeling" in his right eye and thought he might have conjunctivitis. He looked in the mirror and noticed his right eyebrow drooping. He also thought his speech sounded slightly slurred, so he called his wife to confirm this. She told him to go to the emergency room, and he complied. Past medical history was notable for diabetes.

PHYSICAL EXAMINATION
Head: Supple with no bruits.
Lungs: Clear.
Heart: Regular rate and rhythm, with no murmurs, gallops, or rubs.
Abdomen: Normal bowel sounds; soft, nontender.
Extremities: Normal.

Neurological exam:
Cranial nerves: Pupils 4 mm, constricting to 3 mm with light bilaterally. Visual fields full. Extraocular movements intact. Normal opticokinetic nystagmus bilaterally. Intact pinprick sense, light touch sense, and graphesthesia in V1, V2, and V3. Intact corneal reflexes bilaterally. Right eyebrow slightly depressed. Right lower face showed delay of movements with smile. Taste on both sides of tongue intact in response to mustard or sweet preserves on a cotton swab. Hearing normal to finger rub.
Normal gag and normal palate elevation. Speech sounded normal. (The patient felt it was still mildly slurred, but better than earlier in the day). Normal sternomastoid strength. Tongue midline.
Motor: No pronator drift. However, with pronation testing there was trace curling of the right fingers (see KCC 6.4) with palms upward and eyes
CASE 6.3 (CONTINUED)

Closed that was not seen on the left side. Normal sensation. Normal finger and toe taps. Power 5/5 throughout.

REFLEXES:


SENSORY: Intact light touch, pinprick, and vibration sense and graphesthesia.

LOCALIZATION AND DIFFERENTIAL DIAGNOSIS

1. On the basis of the symptoms and signs shown in bold above, what is the lesion?
2. What is the most likely diagnosis? What are some other possibilities?

Discussion

1. The key symptoms and signs in this case are:
   - Right eyebrow slightly depressed; right lower face showed delayed movement with smile; speech mildly slurred
   - Trace curling of the right fingertips

Unilateral facial weakness without other significant deficits is most commonly caused by peripheral lesions of the facial nerve (see KCC 6.3, Figure 6.14G). However, it can occasionally be seen in cortical lesions or lesions of the internal capsule genu (see Figures 6.10A, 6.14F). Our patient's main problem was right facial weakness, but he also had other subtle neurological findings. The presence of mild dysarthria and finger curling suggests involvement of the corticobulbar and corticospinal tracts as well, respectively. Thus, the lesion is most likely located in the left motor cortex face area (see Figure 6.14H), with slight impingement on adjacent structures or in the left capsular genu. One unusual feature of this case is the slight involvement of the eyebrow, which is typically spared in upper motor neuron-type facial weakness.

2. Given the presence of diabetes and the relatively acute onset of deficits, the most likely diagnosis is an embolic infarct (see KCC 10.4). An infarct of the left precentral gyrus face area would be caused by occlusion of a cortical branch of the left middle cerebral artery (see Figure 10.6). Some other less likely causes of a cortical lesion in this setting include a small hemorrhage, brain abscess, or tumor.

Clinical Course and Neuroimaging

A conventional MRI done in the emergency room was normal. However, a diffusion-weighted MRI (see Chapter 4) done at the same time revealed several small areas of decreased diffusion (increased signal) in the left precentral gyrus. The "omega" (or inverted omega) in the central sulcus, a landmark usually corresponding to the hand area on axial MRI sections (see Figures 4.11C, 4.13F), can be identified in Figure 6.17B. Note that the diffusion changes are lateral to this, suggesting that they are in the face motor cortex. Within a few hours of his arrival in the emergency room, the trace curling of this patient's right fingertips on pronation testing disappeared. He was admitted to the hospital, and by the next day the patient and his wife no longer felt that his speech was slurred. However, his right face remained mildly weak. Investigations for an embolic source (see KCC 10.4) were negative. He was discharged home on aspirin to reduce his risk of future strokes.

CASE 6.4 PURE MOTOR HEMIPARESIS

CHIEF COMPLAINT

A 31-year-old woman developed left face, arm, and leg weakness.

HISTORY

Three days prior to admission, while on a business trip, the patient noticed some difficulty walking, veering slightly to the left and bumping into corners and walls on her left side. The next day she had some stuttering of her speech, which subsequently resolved. She returned home, and on the morning of admission she noticed that her left arm and hand were somewhat weak and clumsy. She did not have any sensory symptoms, visual problems, headaches, or changes in bowel or bladder function. Her symptoms worsened in a warm meeting room and improved with a cold shower.

PHYSICAL EXAMINATION


Neck: Supple.

Lungs: Clear.

Heart: Regular rate with no murmurs.

Abdomen: Normal bowel sounds; soft, nontender.

Extremities: Normal.

Neurologic exam:

Mental status: Alert and oriented x 3. Recalled 2/3 words after 5 minutes. Speech fluent, with intact comprehension and repetition. No neglect on drawing a clock face or on line cancellation tasks.

COORDINATION: Normal on finger-to-nose testing bilaterally.

Gait: Tends to veer to the left, especially with eyes closed. Decreased arm swing on the left. Unsteady tandem gait, falling to the left.

Sensory: Intact light touch, pinprick, temperature, vibration, and joint position sense.

LOCALIZATION AND DIFFERENTIAL DIAGNOSIS

1. On the basis of the symptoms and signs shown in bold above, what is the lesion?
2. What is the most likely diagnosis? What are some other possibilities?

Discussion

1. The key symptoms and signs in this case are:
   - Left face, arm, and leg weakness, clumsiness, slowness, increased tone, hyperreflexia, and equivocal Babinski's sign
   - Dysarthria
   - Unsteady gait, falling to the left, with decreased left arm swing

This patient has pure motor hemiparesis, with left face, arm, and leg upper motor neuron-type weakness and no sensory or cortical deficits such as neglect, aphasia, or other cognitive or visual disorders. Pure motor hemiparesis can be caused by lesions of the corticobulbar and corticospinal tracts, most commonly in the internal capsule or pons (see KCC 6.5, Figure 6.14A). Dysarthria can be caused by lesions in numerous locations (see KCC 12.8) but often accompanies pure motor hemiparesis, giving rise to the term "dysarthria-hemiparesis." Similarly, the unsteady gait could be caused by numerous lesions (see KCC 6.5) but is most easily explained by the patient's apastic left hemiparesis.

The most likely clinical localization is right corticobulbar and corticospinal tracts in the posterior limb of the internal capsule or ventral pons.

2. Pure motor hemiparesis is usually caused by lacunar infarction (see Table 10.3) of the contralateral internal capsule or pons. However, given that the patient is a woman in her 30s with no vascular risk factors whose symptoms worsen...
with warm temperature, the possibility that this is the first episode of multiple sclerosis should be seriously considered (see KCC 6.6). Other, less likely possibilities include a small tumor, abscess, or hemorrhage in the right internal capsule, cerebral peduncle, or ventral pons.

**Clinical Course and Neuroimaging**

A head MRI (Figure 6.18) showed increased T2 signal in the posterior limb of the right internal capsule. Note that there was enhancement with gadolinium, signifying breakdown of the blood-brain barrier. This is often seen with inflammatory lesions such as demyelinating plaques (see KCC 6.6), but it can also be seen a few days after infarcts. There were a few additional areas of increased T2 signal adjacent to the left frontal horn, suggesting possible prior episodes of demyelination.

An extensive workup for thromboembolic, demyelinating, inflammatory, infectious, and neoplastic disorders was done. All results were negative, except for two oligoclonal bands in the patient’s cerebrospinal fluid (see KCC 6.6). Her left-sided weakness was improving by the time of discharge, 1 week after admission. Fortunately, she continued to improve and had no further problems over the following year. At a follow-up appointment 15 months after admission, her neurologic exam was entirely normal except for slightly slow rapid alternating movements with the left hand, and 3° reflexes on the left side compared to 2° on the right. Her diagnosis remained uncertain, and she was subsequently followed periodically for the possible development of recurrent neurological signs.

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**CASE 6.3 SUDDEN ONSET OF RIGHT FACE WEAKNESS**

Figure 6.17: Infarct in Left Precentral Gyrus Face Area

**Diffusion-weighted MRI with (a) and (b) sequentially higher horizontal slices.** The infarct is visible in left precentral gyrus face area, just lateral to omega-shaped bend in central sulcus where the hand area is usually located.

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**CASE 6.5 PURE MOTOR HEMIPARESIS II**

**CHIEF COMPLAINT**

A 74-year-old woman developed right face, arm, and leg weakness.

**HISTORY**

The patient was residing in a rehabilitation facility while recovering from an infection. She was doing well until one morning, when she suddenly developed slurred speech and right-sided weakness. An emergency neurology consultation was called. Medical history was notable for hypertension, coronary artery disease, and recent onset of atrial fibrillation.

**PHYSICAL EXAMINATION**

Vitals: T = 99.3°F, P = 84, BP = 110/70, R = 18.

- **Neck:** No bruits.
- **Lungs:** Clear.
- **Heart:** Regular rate with no murmurs.
- **Abdomen:** Normal bowel sounds, soft.

**Neurologic exam:**

- **MINIMAL STATUS:** Alert and oriented, x 3. Intact comprehension, repetition, and reading. Intact calculations.
- **CRANIAL NERVES:** Pupils equal round and reactive to light. Visual fields full. Extraocular movements intact. Corneal reflex present bilaterally. Decreased right nasolabial fold. Weak movements of the right face, but with only mild forehead involvement.

Gag reflex present, but with decreased palate movement on the right. Speech slurred and dysarthric. Normal sternomastoid strength. Rightward tongue deviation.

**MOTOR:** Tone flaccid on right side, normal on left. Marked right hemiparesis, with power 2/5 in right deltoid, 0/5 in right triceps, hirps, and hand muscles. Power 2/5 in right iliopsoas and quadriceps, and 0/5 in right foot.

**REFLEXES:**

- **ANTERIOR:** Anterior horn: 2° thickness, 2° motor, 2° sensory. 1° motor; 3° sensation.
- **POSTERIOR:** Posterior horn: 2° thickness, 2° motor, 2° sensory. 1° motor; 3° sensation.

**COORDINATION:** Normal on the left; too weak to test on the right.

**GAIT:** Unable to stand.

**SPEECH:** Intact light touch, pinprick, and joint position sense. No extinction.

**LOCALIZATION AND DIFFERENTIAL DIAGNOSIS**

1. On the basis of the symptoms and signs shown in bold above, where is the lesion?
2. What is the most likely diagnosis? What are some other possibilities?
Discussion

1. The key symptoms and signs in this case are:
   • Right face, arm, and leg weakness, hyperreflexia, and Babinski’s sign
   • Dysarthria, decreased right palatal movement, rightward tongue deviation

Like the patient in the previous case, this patient has pure motor hemiparesis with dysarthria (dysarthria-hemiparesis). The reflexes are decreased on the left side, probably from a chronic neuropathy (see KCC 8.1), and the reflexes on the right are relatively increased, confirming that this is an upper motor neuron lesion. Again, there are no sensory or cortical deficits such as neglect, aphasia, or other cognitive or visual disorders. Pure motor hemiparesis can be caused by lesions of the contralateral corticobulbar and corticospinal tracts, most commonly in the internal capsule or pons (see KCC 6.3; Figure 6.14A). Control of right CN IX and X (right palatal movement) and right CN XII (rightward tongue deviation) have been affected as well, also probably because of a contralateral corticobulbar tract lesion.

The most likely clinical localization is left corticobulbar and corticospinal tracts in the posterior limb of the internal capsule or ventral pons.

2. Pure motor hemiparesis is usually caused by lacunar infarction (see Table 10.3) of the contralateral internal capsule or pons. This patient has multiple vascular risk factors, and lacunar infarction from small-vessel disease (see KCC 10.4) is the most likely diagnosis. Given the history of atrial fibrillation, an embolus to a small perforating vessel of the left internal capsule or pons should be considered as well.

Clinical Course and Neuroimaging

The patient was transferred to a nearby hospital and started on anticoagulation therapy because of her history of atrial fibrillation. An MRI scan (Figure 6.19) showed a large area in the left ventral pons consistent with lacunar infarction (see also Figure 14.20B). A magnetic resonance angiogram (see Chapter 4) showed no significant narrowing of the circle of Willis vessels. The patient’s hemiparesis had improved slightly by the time of discharge, with power in the right arm and leg 5/5 proximally and 0/5 distally. Over the next year she had continued problems with dysarthria and swallowing difficulties, ultimately requiring a feeding tube for nutrition.

CASE 6.4 PURE MOTOR HEMIPARESIS I

Figure 6.18 Lesion in Posterior Limb of Right Internal Capsule. MRI of the brain. (A) Axial (horizontal) proton density-weighted section; (B) Coronal T1-weighted section after intravenous administration of gadolinium contrast.

- Anterior limit of internal capsule
- Head of caudate
- Putamen
- Globus pallidus
- Posterior limb of internal capsule
- Thalamus

(B) Thalamus
- Cerebral peduncle
- Putamen
CASE 6.6 PROGRESSIVE WEAKNESS, MUSCLE TWITCHING, AND CRAMPS

CHIEF COMPLAINT
A 52-year-old right-handed man referred to a neurologist for evaluation of weakness and difficulty walking.

HISTORY
The patient first noticed gait difficulty 6 months prior to the appointment. He felt "off balance" and over the next 2 months developed difficulty raising his feet off the floor while seated in a chair. A few months later his leg weakness had become worse, making it difficult to walk downstairs. In addition, his arms and hands had become weak, making it difficult for him to carry out his work as a carpenter. He also noticed constant twitching of his arm and leg muscles and painful cramps in his legs. He did not complain of diplopia, dysarthria, or dysphagia. There was no history of trauma or neck pain, and no history of toxin exposure. Family history was negative. Initial evaluation by his primary care physician included an MRI of the cervical spine, which was normal.

PHYSICAL EXAMINATION
Vitals: T: 98.5; P: 96, BP: 120/70, R: 18.
Neck: No bruits.
Lungs: Clear.
Heart: Regular rate with no murmurs.
Abdomen: Normal.
Extremities: Normal.
Neurologic exam:
MENTAL STATUS: Alert and oriented x 3. Intact naming, comprehension, and repetition.

MOTOR: Increased tone in bilateral lower extremities. Nearly continuous fasciculations in all four extremities. Atrophy present in the left hand interosseous muscles and bilateral foot intrinsic muscles. Weakness present bilaterally (see the table below), affecting the legs more than the arms, and the right side slightly more than the left.
Gait: Required assistance to walk. Paraparetic and spastic gait.
Sensory: Intact light touch, pinprick, vibration, and joint position sense. No extinction.

LOCALIZATION AND DIFFERENTIAL DIAGNOSIS
1. Which of the symptoms and signs shown in bold above are upper motor neuron signs? Which are lower motor neuron signs (see Table 6.4)? Could these findings be caused by cervical cord compression?
2. What is the most likely diagnosis? What are some other possibilities?

Results of Strength Testing

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<td>Biceps</td>
<td>Triceps</td>
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<tr>
<td>Extensors</td>
<td>Flexors</td>
<td>Extensors</td>
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<td>4/5</td>
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<table>
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<th>Leg</th>
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<td>R</td>
<td>5/5</td>
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<tr>
<td>L</td>
<td>5/5</td>
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</tbody>
</table>

Discussion
1. As Table 6.4 indicates, weakness is both an upper motor neuron and a lower motor neuron sign. Fasciculations and atrophy are lower motor neuron signs. Increased tone, spastic gait, and hyperreflexia including Babinski's sign, Hoffmann's sign, and jaw jerk reflex are upper motor neuron signs.

Cervical cord compression can cause upper motor neuron findings in the arms and legs, as well as lower motor neuron findings in the arms due to local nerve root compression. In this patient, however, lower motor neuron findings of fasciculations and atrophy were present in the lower extremities as well. In addition, a jaw jerk reflex was present, which is a sign of hyperreflexia produced by upper motor neuron dysfunction in the corticospinal pathways well above the level of the cervical cord. Thus, this patient's findings result from diffuse upper and lower motor neuron dysfunction extending from the brain to the lumbosacral spinal cord.

2. Focal weakness progressing to become more diffuse with upper and lower motor neuron signs, muscle cramping, and fasciculations with no sensory deficits form the classic presentation of amyotrophic lateral sclerosis (see KCC 6.7). Also possible, but far less likely, are paraneoplastic motor neuron disease, hexosaminidase deficiency, lead toxicity, or a variety of other disorders listed in KCC 6.7.
Clinical Course

The diagnosis of probable ALS and its implications were discussed at length with the patient and his family. He decided to try treatment with riluzole and was enrolled in a comprehensive rehabilitation program. Additional testing included an EMG (see KCC 9.2), which showed evidence of denervation and reinnervation in all four extremities, compatible with the diagnosis of ALS. Other tests included serum protein electrophoresis, serum β2-microglobulin, and complete blood count, all of which were normal.

The patient was followed over the following months as his symptoms worsened. Within 1 year after initial symptoms he was wheelchair bound because of increasing weakness. By approximately 2 years into the illness, and his last follow-up appointment, he had developed profound dysarthria, dysphagia, and tongue atrophy with fasciculations, and 0.5 to 4/5 strength in his extremities. He continued to live at home with family support and hospice care, and he died a few weeks later of respiratory failure.

Additional Cases

Related cases can be found in other chapters for the following topics: weakness caused by corticospinal and corticobulbar dysfunction (Cases 3.1–3.4, 7.3, 7.4, 10.1, 10.4, 10.5, 10.7, 10.9, 10.11, 10.12, 12.8, 13.7, 14.1–14.3, 14.5, 14.6, 18.3). Other relevant cases can be found using the Case index.

Brief Anatomical Study Guide

1. Motor and sensory pathways are somatotopically organized, with the cortical representations for the face located lateral to the hand, and with the leg represented most medially (see Figure 6.2).

2. The spinal cord has dorsal sensory roots, ventral motor roots, central gray matter, and surrounding white matter columns (see Figure 6.3). The appearance of the spinal cord varies at different levels and is thickest at the cervical enlargement and lumbosacral enlargement, where nerves for the arms and legs, respectively, arise (see Figure 6.4). Blood supply for the spinal cord derives from the anterior and posterior spinal arteries (see Figure 6.5).

3. The lateral corticospinal tract is the most clinically important pathway in the nervous system, and knowledge of its anatomy is sufficient to localize many neurologic disorders (see Figures 6.8, 6.11A). The lateral corticospinal tract originates mainly in the primary motor cortex of the precentral gyrus, descends through the posterior limb of the internal capsule (see Figure 6.10), down through the cerebral peduncle in the midbrain, and penetrates through the ventral pons to form fiber bundles along the ventral medulla called the pyramids (see Figure 6.11A; see also Figure 2.22A). The lateral corticospinal tract crosses to the opposite side at the pyramidal decussation located at the junction between the medulla and spinal cord—an essential piece of information for localizing lesions (see Figures 6.8, 6.11A, and 6.14). It then continues in the lateral spinal cord white matter to synapse onto motor neurons in the spinal cord anterior (ventral) horn.

4. Motor neurons projecting from the motor cortex to the spinal cord are called upper motor neurons; those projecting from the spinal cord to the muscles are called lower motor neurons (see Figure 6.8). Upper motor neuron versus lower motor neuron signs (see Table 6.4) often have important implications for determining whether patients are suffering from lesions of the central nervous system versus peripheral nerves.

5. Patterns of weakness can also be very useful for localizing lesions (see Figure 6.14).

6. Although the lateral corticospinal tract is clinically the most important, there are several additional descending motor pathways. Descending motor pathways are organized into lateral motor systems, such as the lateral corticospinal tract involved in limb control, and medial motor systems, which are involved in controlling proximal trunk muscles (see Table 6.3; Figures 6.6, 6.11).

7. The autonomic nervous system generally controls homeostatic body functions that are not under voluntary control and has two main divisions (see Figures 6.12, 6.13). The sympathetic division is involved in "flight-or-flight" functions such as increased heart rate and blood pressure and use norepinephrine as its neurotransmitter on end organs. The parasympathetic division suberves "rest and digest" functions such as increased salivation and peristalsis, using acetylcholine as its peripheral neurotransmitter. Sympathetic (thoracolumbar) efferents arise from the intermediolateral cell column of the thoracic and upper lumbar spinal cord and synapse in paravertebral and prevertebral ganglia en route to their target. Parasympathetic (craniosacral) efferents arise from brainstem and sacral spinal cord, synapsing in ganglia located in or near their end organs.

References

General References

Motor Cortex, Sensory Cortex, and Somatosensory Organization
71-year-old woman developed gradually worsening numbness and tingling in her right leg, along with weakness in her left leg. She also had experienced occasional urinary incontinence. A neurologic examination revealed decreased pinprick sensation on her right side below the level of the umbilicus and decreased vibration and joint position sense in the left foot. Her left leg had brisk reflexes and was slightly weak. In this patient, these complex sensory and motor deficits arose from a single lesion. In this chapter, we will learn about the pathways for sensations such as touch, pain, and position sense of the limbs, and we will use this knowledge to accurately localize lesions of these pathways in clinical cases.
ANATOMICAL AND CLINICAL REVIEW

In Chapter 6 we discussed the anatomy of the corticospinal tract and other descending motor pathways. In this chapter we will discuss the other two major "long tracts" of the nervous system (Table 7.1). These are the somatosensory pathways: 

- Posterior column–medial lemniscal system and anterior lateral systems. Like the corticospinal tract, these pathways are somatotopically organized (see Figure 6.2). Understanding the functions and points of decussation of the three major long tracts (see Table 7.1) is fundamental to clinical neuroanatomical localization.

In the sections that follow, we will learn to use the anatomy of the three major long tracts to localize lesions in the nervous system. We will discuss common disorders of the spinal cord and other locations that affect these pathways. In addition, brainstem and spinal cord mechanisms of pain modulation will be addressed. The organization of the thalamus, serving as the major relay for sensory and other information traveling to the cortex, will be reviewed as well. Finally, we will discuss the roles of sensory and motor pathways in bowel, bladder, and sexual function.

Main Somatosensory Pathways

The term somatosensory generally refers to bodily sensations of touch, pain, temperature, vibration, and proprioception (limb or joint position sense). There are two main pathways for somatic sensation (see Table 7.1; see Figures 7.1 and 7.2):

- **The posterior column–medial lemniscal pathway** conveys proprioception, vibration sense, and fine, discriminative touch (Figure 7.3). The **anterolateral pathways** include the spinothalamic tract and other associated tracts that convey pain, temperature sense, and crude touch (Figure 7.2).

Since some aspects of touch sensation are carried by both pathways, touch sensation is not eliminated in isolated lesions to either pathway. Four types of sensory neuron fibers are classified according to axon diameter (Table 7.2). These different fiber types have specialized peripheral receptors that subserving different sensory modalities. Larger-diameter, myelinated axons conduct faster than smaller-diameter or unmyelinated axons.

Sensory neuron cell bodies are located in the **dorsal root ganglia** (see Figures 7.1, 7.2). Each dorsal root ganglion cell has a somatic axon that bifurcates, resulting in one long process that conveys sensory information from the periphery, and a second process that carries information into the spinal cord through the dorsal nerve roots. A peripheral region innervated by sensory fibers from a single nerve root level is called a dermatome. The dermatomes for the different spinal levels form a map over the surface of the body (see Figure 8.4) that can be useful in localizing lesions of the nerve roots or spinal cord. In Chapters 8 and 9 we will discuss localization based on dermatome and peripheral nerve patterns of sensory and motor loss. In this chapter we will focus on the central course of the somatosensory pathways in the spinal cord.

<table>
<thead>
<tr>
<th>PATHWAY(S)</th>
<th>FUNCTION</th>
<th>NAME (AND LEVEL) OF DECUSATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lateral corticospinal tract</td>
<td>Motor</td>
<td>Pyramidal decussation (cortico-medullary junction)</td>
</tr>
<tr>
<td>Posterior column–medial lemniscal pathway</td>
<td>Sensory (vibration, joint position, fine touch)</td>
<td>Internal arcuate fibers (lumbar medulla)</td>
</tr>
<tr>
<td>Anterolateral pathways</td>
<td>Sensory (pain, temperature, crude touch)</td>
<td>Anterior commissure (spinal cord)</td>
</tr>
</tbody>
</table>

**Figure 7.1 Posterior Column–Medial Lemniscal Pathway**
and brain. Just as our knowledge that the corticospinal tract crosses over at the pyramidal decussation helps us localize CNS lesions (see Figure 6.11A), it is equally important to know the points of decussation of the two main somatosensory pathways (see Table 7.1; Figures 7.1 and 7.2). We will therefore now trace the course of these pathways from spinal cord to primary somatosensory cortex.

**Posterior Column–Medial Lemniscal Pathway**

Large-diameter, myelinated axons carrying information about proprioception, vibration sense, and fine touch enter the spinal cord via the medial position of the dorsal root entry zone (see Figure 7.1). Many of those axons then enter the ipsilateral posterior columns to ascend all the way to the posterior columns nuclei in the medulla. In addition, some axons collateralize into the spinal cord central gray matter to synapse onto interneurons and motor neurons. It is easier to remember the somatotopic organization of the posterior columns (Figure 7.3) if you picture fibers adding on laterally from higher levels as the posterior columns ascend. Thus, the medial portion, called the gracile fasciculus ("gracile" means "slim"), carries information from the legs and lower trunk. The more lateral cuneate fasciculus ("cuneate" means "wedge shaped") carries information from the upper trunk above about T6, and from the arms and neck. The first-order sensory neurons that have axons in the gracile and cuneate fasciculi (also called fasciculus gracilis and fasciculus cuneatus) synapse onto second-order neurons in the nucleus gracilis and nucleus cuneatus, respectively (see Figure 7.1).

### Table 7.2 Sensory Neuron Fiber Types

<table>
<thead>
<tr>
<th>Name</th>
<th>Alternate Name</th>
<th>Fiber Diameter (μm)</th>
<th>Myelinated</th>
<th>Receptors</th>
<th>Sensory Modalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-α</td>
<td>1</td>
<td>13–20</td>
<td>Yes</td>
<td>Muscle spindle</td>
<td>Proprioception</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Golgi tendon organ</td>
<td>Proprioception</td>
</tr>
<tr>
<td>A-β</td>
<td>2</td>
<td>6–12</td>
<td>Yes</td>
<td>Muscle spindle</td>
<td>Proprioception</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Meissner's corpuscle</td>
<td>Superficial touch</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Merkel's receptor</td>
<td>Superficial touch</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pacinian corpuscle</td>
<td>Deep touch, vibration</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ruffini ending</td>
<td>Deep touch, vibration</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hair receptor</td>
<td>Touch, vibration</td>
</tr>
<tr>
<td>A-γ</td>
<td>3</td>
<td>1–5</td>
<td>Yes</td>
<td>Bare nerve ending</td>
<td>Pain</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Bare nerve ending</td>
<td>Temperature (cool)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Bare nerve ending</td>
<td>Pain</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Bare nerve ending</td>
<td>Temperature (warm)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Bare nerve ending</td>
<td>Itch</td>
</tr>
</tbody>
</table>

**Figure 7.2 Anterolateral Pathways**
Figure 7.2 Somatosensory Organization of Posterior Column and Anterolateral Pathways in the Spinal Cord. Compare to somatosensory organization of the lateral corticospinal tract shown in Figure 6.103. Spinal section from Desmedt SJ, Heacox MM. Maynard MD. 1989. Structure of the Human Brain: A Photographic Atlas, 3rd Ed. Oxford University Press, New York.

Axons of these second-order neurons decussate as internal arcuate fibers and then form the medial lemniscus on the other side of medulla (see Figure 14.8). The medial lemniscus initially has a vertical orientation, and then courses to occupy a progressively more lateral and inclined position as it ascends in the brainstem (see Figures 7.1, 14.3, and 14.4). The next major synapse occurs when the medial lemniscus axons terminate in the ventral posterior lateral nucleus (VPL) of the thalamus. The neurons of the VPL then project through the posterior limb of the internal capsule in the thalamic somatosensory radiations (see Figure 6.9B) to reach the primary somatosensory cortex (see Figures 6.10A, 7.1, and 2) in the postcentral gyrus (see Figure 7.1). As we will discuss in Chapter 12 (see Figure 12.8), an analogous pathway called the trigeminal lemniscus conveys touch sensation for the face via the ventral posterior medial nucleus of the thalamus (VPM) to the somatosensory cortex. Synaptic inputs to the primary somatosensory cortex from both the face and body occur mainly in cortical layer IV and the deep portions of layer III, with some inputs also reaching layer VI (see Figure 2.14).

Spinothalamic Tract and Other Anterolateral Pathways

Smaller-diameter and unmyelinated axons carrying information about pain and temperature sense also enter the spinal cord via the dorsal root entry zone (see Figure 7.2). However, these axons make their first synapses immediately in the gray matter of the spinal cord, mainly in the dorsal horn, marginal zone (laminas I and II), and deeper in the dorsal horn, lamina V (see Figure 6.3B; Table 6.2). Some axon collaterals ascend or descend for a few segments in Lissauer's tract before entering the central gray (see Figure 6.4, 7.2). Axons from the second-order sensory neurons in the central gray cross over in the spinal cord anterior (ventral) commissure to ascend in the anterolateral white matter. It should be noted that it takes two or three spinal segments for the decussating fibers to reach the opposite side, so a lateral cord lesion will affect contralateral pain and temperature sensation beginning a few segments below the level of the lesion. The anterolateral pathways in the spinal cord have a somatosensory organization (see Figure 7.3) in which the feet are more laterally represented. To help you remember this organization, picture fibers from the anterior commissure adding on medially as the anterolateral pathways ascend in the spinal cord. When the anterolateral pathways reach the medulla, they are located laterally, running in the groove between the olive and the inferior cerebellar peduncles (see Figures 7.2, 14.5). Then they enter the pontine tegmentum to lie just lateral to the medial lemniscus in the pons and medulla (see Figures 14.3, 14.4). The next major synaptic relay is, again, in the thalamus, which projects via the thalamic somatosensory radiations (see Figure 6.9B) to primary somatosensory cortex (see Figure 6.1) in the somatosensory cortex (see Figures 6.3, 3.1, and 2) in the postcentral gyrus (see Figure 7.2). Pain and temperature sensation for the face is carried by an analogous pathway called the trigeminothalamic tract, to be discussed further in Chapter 12 (see Figures 12.8).

The anterolateral pathways consist of three tracts (see Figure 7.2): the spinothalamic, spinoreticular, and spinomesencephalic tracts. The spinothalamic tract is the best known and mediates discriminative aspects of pain and temperature sensation, such as location and intensity of the stimuli. As the posterior columns–medial lemniscal pathway, the main relay for the spinothalamic tract is in the ventral posterior lateral nucleus (VPL) of the thalamus. However, the terminations of the spinothalamic tract and the posterior columns–medial lemniscal pathway in the VPL are separate. There are also spinothalamic projections to other thalamic nuclei, including intralaminar thalamic nuclei (central lateral nuclei) and medial thalamic nuclei such as the mediodorsal nuclei.

These projections probably participate together with the spinoreticular tract in a phylogenetically older pain pathway responsible for conveying the emotional and arousal aspects of pain. The spinoreticular tract terminates on the medulary pontine reticular formation, which in turn projects to the intralaminar thalamic nuclei (centromedian nuclei). Unlike the VPL, which projects specifically in a somatosensory fashion to the primary sensory cortex, the intralaminar nuclei project diffusely to the entire cerebral cortex and are thought to be involved in behavioral arousal (see the section on the thalamus later in this chapter).

The spinomesencephalic tract projects to the midbrain periaqueductal gray matter and the superior colliculus (see Figure 7.2). The periaqueductal gray participates in central modulation of pain, as we will discuss shortly.

The spinothalamic and spinomesencephalic tracts arise mainly from spinal cord lamina I and V, while the spinoreticular tract arises diffusely from intermediate zone and ventral horn laminae 6 through 8 (see Figure 6.3). In addition to pain and temperature, some crude touch sensation can be conveyed by the anterolateral pathways when the posterior columns are damaged. To summarize: if you step on a thumb tack with your left foot, your spinothalamic tract enables you to realize "something sharp is puncturing the sole of my left foot"; your spinomesencephalic projections and spinoreticular tract cause you to feel "ouch that hurts!"; and your spinomesencephalic tract leads to pain modulation, allowing you to eventually think "ahh, that feels better."

A summary of spinal cord sensory and motor pathways is shown in Figure 7.4. (The sensory pathways shown on the left are discussed in this chapter; the spinocerebellar tracts are covered in Chapter 15. The motor pathways shown on the right are discussed in Chapter 6 (see Figure 6.11). As we will see in Chapter 7, clinical syndromes of the spinal cord provide a practical review of regional spinal cord anatomy. We will now discuss the continuation of the somatosensory pathways, from the thalamus to the cerebral cortex.)
Somatosensory Cortex

From the thalamic VPL and VPM nuclei, somatosensory information is conveyed to the primary somatosensory cortex in the postcentral gyrus, which includes Brodmann's areas 1, 2, and 3 (see Figures 7.1, 7.2; see also Figure 6.1). Like the primary motor cortex, the primary somatosensory cortex is somatotopically organized, with the face represented most laterally, and the leg most medially (see Figure 6.2). Information from the primary somatosensory cortex is conveyed to the secondary somatosensory association cortex located within the Sylvian fissure, along its superior margin in a region called the parietal operculum (see Figure 6.3). The secondary somatosensory cortex is also organized somatotopically. Further processing of somatosensory information occurs in association cortex of the posterior parietal lobule, including Brodmann's areas 5 and 7 (see Figure 6.4). Primary somatosensory cortex and somatosensory association cortex also have extensive connections with the motor cortex. Lesions of the somatosensory cortex and adjacent regions produce characteristic deficits referred to as cortical sensory loss (see KCC 7.3).

Central Modulation of Pain

Pain modulation involves interactions between local circuits at the level of the spinal cord dorsal horn and long-range modulatory inputs (Figure 7.5). In a mechanism called the gate control theory, sensory inputs from large-diameter, nonpain A-β fibers (see Table 7.2) reduce pain transmission through the dorsal horn. Thus, for example, transcutaneous electrical nerve stimulation (TENS) devices work to reduce chronic pain by activating A- β fibers. This is also why shaking your hand after striking your thumb with a hammer temporarily helps relieve the pain. The periaqueductal gray receives inputs from the hypothalamus, amygdala, and cortex, and inhibits pain transmission in the dorsal horn via a relay in a region at the postremamentary junction called the rostral ventral medulla (RVM) (see Figure 7.5). This region includes serotoninergic (5-HT1) neurons of the raphe nuclei (see Figure 14.12) that project to the spinal cord, modulating pain in the dorsal horn. The RVM also sends inputs mediated by the neuropeptide substance P to the locus ceruleus (see Figure 14.21), which in turn sends noradrenergic (NE) projections to modulate pain in the spinal cord dorsal horn (see Figure 7.5).

Opiate medications such as morphine are likely to exert their analgesic effects through receptors found in widespread locations throughout the nervous system, including receptors located on peripheral nerves. However, opiate receptors and endogenous opiate peptides, such as enkephalin, β-endorphin, and dynorphin, are found in particularly high concentrations at key points in the pain modulatory pathways. Thus, enkephalin- and dynorphin-containing neurons are concentrated in the periaqueductal gray, RVM, and spinal cord dorsal horn, while β-endorphin-containing neurons are concentrated in regions of the hypothalamus that project to the periaqueductal gray.

The Thalamus

The thalamus (meaning "inner chamber" or "bedroom" in Greek) is an important processing station in the center of the brain. Nearly all pathways that project to the cerebral cortex do so via synaptic relays in the thalamus. The thalamus is often thought of as the major sensory relay station, and is therefore appropriate to introduce thalamic networks in this chapter. However, in addition to sensory information, the thalamus also conveys nearly all other inputs to the cortex, including motor inputs from the cerebellum and basal ganglia (see Chapters 15 and 16), limbic inputs (see Chapter 18), widespread modulatory inputs involved in behavioral arousal and sleep-wake cycles (see Chapter 14), and other inputs. We will introduce the thalamus in some detail here, both because of its relevance to sensory processing discussed in this chapter and because thalamic nuclei are important in several subsequent chapters.

Some thalamic nuclei have specific topographical projections to restricted cortical areas, while others project more diffusely. Thalamic nuclei typically receive dense reciprocal feedback connections from the cortical areas to which they project. In fact, corticothalamic projections outnumber thalamocortical projections.

As mentioned in Chapter 2, the thalamus is part of the diencephalon, together with the hypothalamus and epithalamus. The diencephalon is located just rostral to the midbrain (see Figure 2.2). The hypothalamus, located immediately ventral to the thalamus, is discussed in Chapter 7 (the epithalamus consists of several small nuclei including the habenula, parts of the pretectum, and the pineal body. In horizontal sections, the thalamus are visible as deep gray matter structures, shaped somewhat like eggs, with their posterior ends angled outward, forming an inverted V (see Figures 6.1, 6.9B, 6.10A, 16.3). The thalamus is divided into a medial nuclear group, lateral nuclear group, and anterior nuclear group by a Y-shaped white matter structure called the internal medullary lamina (Figure 7.6). Nuclei located within the internal medullary lamina itself are called the intralaminar nuclei.

The midline thalamic nuclei are an additional thin layer of nuclei lying adjacent to the third ventricle, several of which are continuous with and functionally very similar to the intralaminar nuclei. Finally, the thalamic reticular nuclei (see Figure 7.2) are distinguished from the reticular nuclei of thebrainstem) forms an extensive but thin sheet enveloping the lateral aspect of the thalamus. We will now discuss three main categories of thalamic nuclei (Table 7.3):
**TABLE 7.3 Major Thalamic Nuclei**

<table>
<thead>
<tr>
<th>NUCLEI</th>
<th>MAIN INPUTS</th>
<th>MAIN OUTPUTS</th>
<th>DIFFUSIONS OF PROJECTIONS TO CORTEX</th>
<th>PROPOSED FUNCTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relay Nuclei</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lateral nucleus group</td>
<td>Medial lemniscus, spinothalamic tract</td>
<td>Somatosensory cortex</td>
<td>+</td>
<td>Relays somatosensory spinal inputs to cortex</td>
</tr>
<tr>
<td>Ventral posterior lateral nucleus (VPL)</td>
<td>Medial lemniscus, spinothalamic tract</td>
<td>Somatosensory cortex</td>
<td>+</td>
<td>Relays somatosensory spinal inputs to cortex</td>
</tr>
<tr>
<td>Ventral posteromedial nucleus (VPM)</td>
<td>Medial lemniscus, spinothalamic tract</td>
<td>Somatosensory cortex</td>
<td>+</td>
<td>Relays somatosensory spinal inputs to cortex</td>
</tr>
<tr>
<td>Lateral geniculate nucleus (LGN)</td>
<td>Inferior colliculus</td>
<td>Primary sensory cortex</td>
<td>+</td>
<td>Relays visual inputs to cortex</td>
</tr>
<tr>
<td>Medial geniculate nucleus (MGN)</td>
<td>Inferior colliculus</td>
<td>Primary sensory cortex</td>
<td>+</td>
<td>Relays auditory inputs to cortex</td>
</tr>
<tr>
<td>Ventral lateral nucleus (VL)</td>
<td>Medial globus pallidus, deep cerebellar nuclei, substantum nigra pars reticulata</td>
<td>Motor, premotor, and supplementary motor cortex</td>
<td></td>
<td>Relays basal ganglia and cerebellar inputs to cortex</td>
</tr>
<tr>
<td>Ventral anterior nucleus (VA)</td>
<td>Substantia nigra pars reticulata, internal globus pallidus, deep cerebellar nuclei</td>
<td>Widespread to frontal lobe, including prefrontal, premotor, motor, and supplementary motor cortex</td>
<td>+</td>
<td>Relays basal ganglia and cerebellar inputs to cortex</td>
</tr>
<tr>
<td>Pulvinar</td>
<td>Tectum (extrageniculate visual pathway), other sensory inputs</td>
<td>Functional orientation toward relevant visual and other stimuli</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lateral dorsal nucleus</td>
<td>See anterior nucleus</td>
<td></td>
<td></td>
<td>Functions with anterior nucleus</td>
</tr>
<tr>
<td>Lateral posterior nucleus</td>
<td>See pulvinar</td>
<td></td>
<td></td>
<td>Functions with pulvinar</td>
</tr>
<tr>
<td>Ventral medial nucleus</td>
<td>Midbrain reticular formation</td>
<td>Widespread to cortex</td>
<td>+</td>
<td>May help maintain alert, consciousness</td>
</tr>
</tbody>
</table>

**TABLE 7.3 (continued)**

<table>
<thead>
<tr>
<th>NUCLEI</th>
<th>MAIN INPUTS</th>
<th>MAIN OUTPUTS</th>
<th>DIFFUSIONS OF PROJECTIONS TO CORTEX</th>
<th>PROPOSED FUNCTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medial nucleus group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mediodorsal nucleus (MD)</td>
<td>Amygdala, olfactory cortex, limbic basal ganglia</td>
<td>Frontal cortex</td>
<td>++</td>
<td>Limbic pathways, major relay to frontal cortex</td>
</tr>
<tr>
<td>Anterior nucleus group</td>
<td>Mammary body, hippocampal formation</td>
<td>Cingulate gyrus</td>
<td>+</td>
<td>Limbic pathways</td>
</tr>
<tr>
<td>Medial thalamic nuclei</td>
<td>Hypothalamus, basal forebrain, amygdala, hippocampus</td>
<td>Amygdala, hippocampus, limbic cortex</td>
<td>+</td>
<td>Limbic pathways</td>
</tr>
<tr>
<td>INTRALAMINAR NUCLEI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ventral lateral nucleus (VL)</td>
<td>Deep cerebellar nuclei, globus pallidus, brainstem, ascending reticular activating systems (ARAS), sensory pathways</td>
<td>Cerebral cortex, striatum</td>
<td>++</td>
<td>Maintain alert consciousness, motor relay for basal ganglia and cerebellum</td>
</tr>
<tr>
<td>Pulvinar</td>
<td>Globus pallidus, ARAS, sensory pathways</td>
<td>Striatum, cerebral cortex</td>
<td></td>
<td>Motor relay for basal ganglia</td>
</tr>
<tr>
<td>Reticular nucleus</td>
<td>Cerebral cortex, thalamic relay and intralaminar nuclei, ARAS</td>
<td>Thalamic relay and intralaminar nuclei, ARAS</td>
<td></td>
<td>Regulates state of other thalamic nuclei</td>
</tr>
</tbody>
</table>

Notes:
- *The most well known and clinically relevant nuclei are shown in boldface. Some additional smaller nuclei have not been included.*
- In addition to the inputs listed, all thalamic nuclei receive reciprocal connections from the cortex and from the thalamic intralaminar nuclei.
- Moderately diffuse (specific thalamic relay nuclei): ++ -- moderately diffuse; +++ -- most diffuse.

Relay Nuclei
Most of the thalamus is made up of relay nuclei, which receive inputs from numerous pathways and then project to the cortex. In addition, relay nuclei receive massive reciprocal connections back from the cortex. Projections of relay nuclei to the cortex may be fairly localized to specific cortical regions or more diffuse (Table 7.3).

Specific Thalamic Relay Nuclei
Among the thalamic relay nuclei, projections to the primary sensory and motor areas tend to be the most localized. These specific relay nuclei lie mainly in the lateral thalamus. All sensory modalities, with the exception of olfaction, have specific relays in the lateral thalamus en route to their primary cortical areas (see Table 7.3; Figures 7.7, 7.8). For example, as we have discussed, somatosensory pathways from the spinal cord and cranial nerves relay in the ventral posterior lateral (VPL) and ventral posterior medial (VPM) nuclei, respectively. The VPL and VPM in turn project to the primary somatosensory cortex. Visual pathways then project to the sensory cortex in the parietal lobe. Motor pathways focus on the ventral motor thalamus, which projects to the primary motor cortex (Brodmann area 4), which, in turn, projects to the spinal cord and cranial nerves.
Figure 7.7 Noncortical inputs to the Thalamus. Main noncortical inputs to the different thalamic nuclei are shown. Cortical connections are shown in Figure 7.8. See Table 7.3 for additional details. Ant., anterior nuclear group; Iu, intralaminar nuclei; UD, lateral dorsal nucleus; LGN, lateral geniculate nucleus; LB, lateral posterior nucleus; MD, mediodorsal nucleus; MGN, medial geniculate nucleus; VA, ventral anterior nucleus; VL, ventral lateral nucleus, pars caudalis; VLO, ventral lateral nucleus, pars oralis; VPL, ventral posterior lateral nucleus; VMp, ventral posterior medial nucleus.

Information is relayed in the lateral geniculate nucleus (LGN), as we will discuss further in Chapter 11, and auditory information is relayed in the medial geniculate nucleus (MGN), as we will discuss in Chapter 12 (see also Figure 6.9b). A useful mnemonic for these two nuclei is lateral light (vision), medial music ( audition). Motor pathways leaving the cerebellum and basal ganglia (see Figures 2.17, 15.9, and 16.6) also have specific thalamic relays in the ventral lateral nucleus (VL) en route to the motor, premotor, and supplementary motor cortex (see Table 7.3; Figures 7.7, 7.8). Even some limbic pathways (see Chapter 18) have fairly specific cortical projections, such as those carried by the anterior nuclear group to the anterior cingulate cortex. The anterior thalamic nuclear group forms a prominent bulge in the anterior superior thalamus (see Figure 7.6).

Widely Projecting (Nonspecific) Thalamic Relay Nuclei. Many thalamic nuclei have more widespread cortical projections (see Table 7.3; see Figures 7.7, 7.8). For example, visual and other sensory inputs to the pulvinar are relayed to large regions of the parietal, temporal, and occipital association cortex involved in behavioral orientation toward relevant stimuli. The pulvinar (“couch” or “cushion” in Latin) is a large, pillow-shaped nucleus that occupies most of the posterior thalamus (see Figure 7.6). Diffuse relays of limbic inputs, and other information involved in cognitive functions, occur in the mediodorsal nuclei (MD), as well as in the midline and intralaminal thalamic nuclei. The mediodorsal nucleus, sometimes called the diencephalic nucleus, forms a large bulge lying medial to the internal medullary lamina, best seen in coronal sections (see Figure 16.4). The MD serves as the major thalamic relay for information traveling to the frontal association cortex (see Figure 7.8; see also Chapters 16, 18, 19). Other examples of widely projecting thalamic nuclei are also listed in Table 7.3.

Intralaminar Nuclei. The intralaminar nuclei lie within the internal medullary lamina (see Figure 7.6). Like the relay nuclei, they receive inputs from numerous pathways and have reciprocal connections with the cortex. They are sometimes classified along with other “nonspecific” relay nuclei. However, we have placed them in a separate category here because unlike relay nuclei, their main inputs and outputs are from the basal ganglia. Intralaminar nuclei can be divided into two functional regions (see Table 7.3): The caudal intralaminar nuclei include the large centromedian nucleus and are involved mainly in basal ganglia circuitry (see Chapter 16); the rostral intralaminar nuclei also have input and output connections with the basal ganglia. In addition, the rostral intralaminar nuclei appear to have an important role in relaying inputs from the ascending reticular activating systems (ARAS) to the cortex, maintaining the alert, conscious state (see Figure 2.23; Chapter 14).

Reticular Nucleus. The reticular nucleus forms a thin sheet located just lateral to the rest of the thalamus, and just medial to the internal capsule (see Figures 7.6, 16.42). It should not be confused with the similarly named reticular formation, located in the brainstem (see Chapter 14). The reticular nucleus is the only nucleus of the thalamus that does not project to the cortex. Instead, it receives inputs mainly from other thalamic nuclei and the cortex and then projects back to the thalamus. The reticular nucleus consists of an almost pure population of inhibitory GABAergic neurons. This composition, together with its conne-

Figure 7.8 Reciprocal Connections between Thalamus and Cortex. Major connections between thalamic nuclei and cortical areas are shown using corresponding colors. (A) Cortex, lateral view. (B) Cortex, medial view. (C) Thalamus. See Table 7.3 for additional details. Abbreviations are the same as in Figure 7.7.

REVIEW EXERCISE
Name the thalamic nuclei that are most important in relaying the following information to the cortex: somatosensory input, somatosensory face input, visual input, auditory input, basal ganglia and cerebellar input, limbic input (see the boldfaced entries in Table 7.3).
tions with the entire thalamus, make it well suited to regulate thalamic activity. In addition to cortical and thalamic inputs, other inputs to the reticular nucleus arising from the brainstem reticular activating systems and the basal forebrain may participate in modulating the state of alertness and attention (see Chapters 14, 19).

In summary, the thalamus has major reciprocal connections with all regions of the cerebral cortex. It contains many different nuclei with different functions. These nuclei convey information from other parts of the nervous system, as well as from the periphery to the cortex.

### KEY CLINICAL CONCEPT
**PARESTHESIAS**

In addition to negative symptoms of sensory loss, lesions of the somatosensory pathways can cause abnormal positive sensory phenomena called paresthesias. Both the character and the location of these abnormal sensations reported by the patient can have localizing value. In lesions of the posterior column-medial lemniscal pathways, patients commonly describe a tingling, numb sensation, a feeling of a tight band-like sensation around the trunk or limbs, or a sensation similar to gauze on the fingers when trying to palpate objects. In lesions of the anterolateral pathways, there is often sharp, burning, or searing pain. Lesions of the parietal lobe or primary sensory cortex may cause contralateral numb tingling, although pain can also be prominent. Lesions of the thalamus can cause severe contralateral pain, called Dejerine-Roussy syndrome. Lesions of the cervical spine may be accompanied by Dejerine’s sign, an electricity-like sensation running down the back and into the extremities upon neck flexion. Lesions of nerve roots often produce radicular pain (see KCC 8.3) that radiates down the limb in a dermatomal distribution, is accompanied by numbness and tingling, and is provoked by movements that stretch the nerve root. Peripheral nerve lesions, similarly, often cause pain, numbness, and tingling in the sensory distribution of the nerve.

In addition to “paresthesia,” other common terms for sensory abnormalities include dysesthesia (unpleasant, abnormal sensation), and hyperesthesia or allodynia (painful sensations provoked by minor stimuli such as light touch). The term hyposthesia means decreased sensation, but it may be interpreted (does the “hy-” refer to “hyper-” or “hypo-?”) and is thus best avoided.

### KEY CLINICAL CONCEPT
**SPINAL CORD LESIONS**

Spinal cord lesions are a major source of disability because they affect motor, sensory, and autonomic pathways. Suspected dysfunction of the spinal cord must therefore be treated as a medical emergency in an attempt to prevent irreversible damage. The most common causes of spinal cord dysfunction are compression due to trauma, and metastatic cancer. Other causes of spinal cord dysfunction are listed in Table 7.4.

Symptoms and signs of spinal cord dysfunction may be obvious when a sensory level and motor dysfunction corresponding to the level of the lesion are present (KCC 7.4). Reflex abnormalities, including abnormal sphincteric function can help confirm the diagnosis (see Tables 3.6, 3.7, KCC 7.5). In more subtle cases, however, minor sensory or motor changes, back or neck pain, or fever (in epidural abscess) may be the only clues warning of incipient disastrous loss of function. Clinicians should therefore have a low threshold for ordering an urgent MRI scan in cases of suspected spinal cord lesions. In this regard note that although a sensory level can suggest the level of a lesion, sometimes the lesion may actually be much higher in the spinal cord. Therefore, higher levels, such as the thoracic and cervical cord, often must be imaged as well, even in cases of suspected lumbosacral pathology.

### TABLE 7.4 Differential Diagnosis of Spinal Cord Dysfunction

<table>
<thead>
<tr>
<th>Tract or mechanical</th>
<th>Tertiary syphilis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compromise in</td>
<td>Tropical spastic paraparesis</td>
</tr>
<tr>
<td>Compression</td>
<td>Schizosporidiosis</td>
</tr>
<tr>
<td>Disc herniation</td>
<td>Inflammatory myelitis</td>
</tr>
<tr>
<td>Degenerative disorders of</td>
<td>Multiple sclerosis</td>
</tr>
<tr>
<td>vertebral bones</td>
<td>Lesions</td>
</tr>
<tr>
<td>Disc embolus</td>
<td>Postinfected myelitis</td>
</tr>
<tr>
<td>Vascular (see Figure 6.5)</td>
<td>Neoplasms</td>
</tr>
<tr>
<td>Anterior spinal artery infarct</td>
<td>Epidural metastasis</td>
</tr>
<tr>
<td>Wernicke infarct</td>
<td>Menigitis</td>
</tr>
<tr>
<td>Spinal dura AVM (arteriovenous malformation)</td>
<td>Schwannoma</td>
</tr>
<tr>
<td>Epidural hematoma</td>
<td>Carcinomatous meningitis</td>
</tr>
<tr>
<td>Nutritional deficiency</td>
<td>Astrocytoma</td>
</tr>
<tr>
<td>Vitamin B12</td>
<td>Ependymoma</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>Hemangioblastoma</td>
</tr>
<tr>
<td>Epidural abscess</td>
<td>Degenerative/developmental</td>
</tr>
<tr>
<td>Infections myelitis</td>
<td>Spinal bifida</td>
</tr>
<tr>
<td>Viral, including HIV</td>
<td>Chiari malformation</td>
</tr>
<tr>
<td>Lyme disease</td>
<td>Syringomyelia</td>
</tr>
</tbody>
</table>

*(Following format of Table 1.1)*

In acute, severe lesions such as trauma, there is often initially a phase of spinal shock characterized by flaccid paralysis below the lesion, loss of tendon reflexes, decreased sympathetic outflow to vascular smooth muscle causing moderately decreased blood pressure, and absent sphincteric reflexes and tone. Over the course of weeks to months, spasticity and upper motor neuron signs usually develop. Some sphincteric and erectile reflexes may return, although often without voluntary control. Acute traumatic spinal cord lesions may have improved outcome if treated within the first 6 hours with high doses of steroids. In cord compression caused by tumors, it is essential to institute radiation and/or surgical intervention promptly to prevent irreversible loss of ambulation. An approximate rule of thumb is that 80% of patients treated for metastatic spinal cord compression after they lose ambulation will remain permanently nonambulatory, while 80% of patients treated before losing ambulation remain ambulatory for the rest of their lives. **Myelitis** is another important and common cause of spinal cord dysfunction, which can be infectious or inflammatory in etiology (see Table 7.4; also KCC 5.9, 6.6).

### KEY CLINICAL CONCEPT
**SENSORY LOSS: PATTERNS AND LOCALIZATION**

Sensory loss can be caused by lesions anywhere in the somatosensory pathways (see Figures 7.1, 7.2), including peripheral nerves, nerve roots, posterior column-medial lemniscal and anterolateral pathways, the thalamus, thalamocortical white matter pathways, and the primary somatosensory cortex. In this section and in KCC 7.4, we will review localizing patterns of sensory loss and associated deficits. Sensory loss in the face is discussed further in KCC 12.2. In the illustrations for this section, lesions are indicated in red, while regions of sensory loss are indicated in purple.
Figure 7.9 Patterns of Sensory Loss in Lesions of the Brain or Peripheral Nerves
Lesions are shown in red; regions of sensory loss are shown in purple.

Primary Somatosensory Cortex (Figure 7.9A)
Deficit is contralateral to the lesion. Despite the depiction in Figure 7.9A, sensory loss does not begin neatly at the midline, and various subregions may be differentially affected depending on lesion size and location. Discriminative touch and joint position sense are often most severely affected (see neuroexam.com Videos 73), but all modalities may be involved. Sometimes primary modalities are relatively spared, but a pattern called cortical sensory loss is present, with extinction, or decreased stereognosis, and graphesthesia (see Chapter 3; neuroexam.com Videos 75–77). Associated deficits from involvement of adjacent cortical areas may include upper motor neuron-type weakness (Table 6.4), visual field deficits, or aphasia (see KCC 19.6).

Thalamic Ventral Posterior Lateral (VPL) and Ventral Posterior Medial (VPM) Nuclei or Thalamic Somatosensory Radiations (Figure 7.9A)
Deficit is contralateral to the lesion. As with lesions of the primary somatosensory cortex, sensory loss does not begin neatly at the midline, and various subregions may be differentially affected. The deficit may be more noticeable in the face, hand, and foot than in the trunk or proximal extremities. All sensory modalities may be involved, sometimes with no motor deficit. Larger lesions may be accompanied by hemiparesis or hemianopia caused by involvement of the internal capsule, lateral geniculate, or optic radiations. Lesions of the thalamic somatosensory radiations can also cause contralateral hemisensory loss, which is associated with hemiparesis because of the involvement of adjacent corticobulbar and corticospinal fibers (see Figure 6.9B).

Lateral Pons or Lateral Medulla (Figure 7.9B)
The lesion involves anterolateral pathways and the spinal trigeminal nucleus on the same side. It causes loss of pain and temperature sensation in the body opposite the lesion, and loss of pain and temperature sensation in the face on the same side as the lesion. Associated deficits of the lateral pontine and the lateral medullary syndromes are discussed in KCC 14.3.

Medial Medulla (Figure 7.9C)
The lesion involves the medial lemniscus, causing contralateral loss of vibration and joint position sense. Associated deficits of the medial medullary syndrome are discussed in Chapter 14.

Spinal Cord
For patterns of sensory and motor loss in spinal cord lesions, see KCC 7.4.

Nerve Roots or Peripheral Nerves (Figure 7.9D,E)
Dorsal symmetrical polyneuropathies cause bilateral sensory loss in a "glove and stocking" distribution, in all modalities. Specific nerve or nerve root lesions (Figure 7.9E) cause sensory loss in specific territories, as will be discussed in greater detail in KCC 8.3 and 9.1. Associated deficits of lesions of the peripheral nerves or nerve roots often include lower motor neuron-type weakness (see Table 6.4).

Key Clinical Concept
Spinal Cord Syndromes
Common causes of spinal cord dysfunction were discussed earlier in this chapter in KCC 7.2. In this section, we will describe several important spinal cord syndromes that have sensory and motor findings that can often be used to localize the lesion.
Transverse Cord Lesion

See Figure 7.10A. All sensory and motor pathways are either partially or completely interrupted. There is often a sensory level corresponding to the level of the lesion (see Figure 8.4). The pattern of weakness and reflex loss can also help determine the spinal cord level (see Tables 3.4-3.7; KCC 8.2; neuroscape.com; Videos 54, 56, and 58). Common causes of transverse cord lesions include trauma, tumors, multiple sclerosis, and transverse myelitis.

Hemisected Lesions: Brown-Séquard Syndrome

See Figure 7.10B. Damage to the lateral corticospinal tract causes ipsilateral upper motor neuron-type weakness. Interruption of the posterior columns causes bilateral loss of vibration and joint position sense. Interruption of the anterolateral systems, however, causes contralateral loss of pain and temperature sensation. This often begins slightly below the lesion because the anterolateral fibers ascend two to three segments as they cross in the ventral commissure. There may also be a strip of one or two segments of sensory loss to pain and temperature ipsilateral to the lesion, caused by damage to posterior horn cells before their axons have crossed over. Common causes of Brown-Séquard syndrome include penetrating injuries, multiple sclerosis, and lateral compression from tumors.

Central Cord Syndrome

See Figure 7.10C.D. In small lesions, damage to spinothalamic fibers crossing in the ventral commissure (see Figure 7.2) causes bilateral regions of suspended sensory loss to pain and temperature. Lesions of the cervical cord (see Figure 8.4) produce the classic cape distribution; however, suspended dermatomes of pain and temperature sensory loss can occur with lesions at other levels as well. With larger lesions (see Figure 7.10D), the anterior horn cells are damaged, producing lower motor neuron deficits at the level of the lesion. In addition, the corticospinal tracts are affected, causing upper motor neuron signs, and the posterior columns may be involved as well. Because the anterolateral pathways are compressed from their medial surface by large lesions, there may be near complete loss of pain and temperature sensation below the lesion except for a region of sacral sparing (review the somatotopic distribution of anterolateral systems in the spinal cord; see Figure 7.3). Common causes of central cord syndrome include spinal cord contusion, posttraumatic syringomyelia, and intrinsic spinal cord tumors such as hemangioblastoma, ependymoma, or astrocytoma.

Posterior Cord Syndrome

See Figure 7.10E. Lesions of the posterior columns cause loss of vibration and position sense below the level of the lesion. With larger lesions, there may also be encroachment on the lateral corticospinal tracts, causing upper motor neuron-type weakness. Common causes include trauma, extrinsic compression from posteriorly located tumors, and multiple sclerosis. In addition, vitamin B12 deficiency and tubal obsolescence (uterine syphilis; KCC 5.9) preferentially affect the posterior cord.
Anterior Cord Syndrome

See Figure 7.10F. Damage to the anterolateral pathways causes loss of pain and temperature sensation below the level of the lesion, and damage to the anterior horn cells produces lower motor neuron weakness at the level of the lesion. With larger lesions, the lateral corticospinal tracts may also be involved, causing upper motor neuron signs. Incontinence is common because the descending pathways controlling sphincter function tend to be more ventrally located (Figure 7.11). Common causes include trauma, multiple sclerosis, and anterior spinal artery infarct.

Bladder Function

Bladder emptying in normal adults is completely under voluntary control. A sense of bladder fullness reaches the sensory cortex, and micturition is initiated by descending pathways from medial frontal micturition centers that activate the voiding, or detrusor, reflex (see Figure 7.11). The detrusor reflex is mediated by intraspinal cord circuits and regulated by the pontine micturition center, and possibly also by cerebellar and basal ganglia pathways. The reflex is normally initiated by voluntary relaxation of the external urethral sphincter, which inhibits the inhibition of sympathetic to the bladder neck, causing it to relax, and the activation of parasympathetics, causing detrusor muscle contraction. The sensation of urine flow through the urethra activates continued sphincter relaxation and detrusor contraction. When flow stops, the urethral sphincters contract, thereby triggering detrusor relaxation through the urethral reflex. Flow can also be interrupted at any time by voluntary closure of the urethral sphincter, which similarly triggers detrusor relaxation.

Lesions affecting bilateral medial frontal micturition centers result in reflex activation of pontine and spinal micturition centers when the bladder is full. Urine flow and bladder emptying are normal; however, they are no longer under voluntary control, and the individual may or may not be aware of the incontinence. Common causes of frontal-type incontinence include hydrocephalus, parasagittal meningioma, bifrontal glioblastoma, traumatic brain injury, and neurodegenerative disorders.

Table 7.5 Nuclei and Nerve Roots for Bladder, Bowel, and Sexual Function

<table>
<thead>
<tr>
<th>PATHWAYS</th>
<th>NUClEi FOR MOTOR PATHWAYS</th>
<th>NERVE ROOTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>BLADDER FUNCTION</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Detrusor and urethral afferents</td>
<td>—</td>
<td>S2, S3, S4</td>
</tr>
<tr>
<td>Somatic innervation of urethral sphincter</td>
<td></td>
<td>S3, S4</td>
</tr>
<tr>
<td>Somatic innervation of pelvic floor muscles</td>
<td></td>
<td>S2, S3, S4</td>
</tr>
<tr>
<td>Sympathetic innervation of detrusor</td>
<td>S2, S3, S4</td>
<td></td>
</tr>
<tr>
<td>Sympathetic (a and b) innervation of bladder neck, urethra, and bladder dome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediolateral cell column</td>
<td>T11, T12, L1</td>
<td></td>
</tr>
<tr>
<td>BOWEL FUNCTION</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rectal and pelvic floor afferents</td>
<td>—</td>
<td>S2, S3, S4</td>
</tr>
<tr>
<td>Somatic innervation of external anal sphincter</td>
<td></td>
<td>S3, S4</td>
</tr>
<tr>
<td>Somatic innervation of pelvic floor muscles</td>
<td></td>
<td>S2, S3, S4</td>
</tr>
<tr>
<td>Sympathetic innervation of external anal sphincter, descending colon, and rectum</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sympathetic innervation of gut above the sphincteric flexure</td>
<td></td>
<td>Dorsal motor nucleus of vagus</td>
</tr>
<tr>
<td>S2, S3, S4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CN X</td>
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<td></td>
</tr>
<tr>
<td>SEXUAL FUNCTION</td>
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<tr>
<td>Genital afferents</td>
<td>—</td>
<td>S2, S3, S4</td>
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<tr>
<td>Parasympathetic innervation of Bartholin's glands</td>
<td>S2, S3, S4</td>
<td></td>
</tr>
<tr>
<td>Sympathetic innervation of vaginal wall</td>
<td>Intermediateolateral cell column</td>
<td></td>
</tr>
<tr>
<td>Transsacral erectile pathways</td>
<td>S2, S3, S4</td>
<td></td>
</tr>
<tr>
<td>Sympathetic erectile and anti-erectile pathways</td>
<td>Intermediateolateral cell column</td>
<td></td>
</tr>
<tr>
<td>Sympathetic ejaculatory pathways</td>
<td>Intermediateolateral cell column</td>
<td></td>
</tr>
<tr>
<td>Somatic motor pathway for erection of penis</td>
<td></td>
<td>S2, S3, S4</td>
</tr>
</tbody>
</table>

*Bold indicates the most important nerve roots, where applicable.

*Bold motor and sensory nerves are also regulated by intrinsic networks of neurons in the wall of the gut referred to as the enteric nervous system (see Chapter 6).
Lesions below the pontine micturition center and above the conus medullaris levels S2 to S4 often initially cause a flaccid, acricritic (atonic) bladder, (Fig. 7.12A) which usually evolves over weeks to months into a hypertonic (spastic) bladder (Fig. 7.12B). When the bladder is atonic, reflex contractions of the urethral sphincters often persist, resulting in urinary retention and bladder distention (Fig. 7.12A). Catheterization is usually necessary. The postvoid residual volume, measured by catheterization after voluntary voiding, is increased in this condition (normal volume is less than 100 cc). In a hypertonic bladder (Fig. 7.12B), detrusor-sphincter dyssynergia often occurs, in which both detrusor and urethral sphincter tone are increased in an uncoordinated, and at times antagonistic, fashion. When involuntary reflex bladder contractions occur, there may be a sense of urgency, pain, or urge incontinence. Often residual volume increases because of incomplete emptying, although volumes are typically smaller than with atonic bladder. Common spinal cord lesions causing the contractions or hypertonic bladder include trauma, tumors, transverse myelitis, and multiple sclerosis.

However, lesions of the peripheral nerves or of the spinal cord at S2 to S4, usually cause a flaccid, acricritic, or significantly impaired bladder contractility resulting in an atonic bladder capacity. This result can be due, to loss of parasympathetic efferent discharge to the detrusor and/or loss of afferent sensory information from the bladder and urethra. Overflow incontinence is often present. Common causes include diabetic neuropathy and compression of the conus medullaris or cauda equina by trauma, tumor, or disc herniation. Urinary retention can also occur due to a large variety of non-neurologic conditions, such as prostatic hypertrophy, urethral strictures, and intrinsic sphincter deficiency. The term neurogenic bladder is a broad, nonspecific term used to refer to both flaccid and hypertonic bladder disorders of neurologic origin.

Bowel Function

Like urinary function, rectal control is mediated by descending pathways originating mainly in the spinal cord. Anal sphincter control is maintained by an internal smooth muscle sphincter innervated by sacral parasympathetics, an external striated muscle sphincter innervated by pelvic nerves arising from the sacral roots, and the pelvic floor muscles innervated by sacral anterior horn cells (Figures 7.11, 7.12). Sensory inputs enter at S2 to S4 and play an important role in feedback control. Lower bowel control depends on parasympathetics from S2 to S4 for coordinated smooth muscle beyond the anal flexure. The portio of the gastrointestinal tract above the splenic flexure receive parasympathetic innervation from the vagal nerves (see Figure 6.13). Vagal innervation can be by irritative centers or by direct pelvic nerves, by spinal cord lesions, or by lesions of the sacral nerve roots or the pelvic or pudendal nerves (see the previous section on bladder function). In the absence of spinal cord lesions the anal sphincter is completely flaccid. There is also a tone of sacral parasympathetic outflow, causing some variability.

Sexual Lubrication, Erection, and Ejaculatory Function

During sexual arousal, stimuli from multiple sensory modalities, together with internal psychological factors, result in activation of spinal cord autonomic pathways involved in sexual function. Sensation from the genitilia is conveyed by the pudendal nerve, reaching S2 to S4. In the female, sensation of lubricating mucosa by Bartholins gland is parasympathetically mediated, and increased vaginal blood flow and secretions are sympathetically mediated. In the male, both parasympathetic and sympathetic pathways contribute to erection (see Table 7.5), with the relative contributions of these two systems varying from individual to individual. Ejaculation occurs through sympathetically mediated contractions of smooth muscle (skeletal muscles, vas deferens, prostate, bladder neck), causing emission of semen into the urethra, followed by rhythmic reflex contractions of striated muscles (pelvic floor, urethral sphincter, bulbocavernosus, ischiocavernosus), resulting in forcible expulsion of semen.

In spinal cord lesions, reflex erection and reflex ejaculation may occur, but this is highly variable. Peripheral nerve lesions, higher-order cortical lesions, and psychological factors can also cause sexual dysfunction.

**CLINICAL CASES**

**CASE 7.1 Sudden Onset of Right Arm Numbness**

**Chief Complaint**

An 81-year-old right-handed man came to the emergency room because of right arm numbness and mild language difficulties.

**History**

The patient had not seen a doctor in many years. Past medical history was notable for hypertension, diabetes, and arthritis. At 8:40 am, on the day of admission, he suddenly became confused and had difficulty combining words correctly into sentences. He also complained that he could not feel things with his right arm, and that it felt numb. Furthermore, he had some difficulties using his right hand, saying he could not "grasp it." Finally, he also had a vague feeling of vision that he could not explain in greater detail.

**Physical Examination**


Neck: No bruits.

Lungs: Clear.

Heart: Regular rate with no murmurs.

Abdomen: Normal bowel sounds; soft, non-tender.

Neurologic Exam:

Mental Status: Alert and oriented x 3. Speech fluent, but with occasional paraphasic errors, substituting some letters in words incorrectly (e.g., "History" above when the patient described use of his right hand).

**Localization and Differential Diagnosis**

1. On the basis of the symptoms and signs shown in bold above, where is the lesion?

2. What is the most likely diagnosis? What are some other possible diagnoses?
Discussion

1. The key symptoms and signs in this case are:
   - Right arm numbness, extinction, agnosiosis, and astereognosis with preserved primary sensory modalities
   - Mild fluent aphasia
   - Difficulty at times seeing fingers on his right side
   - Right pronator drift

The patient has a pattern of cortical sensory loss in the right arm consistent with a lesion in the left postcentral gyrus, primary somatosensory cortex, arm area (KCC 7.3). The loss of vibration sense in the toes is probably not relevant to his current problem and is likely due to long-standing distal symmetrical polyneuropathy (KCC 8.1), commonly seen in diabetes (this conclusion is also supported by the patient's generally diminished reflexes). The mild fluent aphasia can be explained by a lesion in the dominant (left) parietal lobe. The right pronator drift suggests some mild involvement of corticospinal fibers to the arm arising from the nearby motor cortex.

The most likely clinical localization is left postcentral gyrus, primary somatosensory cortex, arm area, and some adjacent left parietal cortex.

2. The patient is an elderly man with hypertension, diabetes, and cardiac disease, with sudden onset of deficits suggesting embolic stroke (see KCC 10.4). An infarct of the left postcentral gyrus arm area and adjacent parietal cortex would be caused by occlusion of a cortical branch of the middle cerebral artery (see Figure 10.6). Other risk factors include a small hemorrhage, brain abscess, or tumor. A left subdural hematoma should also be considered, which would cause several left hemispheric deficits, as seen in this patient.

Clinical Course and Neuroimaging

A head MRI was done (Figure 7.13), showing an area of increased T2 signal consistent with an infarct in the left postcentral gyrus and adjacent parietal lobe. The patient was admitted to the hospital, and an embolic workup (see KCC 10.4) was significant only for regional wall motion abnormalities on his echocardiogram suggesting prior cardiac ischemia. His language improved back to normal within 5 days, and his right hand sensation also recovered. He was discharged home on aspirin.

CASE 7.2 Sudden Onset of Right Face, Arm, and Leg Numbness

CHIEF COMPLAINT
A 62-year-old, right-handed woman came to a medical clinic on the basis of two days of numbness in her right face, arm, and leg.

HISTORY
On the morning prior to the presentation, the patient awoke with decreased sensation in her right face and arm "as though they were asleep." She had no difficulties with language, motor skills, or vision. Her symptoms continued until the next morning, when she also noticed loss of sensation in her right foot. She became concerned and came to her medical clinic for evaluation. Past medical history was notable for hypertension, cigarette smoking, and depression. Her father had a stroke at age 64.

PHYSICAL EXAMINATION
- Vital signs: T = 97.4°F, P = 80, BP = 130/114, R = 16.
- Need: Supplies with no bruises.
- Lungs: Clear.
- Heart: Regular rate with no murmurs, gallops, or rubs.
- Abdomen: Normal bowel sounds; soft.
- Extremities: No edema.
- Neurologic exam:

CASE 7.2 (CONTINUED)

COORDINATION: Normal on finger-to-nose and heel-to-shin testing.
Gait: Normal. Tandem gait normal.
Sensory: Decreased pinprick, temperature, light touch, vibration sense on the right half of the body, especially in the right hand and foot, and less so in the trunk. Two-point discrimination 15 mm in the right index finger, compared to 4 mm in the left index finger (using a ruler and the ends of a paper clip). Normal graphesthesia. No extinction on double simultaneous stimulation.

LOCALIZATION AND DIFFERENTIAL DIAGNOSIS
1. On the basis of the symptoms and signs shown in bold above, where is the lesion?
2. What is the most likely diagnosis? What are some other possibilities?

Discussion

1. The key symptoms and signs in this case are:
   - Decreased pinprick, temperature, vibration, and light touch sensation in the right face and body, with decreased two-point discrimination in the right hand

Decreased primary sensation in half of the body, including the face, with no other deficits is sometimes thought to be psychologically based because there may be no objective findings on exam. However, this symptom combination can be caused by lesions in the ventral posterior medial and ventral posterior lateral nuclei of the contralateral thalamus (see KCC 7.3).

The most likely clinical localization is left ventral posterior thalamus.

2. Given the relatively sudden onset of deficits, and the history of hypertension, cigarette smoking, and family history of stroke, the most likely diagnosis is ischemic infarct of the left thalamus. Thalamic infarcts are usually caused by occlusion of small penetrating arteries such as the lenticulostriate (middle cerebral), anterior choroidal (internal carotid), or thalamoperforator (posterior cerebral) branches, resulting in lacunar infarction (see KCC 10.4, Table 10.3). Hemorrhage is also not uncommon in this location. Other possibilities include tumor or abscess.

Clinical Course and Neuroimaging

The patient was sent from the medical clinic to the emergency room, where a head CT showed a small hypodensity in the left thalamus. This was confirmed with a head MRI (Figure 7.14), showing increased T2 signal in the lateral thalamus consistent with a lacunar infarct. She was admitted to the neurology stroke service, and embolic workup did not reveal a cause for her infarct. She was started on medication to better control her hypertension and was entered into a clinical trial for patients with stroke of unknown cause, comparing aspirin to Coumadin in preventing stroke recurrence. Her numbness gradually improved and was completely gone by 5 days after admission.
CASE 7.1 SUDDEN ONSET OF RIGHT ARM NUMBNESS

Figure 7.13: Infarct in Left Postcentral Gyrus Somatosensory Cortex and Adjacent Parietal Lobe

T2-weighted axial (horizontal) MRI sections. (A) More inferior; (B) More superior.

Discussion
1. The key symptoms and signs in this case are:
   - Bilateral leg flaccid paralysis
   - Decreased rectal tone, and absent bulbocavernous reflex
   - T10 sensory level to all modalities

   Bilateral leg weakness can be caused by lesions of the bilateral medullary frontal lobes, the spinal cord, nerve roots, peripheral nerves, or muscles (see KCC 6.3). However, complete paralysis of both legs with no weakness elsewhere, along with decreased rectal tone and reflexes (see KCC 7.4, 7.5; see also Tables 35, 37), strongly suggests a spinal cord or cauda equina lesion. The T10 sensory level localizes the lesion more specifically to the T10 level of the spinal cord (cauda equina cannot cause deficits above L3 or L2). The absent bulbocavernous reflex suggests an acute spinal cord injury causing spinal shock (see KCC 7.2, 7.5).

   The most likely clinical localization is spinal cord at T10 level (approximately T9 vertebral bone [see Figure 8.1], spinal cord, and root exit points).

2. Given the history of a significant fall, a fractured spine with cord compression at T10 is likely.

Clinical Course and Neuroimaging

The patient was given high-dose intravenous methylprednisolone (a steroid) in a standardized protocol for acute spinal cord injuries. Plain radiographs were done, followed by a CT of the spine (Figure 7.16), showing a burst fracture of the T9 vertebral bone leading to complete obliteration of the spinal canal. CT images at other levels showed less severe fractures of the T10 and T11 vertebral bones as well. Lateral radiographs showed anterior displacement of T9 on T10 by about 4 cm, further compressing the spinal canal. The patient was admitted to the intensive care unit and placed on a special bed for spinal stabilization. Because the spinal compression seemed complete, there was little hope for recovery of function. However, he was taken to the operating room to mechanically stabilize his thoracic spine, which is functionally important for maintaining a seated posture. A T6-T11 vertebral fusion was done with bone grafts and metal rods. The patient remained paraplegic at the time of transfer to a spinal cord rehabilitation center 2 weeks after admission.
CASE 7.2 SUDDEN ONSET OF RIGHT FACE, ARM, AND LEG NUMBNESS

Figure 7.14 Lacunar Infarct in Left Thalamus Region of VPL and VPM T2-weighted axial (horizontal) MRI section through thalamus and basal ganglia.

CASE 7.3 A FALL CAUSING PARAPLEGIA AND A SENSORY LEVEL

Figure 7.16 T10 Vertebral Fracture with Obliteration of Spinal Canal Axial CT of the spine. (A) Image at level of T10 vertebral body shows smashed T10 vertebral bone with obliteration of spinal canal and spinal cord at that level. (B) Image slightly lower, at level of T11, showing normal appearance of spinal canal.

CASE 7.4 LEFT LEG WEAKNESS AND RIGHT LEG NUMBNESS

CHIEF COMPLAINT
A 71-year-old woman was referred to a neurologist with 10 months of progressive gait difficulty, right leg numbness, and urinary problems.

HISTORY
The patient was in good health, walking 3 to 4 miles per day until about 10 months prior to admission, when she first noticed mild gait unsteadiness and bilateral leg stiffness. She felt her feet were not fully under her control. Her left leg gradually became weaker than her right, with occasional left leg buckling when she walked. Meanwhile, her right leg developed progressive numbness and tingling, and she had intermittent left-sided thoracic back pain. Finally, she had increasing urinary frequency, occasional urinary incontinence, and difficulty completing a bowel movement despite several laxatives.

PHYSICAL EXAMINATION
Vital signs: T = 96.3°F, P = 78, BP = 136/76.
Neck: Supple.
Lungs: Clear.
CASE 7.4 (CONTINUED)

case study: Normal on finger-to-nose and heel-to-shin testing.

sensory: Stiff-legged and unsteady.

sensitivity: Pinprick sensation decreased on the right side below the umbilicus (Figure 7.17). Vibration and joint position sense decreased in the left foot and leg. Otherwise intact.

localization and differential diagnosis
1. On the basis of the symptoms and signs shown in bold above, where is the lesion?
2. What is the most likely diagnosis? What are some other possibilities?

Discussion
1. The key symptoms and signs in this case are:
   - Left leg weakness, increased tone, hyperreflexia, and Babinski’s sign
   - Decreased vibration and joint position sense in the left foot and leg
   - Decreased pinprick sensation on the right side below the umbilicus, with right leg numb, tingling paresthesia
   - Left-sided thoracic back pain
   - Stiff-legged, unsteady gait
   - Impaired bowel and bladder function

Unilateral weakness and upper motor neuron signs (see Table 6.4) in the leg could be caused by a lesion in the ipsilateral spinal cord or corticospinal motor cortex (see KCC 653). The associated sensory abnormalities and left thoracic pain support a left hemisected lesion at approximately T9 or T10 (see Figure 8.4), producing a Brown-Séquard syndrome (KCC 7.4). The presence of bowel and bladder dysfunction suggests some bilateral involvement of the cord (KCC 7.5), as does the spastic gait (see KCC 653), which sounds as if it may have involved both legs.

The most likely clinical localization is left T9 or T10 hemisected lesion, with possible mild involvement of the right cord as well.

2. Given the gradual, progressive onset of deficits over several months in an elderly woman, and the presence of focal pain, the most likely diagnosis is a tumor compressing the thoracic spinal cord from the left side (see KCC 7.2; Table 7.4). Some other, less likely possibilities include arthritic bony changes compressing the spinal cord, or multiple sclerosis.

Clinical Course and Neuroimaging

The patient underwent a spine MRI (Figure 7.18), which showed a lesion arising from the dura consistent with a meningioma compressing the spinal cord from the left side at the T9 level. She was started on steroids and admitted to the hospital. Meningiomas are histologically benign (see KCC 5.8) and can often be treated effectively by local resection. She was therefore taken to the operating room, and a T8-T9 posterior laminectomy (see KCC 8.5) was performed. Once the dural sac was entered, a tanish mass was found on the left side and carefully dissected away from the spinal cord and nerve roots. Pathologic analysis was consistent with meningioma. The patient did well postoperatively, regaining pain and temperature sensation on the right, and position and vibration sense on the left, and experiencing improved ambulation and sphincter control.

CASE 7.5 SENSORY LOSS OVER BOTH SHOULDERS

MINICASE

A 45-year-old man was in a motor vehicle accident at age 18 years, sustaining C2 and C3 fractures. These fractures caused quadriparesis that gradually improved. In recent years, however, he has had increasing difficulty walking. He has also developed pain and numbness in the shoulders and arms, more severe on the left side. Exam was notable for increased tone in all extremities and 3/5 to 4/5 power throughout. These exam findings were slightly worse than in previous years. He had brisk reflexes and bilateral upgoing toes. Gait was shuffling and slow. He had decreased pinprick sensation in the left arm from the shoulder down, and over the right shoulder (Figure 7.19). Vibration sense was intact.

localization and differential diagnosis
1. On the basis of the symptoms and signs shown in bold above, where is the lesion?
2. What is the most likely diagnosis? What are some other possibilities?

Discussion
1. The key symptoms and signs in this case are:
   - Decreased pinprick sensation and painful numb paresthesias in bilateral shoulders and in the left arm
   - Weakness, increased tone, and hyperreflexia in all extremities
   - Slow, shuffling gait

This patient has a region of suspended sensory loss to pinprick in a "cape" distribution over both shoulders consistent with a cervical central cord syndrome affecting approximately the C5 dermatomes bilaterally, and C6-T1 on the left (see KCC 7.4; also see Figure 7.4). A cervical central cord lesion could also explain the diffuse weakness with upper motor neuron signs and abnormal gait, since large central cord lesions can cause bilateral corticospinal dysfunction.

The most likely clinical localization is central cord lesion above approximately C5.

2. Given the past history of spinal cord trauma, and delayed onset of a central cord syndrome, the most likely diagnosis is posttraumatic syringomyelia. Syringomyelia is a fluid-filled cavity in the spinal cord, which can occur with spinal cord tumors, with congenital abnormalities of the craniocervical junction, or following trauma. Posttraumatic syringomyelia is a delayed sequel of about 1 of spinal cord injuries, with symptoms beginning from a few months to up to 30 years after the injury (9 years on average). The pathophysiological mechanism is unknown, but patients present with a central cord syndrome that can progressively worsen or spontaneously stabilize. Surgical decompression has been tried, but the long-term benefits are uncertain. Aside from posttraumatic syringomyelia, other, less likely diagnoses in this patient include central cord involvement by multiple sclerosis or an intrinsic spinal cord tumor such as astrocytoma or ependymoma (see Table 7.4).

Clinical Course and Neuroimaging

A cervical spine MRI (Figure 7.20) showed a T1 dark cavity consistent with fluid in the center of the spinal cord representing a syrinx extending from C3 to C4. The patient underwent decompressive surgery and did well in the immediate postoperative period, but was subsequently lost to follow-up.
CASE 7.4 LEFT LEG WEAKNESS AND RIGHT LEG NUMBNESS

Figure 7.18  Intradural Mass Compatible with Meningioma Compressing Left Spinal Cord at T9 MRI scan. (A) Sagittal T1-weighted image with intravenous gadolinium, showing a homogeneous enhancing mass lesion within spinal canal at T9 level. (B) Axial T2-weighted image at T9 level, showing mass located within the dural sac but outside the spinal cord, compressing cord from the left side.

CASE 7.5 SENSORY LOSS OVER BOTH SHOULDERS

Figure 7.20  Fluid-Filled Syrinx in Cervical Spinal Cord at C3, C4 Levels T1-weighted sagittal MRI.

CASE 7.6 BODY TINGLING AND UNSTEADY GAIT

MINICASE
A 37-year-old woman came to the emergency room complaining of tingling and numbness of her arms, legs, and trunk of 1 week's duration. She also complained of clumsiness when walking quickly or up stairs and of decreased dexterity in her hands. She had no other complaints, except for an occasional brief electric-like sensation that she felt beginning in her spine and running down her arms and legs that was brought on by neck movement. Exam was notable for dysesthesia on finger-to-nose testing, which was markedly worse with the eyes closed. Tandem gait was somewhat unstable. A dramatic Romberg sign was present. There was profound loss of vibration sense, absent in the toes, ankles, and knees and reduced in the knuckles. Joint position sense was markedly decreased in the toes and slightly decreased in the fingers. Pinprick and temperature sensation were intact, but testing elicited a girdlelike band of increased sensation extending from the lower chest to the abdomen. The remainder of the exam was normal.

LOCALIZATION AND DIFFERENTIAL DIAGNOSIS
1. On the basis of the symptoms and signs shown in bold above, where is the lesion?
2. What is the most likely diagnosis? What are some other possibilities?

Discussion
1. The key symptoms and signs in this case are:
   • Loss of vibration and joint position sense in the arms and legs bilaterally
   • Clumsy, unsteady gait, with Romberg sign
   • Decreased dexterity, and dysesthesia of the hands especially with eyes closed
   • Paresthesias: Diffuse tingling and numbness, Uhnertite's sign (see KCC 7.1), and girdlelike band of hyperpathia around the abdomen

Loss of vibration and joint position sense in all extremities with no other associated deficits can be caused by a lesion of the posterior columns in the cer-
vical spinal cord (see KCC 7.4) or by a large fiber neuropathy (see Table 7.2; KCC 8.1). The gait unsteadiness and Romberg sign (see KCC 6.5) can also be explained by the proprioceptive deficit, as can impaired coordination of the hands that is worse with the eyes closed. Hemisite's sign (see KCC 7.1) suggests that the lesion is in the cerebral spinal.

The most likely clinical localization is posterior columns of the cervical spinal cord, extending above approximately C5 (arms are involved).

2. Given the relatively rapid onset of deficits localized to central nervous system while1other tracts in a young woman, these symptoms could represent the first episode of multiple sclerosis (see KCC 6.6), presenting as myelitis (see KCC 7.2). Alternatively, it could represent myelitis (see Table 7.4) from another cause, such as infectious or postinfectious myelitis. Other conditions causing prominent posterior column involvement include tabs dorsalis of tertiary syphilis, and vitamin B₆ deficiency (tabs dorsalis actually affects mainly the dorsal roots, with secondary degeneration of the posterior columns).

**Clinical Course and Neuroimaging**

A cervical spine MRI (Figure 7.21) showed increased T2 signal in the cervical posterior cord. Additional history was elicited of a paternal uncle with multiple sclerosis (see KCC 6.6). In addition, the patient had had a respiratory infection during the preceding month. Additional tests were negative, except for two oligoclonal bands (see KCC 6.6) present in the cerebrospinal fluid. The presumed diagnosis was either postinfectious myelitis or myelitis as a precursor to multiple sclerosis. The patient's gait unsteadiness and loss of vibration sense were improved but still present at the time of discharge.

**CASE 7.7 HAND WEAKNESS, PINPRICK SENSORY LEVEL, AND URINARY RETENTION**

MINICASE

A 26-year-old woman was pushing a shopping cart and suddenly developed neck pain, arm pain, and bilateral hand weakness. Shortly afterward she found that she had urinary retention, being unable to void voluntarily, as well as fecal incontinence. She went to the emergency room, where her exam was notable for upper extremities with bilateral decreased tone, 3/5 triceps strength (C7), and 0/5 grip and finger extensions bilaterally (C8-T1), with absent triceps reflexes. In addition, she had a sensory level (see KCC 7.4) to pinprick and temperature sensation as shown in Figure 7.22, with preserved vibration and joint position sense. Rectal tone was absent, and she required urinary catheterization to void.

**LOCALIZATION AND DIFFERENTIAL DIAGNOSIS**

1. Is the bilateral hand weakness caused by an upper motor neuron or a lower motor neuron lesion (see Table 6.4)? A lesion in what location can cause such weakness (see KCC 6.3)?
2. The reduced sensory level to pinprick occurs at what spinal level (see Figure 8.4)?
3. Lesions in what location can cause acute urinary retention and fecal incontinence with absent rectal tone (see KCC 7.5)?

4. On the basis of the symptoms and signs described above, where is the patient's lesion? What are some possible causes?

**Figure 7.22 Pinprick Testing**

(A) Loss of decreased pinprick sensation.

(B) Region of decreased pinprick sensation.

**Discussion**

1. The key symptoms and signs in this case are:
   - Bilateral hand and triceps weakness, hypotonia, and absent triceps reflexes
   - Sensory level to pinprick and temperature
   - Urinary retention, fecal incontinence, and absent rectal tone

   The patient has weakness, absent reflexes, and hypotonia at C7-T1, suggesting either a lower motor neuron lesion, or an acute upper motor neuron lesion (see Table 6.4). Bilateral hand (C8-T1) and triceps (C7) weakness can be caused by bilateral anterior horn cell lesions at this level (see KCC 6.3; Figure 6.18). The reduced sensory level to pinprick occurs at spinal level C7.

   3. Urinary retention caused by flaccid bladder with preserved hypertensive urinary sphincter reflexes can be caused by acute lesions below the pontine micturition center and above the conus medullaris (KCC 7.5). Fecal incontinence with absent rectal tone can be seen in cauda equina or acute spinal cord lesions. Therefore, the most likely localization is an acute spinal cord lesion.

   4. C7-T1 lower motor neuron weakness, a C7 sensory level to pinprick, and urinary retention with fecal incontinence suggest an anterior cord syndrome (see KCC 7.4) at approximately the C7 to T1 levels. Some possible causes would include anterior spinal artery infarct, infectious or inflammatory myelitis, or possibly undiagnosed trauma (see Table 7.4).

**Clinical Course and Neuroimaging**

A cervical spine MRI (Figure 7.23) showed increased T2 signal in the anterior cervical spinal cord extending from C5 to T1. A very extensive workup for inflammatory, infectious, and embolic disorders was carried out but was negative. The patient's strength and urinary retention gradually improved, and on a follow-up examination 1 year later she had recovered 4/5 strength in both hands. She continued, however, to have bothersome neck and shoulder pain requiring treatment in a comprehensive pain management program.

**Additional Cases**

Related cases of somatosensory deficits (Cases 8.1, 8.5-8.7, 8.11, 9.1, 9.3, 9.4, 9.6-9.10, 10.2, 10.8, 10.10, 10.11, 10.13, 12.2, 13.5, 14.1, 14.4, 15.4, 16.6). Other relevant cases can be found using the Case Index.

**Brief Anatomical Study Guide**

1. This chapter completes our discussion of the three most clinically important long tracts in the nervous system: the lateral corticospinal tract (see Chapter 6), the posterior column-medial lemniscal pathway, and the anterolateral pathways (see Table 7.1). The posterior column-medial lemniscal pathway subserves the sensory modalities of proprioception, vibration sense, and fine touch and has its major decussation in the lower medulla. The anterolateral pathways convey the sensory modalities of pain, temperature, and crude touch and have their major decussation in the spinal cord.

2. In the posterior column-medial lemniscal pathway (proprioception, vibration sense, and fine touch), myelinated fibers enter the spinal cord dorsal roots, ascend in the posterior column gracile fasciculus (legs) or cuneate fasciculus (arms) to synapse in the nucleus gracilis or the nucleus cuneatus of the caudal medulla (see Figure 7.1).
CASE 7.6 BODY TINGLING AND UNSTEADY GAIT

Figure 7.21 Region of Hyperintensity in the Posterior (Dorsal) Cervical Spinal Cord at the C3, C4, C5 Levels Compatible with Demyelination T2-weighted Sagittal MRI of the spine.

CASE 7.7 HAND WEAKNESS, PINPRICK SENSORY LEVEL, AND URINARY RETENTION

Figure 7.23 Anterior Spinal Cord Lesion at C5-T1 Levels. T2-weighted MRI. (A) Sagittal image showing lesion in anterior (ventral) spinal cord at the C5-T1 levels. (B) Axial image at the C5 level showing anterior spinal cord lesion.

Brief Anatomical Study Guide (continued)

3. Second-order sensory neurons then cross to the opposite side of the medulla in the internal arcuate fibers to form the medial lemniscus, which ascends to the ventral posterior lateral (VPL) nucleus of the thalamus. Tertiary sensory neurons from the VPL project to the primary somatosensory cortex (Figure 7.1; see also Figure 6.1) via the posterior limb of the internal capsule.

4. The anterolateral system spinothalamic pathway mediates discriminative aspects of pain and temperature sensation, while other anterolateral pathways are more involved in the arousal, affective, and modulatory aspects of pain perception. In the spinothalamic pathway, small myelinated and unmyelinated fibers enter the spinal cord dorsal roots and synapse in the dorsal horn marginal zone and other layers (see Figure 7.2; see also Figure 6.3B).

5. Secondary sensory neurons in the dorsal horn have axons that cross to the opposite side of the spinal cord and then ascend in the ventral lateral part of the spinal cord and brainstem to reach the VPL of the thalamus. Once again, tertiary sensory neurons from the VPL then project to the primary somatosensory cortex (Figure 7.2; see also Figure 6.1) via the posterior limb of the internal capsule.

6. Like the lateral corticospinal tract, the somatosensory pathways are somatotopically organized (see Figure 7.3; see also Figure 6.2). Spinal cord pathways discussed in Chapters 6 and 7 are summarized in Figure 7.4.

7. The thalamus is the major subcortical relay station for signals traveling to all regions of the cortex. In addition to the VPL and VPM, which relays somatosensory information, the thalamus contains many other nuclei (see Table 7.3; Figures 7.6–7.8) that convey sensory, motor, limbic, associative, modulatory, or other signals to different cortical areas. The most clinically important nuclei of the thalamus are shown in bold in Table 7.3.
Brief Anatomical Study Guide (continued)

8. Control of bladder, bowel, and genital function involves afferent sensory information, as well as sympathetic, parasympathetic, and somatic motor pathways (see Table 7.5). Lesions at multiple levels can affect these functions, since they are controlled by local networks of the sacral spinal cord, as well as by descending inputs from the brainstem and forebrain, including the medial frontal lobes (see Figure 7.11).

References

General References


Posterior Columns and Anterolateral Pathways


Thalamus


Sensory Loss in Stroke


Spinal Cord Disorders


Anatomy of Bowel, Bladder, and Sexual Function

CHAPTER 8

Spinal Nerve Roots

A 38-year-old man was thrown violently to the ground by an explosion while he was working on a road. While in the hospital recovering from burn injuries, he noticed mild back pain with a numb "pins and needles" sensation running down his left leg into the sole and pinky toe of his left foot. He was unable to stand on his toes with his left foot, and his left Achilles tendon reflex was absent. This patient's symptoms illustrate the kind of sensory and motor deficits associated with spinal nerve root damage. In this chapter, we will learn about the anatomical course of exiting spinal nerve roots, nerve root functions, and the clinical consequences of injury to these structures.
ANATOMICAL AND CLINICAL REVIEW

In the preceding two chapters, we studied the three main motor and sensory pathways in the central nervous system (see Table 7.1). We will now follow these somatic sensory and somatic motor pathways into the peripheral nervous system (see Figure 8.1) to explore the anatomy and clinical disorders of the peripheral nerves. In this chapter, we will concentrate on the anatomy of spinal nerve roots and their relation to the vertebral structures, regional innervation, and some clinical disorders. Peripheral autonomic functions were already discussed in Chapter 6. In Chapter 9, we will follow the nerves further into the periphery, and we will discuss the brachial and lumbosacral plexuses and peripheral nerve branches.

Segmental Organization of the Nervous System

Like their invertebrate ancestors, humans retain some degree of segmental organization, especially in the spinal cord. There are seven cervical (C1-C8), twelve thoracic (T1-T12), five lumbar (L1-L5), five sacral (S1-S5), and one coccygeal (C0) spinal segments (Figure 8.1). During development, the bones of the spine continue to grow after the spinal cord has reached its final size. Therefore, in adults, the spinal cord normally ends with the conus medullaris at the level of the L1 or L2 vertebral bodies. The nerve roots (see Figure 8.1) travel downward to their exit points at the appropriate level. Below the L1 or L2 vertebral bodies, the spinal canal contains nerve roots with no spinal cord, forming the cauda equina, meaning "horse's tail" (see Figures 8.1A, 8.3C). The conus medullaris tapers into the filum terminale, a thin strand of connective tissue running in the center of the cauda equina. The roots of the cauda equina are organized such that the most caudally located roots are from the most caudal segments of the spinal cord (see Figure 8.3C).

Figure 8.1 Spinal Cord and Nerve Roots in Relation to the Vertebral Spinal Canal (A) Sagittal view. The cervical (C5-T1) and lumbosacral (L1-S3) spinal cord enlargements correspond to the arms and legs, respectively. At the level of the L1 and L2 vertebral bodies, the spinal cord ends, and nerve roots continue as the cauda equina. (B) Motor (ventral) roots and sensory (dorsal) roots join at each segment to form nerve roots.

Nerve Roots in Relation to Vertebral Bones, Discs, and Ligaments

The vertebral bodies function both as the central mechanical support for the body and as protection for the spinal cord. Each vertebral body has a sturdy cylindrical vertebral body located anteriorly (Figure 8.2A,B). The vertebral bodies are separated from each other by connective tissue intervertebral discs consisting of a central nucleus pulposus surrounded by a capsule called the anulus fibrosus (see Figure 8.2C). Posteriorly, the neural elements are surrounded by an arch of bone formed by the pedicles, transverse processes, laminae, and spinous processes (see Figure 8.2B). The superior and inferior articular processes or facet joints form additional points of mechanical contact between adjacent vertebrae (see Figure 8.2A,B).

The spinal cord runs through the spinal canal (vertebral foramen) and is surrounded by the dura mater, arachnoid, and dura mater (see Figure 8.2). As the dura exits the skull at the foramen magnum, the inner layer continues and the outer layer becomes indistinguishable from peritoneum (see Figure 5.10). Unlike the cranial cavity, there is a layer of epidural fat between the dura and the peritoneum in the spinal canal (see Figure 8.2C,D), which is a useful landmark on MRI scans. In addition, there is a valves-like meshwork of epidural veins called Batson’s plexus that is thought to play a role in the spread of metastatic cancers in the epidural space. The elastic ligamentum flavum is particularly prominent in cervical and lumbar regions and can sometimes become hyper trophyed and constrict spinal cord or nerve root compression.

The nerve roots exit the spinal canal via the neural (intervertebral) foramina (see Figures 8.2A,D, 8.3). Disc herniations (see KCC 8.3) are more common at the cervical and lumbosacral levels. An understanding of the anatomy of the nerve roots and discs should make clear the following important rule of thumb: For both cervical and lumbosacral disc herniations, the nerve root involved usually corresponds to the lower of the adjacent two vertebrae. For example, a C5-C6 disc herniation usually produces a C6 radiculopathy, an L5-S1 disc usually produces an SI radiculopathy, and so on. The explanation for this rule is different for cervical versus lumbosacral discs, as we will now discuss.

Thoracic, lumbar, and sacral nerve roots exit below the corresponding numbered vertebral bone (see Figure 8.1). Cervical nerve roots, on the other hand, exit above the corresponding numbered vertebral bone, except for C1, which has no corresponding vertebral bone and exits between C7 and T1. Cervical nerve roots may have a fairly horizontal course as they emerge from the dorsal thecal sac near the intervertebral disc and exit through the intervertebral foramen (see Figure 8.3B). Cervical discs are usually constrained by the pos-
Figure 8.3 Relation of Cervical and Lumbar Spinal Nerve Roots to Intervertebral Discs (A) Cervical disc herniation usually compresses the nerve root exiting at that level. This corresponds to the number of the lower vertebral bone at that interspace. (B) Lumbar disc herniation usually spares the nerve root exiting at that level, and compresses the nerve root exiting at the next level down. However, this again corresponds to the number of the lower vertebral bone at the level of the herniation. (C) Far lateral lumbar disc herniation affects the nerve root exiting at that level, and central lumbar disc herniation can cause cauda equina syndrome (see K.C. 8.4).

Figure 8.3(C). In addition, a central disc herniation at the level of the cauda equina can impinge on nerve roots lower than the level of herniation, or it can compress the spinal cord if it occurs above L1.

Dermatomes and Myotomes

The sensory region of skin innervated by a nerve root is called a dermatome (Figure 8.4). Interestingly, dermatome maps vary somewhat from one text to the next. This variation is likely due to differences in both the methods of testing and individual patients studied. Nevertheless, some familiarity with the usual locations of dermatomes can be very helpful clinically for localizing lesions.

Sensation for the face is provided by the trigeminal nerve (see Figure 12.7), while most of the remainder of the head is supplied by C2 (via the greater and lesser occipital nerves). The rami are usually at the T4 level, while the umbilicus is at approximately T10. When testing sensation on the chest or back, remember that there is normally a skip between C4 and T2, with C5 through T4 represented mainly on the upper extremities (see Figure 8.4B). C5 is represented in the shoulder, C6 in the lateral arm and first two digits, C7 in the middle digit, and C8 in the fourth and fifth digits. The L4 representation extends over the anteromedial shin, L5 extends down the anterolateral shin and dorsum of the foot to the big toe, and S1 is in the small toe, lateral foot, sole, and calf. S2, S3, and S4 innervate the perineal area in a saddle-like distribution. Note that there is considerable overlap between adjacent dermatomes.
TABLE 8.1 Summary of Peripheral Nerves, Muscles, and Nerve Roots in the Upper and Lower Extremities

<table>
<thead>
<tr>
<th>NERVE</th>
<th>MUSCLE(S)</th>
<th>FUNCTION OF THE MUSCLE(S)</th>
<th>NERVE ROOTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical accessory nerve</td>
<td>Trapezius</td>
<td>Elevates shoulder/arm and fixes scapula</td>
<td>C2, C3, C4</td>
</tr>
<tr>
<td>Phrenic nerve</td>
<td>Diaphragm</td>
<td>Inspiration</td>
<td>C3, C4, C5</td>
</tr>
<tr>
<td>Dorsal scapular nerve</td>
<td>Rhomboids</td>
<td>Draws scapula up and in</td>
<td>C4, C5, C6</td>
</tr>
<tr>
<td>Long (Bell's) phrenic nerve</td>
<td>Serratus anterior</td>
<td>Elevates scapula</td>
<td>C3, C4, C5</td>
</tr>
<tr>
<td>Lateral pectoral nerve</td>
<td>Pectoralis major (clavicular head)</td>
<td>Pulls shoulder forward</td>
<td>C5, C6</td>
</tr>
<tr>
<td>Medial pectoral nerve</td>
<td>Pectoralis major (internal head)</td>
<td>Adducts and medially rotates arm</td>
<td>C6, C7, C8, T1</td>
</tr>
<tr>
<td></td>
<td>Pectoralis minor</td>
<td>Depresses scapula and pulls shoulder forward</td>
<td>C6, C7, C8</td>
</tr>
<tr>
<td>Serricostal nerve</td>
<td>Supraspinatus</td>
<td>Abducts humerus from 0 to 15°</td>
<td>C5, C6</td>
</tr>
<tr>
<td>Subscapular nerve</td>
<td>Supraspinatus</td>
<td>Internally rotates humerus</td>
<td>C5, C6</td>
</tr>
<tr>
<td>Subscapularis</td>
<td>Subscapularis</td>
<td>Internally rotates humerus</td>
<td>C6, C6</td>
</tr>
<tr>
<td>Thyroacromial nerve</td>
<td>Clavicularus</td>
<td>Adducts and internally rotates humerus</td>
<td>C6, C5, C6</td>
</tr>
<tr>
<td>Axillary nerve</td>
<td>Clavicularis</td>
<td>Adducts and internally rotates humerus</td>
<td>C6, C5, C6</td>
</tr>
<tr>
<td>Deltoid</td>
<td>Clavicularis</td>
<td>Adducts humerus beyond 15°</td>
<td>C6, C6</td>
</tr>
<tr>
<td>Musculocutaneous nerve</td>
<td>Biceps brachial</td>
<td>Flexes and supinates arm and forearm</td>
<td>C6, C7</td>
</tr>
<tr>
<td></td>
<td>Brachialis</td>
<td>Flexes forearm</td>
<td>C5, C6</td>
</tr>
<tr>
<td>Radial nerve</td>
<td>Coracobrachialis</td>
<td>Flexes and adducts arm</td>
<td>C6, C7</td>
</tr>
<tr>
<td></td>
<td>Teres major</td>
<td>Extends forearm</td>
<td>C6, C7, C8</td>
</tr>
<tr>
<td></td>
<td>Brachialis</td>
<td>Extends forearm</td>
<td>C6, C7, C8</td>
</tr>
<tr>
<td>Posterior interosseus nerve</td>
<td>Extensor carpi radialis (longus and brevis)</td>
<td>Extends wrist, abducts hand</td>
<td>C6, C8</td>
</tr>
<tr>
<td>(Branch of radial nerve)</td>
<td>Supinator</td>
<td>Supinates forearm</td>
<td>C6, C7</td>
</tr>
<tr>
<td></td>
<td>Extensor carpi ulnaris</td>
<td>Extends wrist, adds hand</td>
<td>C7, C8</td>
</tr>
<tr>
<td></td>
<td>Extensor digitorum communis</td>
<td>Extends fingers (test at metacarpophalangeal joints)</td>
<td>C7, C8</td>
</tr>
<tr>
<td></td>
<td>Extensor digitorum quinti</td>
<td>Extends little finger</td>
<td>C7, C8</td>
</tr>
<tr>
<td></td>
<td>Abductor pollicis longus</td>
<td>Absducts thumb in plane of palm</td>
<td>C7, C8</td>
</tr>
<tr>
<td></td>
<td>Extensor pollicis (longus and brevis)</td>
<td>Absducts thumb in plane of palm</td>
<td>C7, C8</td>
</tr>
<tr>
<td></td>
<td>Extensor indicis proprius</td>
<td>Extends index finger</td>
<td>C7, C8</td>
</tr>
<tr>
<td></td>
<td>Pronator teres</td>
<td>Pronates and flexes forearm</td>
<td>C6, C7</td>
</tr>
<tr>
<td></td>
<td>Flexor carpi radialis</td>
<td>Flexes wrist, abducts hand</td>
<td>C6, C7</td>
</tr>
<tr>
<td></td>
<td>Palmaris longus</td>
<td>Flexes wrist</td>
<td>C7, C8, T1</td>
</tr>
<tr>
<td></td>
<td>Flexor digitorum superficialis</td>
<td>Flexes metacarpophalangeal joints</td>
<td>C7, C8, T1</td>
</tr>
<tr>
<td></td>
<td>Lumbricales (LII)</td>
<td>For second and third digits, flex metacarpophalangeal joints, extended other joints</td>
<td>C8, T1</td>
</tr>
<tr>
<td></td>
<td>Opponens pollicis</td>
<td>Flexes, opposes thumb</td>
<td>C8, T1</td>
</tr>
<tr>
<td></td>
<td>Abductor pollicis brevis</td>
<td>Absducts thumb perpendicular to plane of palm</td>
<td>C8, T1</td>
</tr>
<tr>
<td></td>
<td>Flexor pollicis brevis (superficialis)</td>
<td>Absducts first phalan of thumb</td>
<td>C8, T1</td>
</tr>
</tbody>
</table>

Figure 8.4 Dermatomes

so lesions of a single nerve root ordinarily cause a decrease but not a complete loss of sensation in a given dermatome. There may be less overlap for smaller fibers, so pinprick is a more sensitive test for dermatomal sensory loss than touch.

The muscles innervated by a single nerve root constitute a myotome. The segmental innervation of the muscles is summarized in Table 8.1. This table also includes a summary of nerve roots supplying each peripheral nerve, and the main functions of each muscle (see Chapter 9 for further details). Strength testing and reflexes for individual muscles, nerves, and nerve roots is discussed in Chapter 3 (see Tables 3.4-3.7) and is demonstrated on neuroexam.com Videos 54-60.
<table>
<thead>
<tr>
<th>NERVE</th>
<th>MUSCLE(S)</th>
<th>FUNCTION OF THE MUSCLE(S)</th>
<th>NERVE ROOTS*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior interosseous nerve (branch of median nerve)</td>
<td>Flexor digitorum profundus (digits 2, 3)</td>
<td>Flexes second and third fingers (best tested in distal phalanges)</td>
<td>C7, C8</td>
</tr>
<tr>
<td></td>
<td>Flexor pollicis longus</td>
<td>Flexes distal phalanges of thumb</td>
<td>C7, C8</td>
</tr>
<tr>
<td></td>
<td>Pronator quadratus</td>
<td>Promotes forearm</td>
<td>C7, C8, T1</td>
</tr>
<tr>
<td>Ulnar nerve</td>
<td>Flexor carpi ulnaris</td>
<td>Flexes wrist, addsucts hand</td>
<td>C7, C8, T1</td>
</tr>
<tr>
<td></td>
<td>Flexor digitorum profundus (digits 4, 5)</td>
<td>Flexes fourth and fifth fingers (best tested in distal phalanges)</td>
<td>C7, C8</td>
</tr>
<tr>
<td></td>
<td>Lumbricals (III, IV)</td>
<td>For fourth and fifth digits, flexes metacarpophalangeal joints, extend other joints</td>
<td>C8, T1</td>
</tr>
<tr>
<td>Palmar interossei</td>
<td>Adductor digiti, flex metacarpophalangeal joints, extend other joints</td>
<td>Adductor digiti, flex metacarpophalangeal joints, extend other joints</td>
<td>C8, T1</td>
</tr>
<tr>
<td>Dorsal interossei</td>
<td>Abductor digiti, flex metacarpophalangeal joints, extend other joints</td>
<td>Flexes and addsucts thumb</td>
<td>C8, T1</td>
</tr>
<tr>
<td>Flexor pollicis brevis (deep head)</td>
<td>Adductor pollicis</td>
<td>Adductor pollicis</td>
<td>C8, T1</td>
</tr>
<tr>
<td></td>
<td>Opponens digiti minimi</td>
<td>Internally rotates fifth finger</td>
<td>C8, T1</td>
</tr>
<tr>
<td></td>
<td>Abductor digiti minimi</td>
<td>Abducts fifth finger</td>
<td>C8, T1</td>
</tr>
<tr>
<td></td>
<td>Flexor digiti minimi</td>
<td>Flexes fifth finger at metacarpophalangeal joint</td>
<td>C8, T1</td>
</tr>
<tr>
<td>Obturator nerve</td>
<td>Obturator externus</td>
<td>Adducts and outwardly rotates leg</td>
<td>L2, L3, L4</td>
</tr>
<tr>
<td></td>
<td>Adductor longus</td>
<td>Adducts thigh</td>
<td>L2, L3, L4</td>
</tr>
<tr>
<td></td>
<td>Adductor magnus</td>
<td>Adducts thigh</td>
<td>L2, L3, L4</td>
</tr>
<tr>
<td></td>
<td>Adductor brevis</td>
<td>Adducts thigh</td>
<td>L2, L3, L4</td>
</tr>
<tr>
<td></td>
<td>Gracilis</td>
<td>Adducts thigh</td>
<td>L2, L3, L4</td>
</tr>
<tr>
<td>Femoral nerve</td>
<td>Iliopsoas muscle</td>
<td>Flexes legs at hip</td>
<td>L1, L2, L3</td>
</tr>
<tr>
<td></td>
<td>Psoas</td>
<td>Flexes legs at hip</td>
<td>L2, L3, L4</td>
</tr>
<tr>
<td>Quadriceps femoris</td>
<td>Rectus femoris</td>
<td>Extends leg at knee, flexes hip</td>
<td>L2, L3, L4</td>
</tr>
<tr>
<td></td>
<td>Vastus lateralis</td>
<td>Extends leg at knee</td>
<td>L2, L3, L4</td>
</tr>
<tr>
<td></td>
<td>Vastus intermedius</td>
<td>Extends leg at knee</td>
<td>L2, L3, L4</td>
</tr>
<tr>
<td></td>
<td>Vastus medialis</td>
<td>Extends leg at knee</td>
<td>L2, L3, L4</td>
</tr>
<tr>
<td></td>
<td>Pectineus</td>
<td>Adducts thigh</td>
<td>L2, L3, L4</td>
</tr>
<tr>
<td></td>
<td>Sartorius</td>
<td>Inwardly rotates leg, flexes hip and knee</td>
<td>L2, L3, L4</td>
</tr>
<tr>
<td>Sciatic nerve</td>
<td>Adductor magnus</td>
<td>Adducts thigh</td>
<td>L4, L5, S1</td>
</tr>
<tr>
<td>Hamstring muscles</td>
<td>Semitendinosus</td>
<td>Flexes knee, medially rotates thigh, extends hip</td>
<td>L5, S1, S2</td>
</tr>
<tr>
<td></td>
<td>Semimembranosus</td>
<td>Flexes knee, medially rotates thigh, extends hip</td>
<td>L5, S1, S2</td>
</tr>
<tr>
<td>Tibial nerve (branch of sciatic nerve)</td>
<td>Biceps femoris</td>
<td>Flexes knee, extends hip</td>
<td>L5, S1, S2</td>
</tr>
<tr>
<td></td>
<td>Gastrocnemius</td>
<td>Plantar flexes foot</td>
<td>S1, S2</td>
</tr>
<tr>
<td></td>
<td>Soleus</td>
<td>Plantar flexes foot</td>
<td>S1, S2</td>
</tr>
<tr>
<td></td>
<td>Plantar flexes foot</td>
<td>L4, L5, S1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tibialis posterior</td>
<td>Plantar flexes and inverts foot</td>
<td>L4, L5</td>
</tr>
<tr>
<td></td>
<td>Plantar</td>
<td>Sperns, brings together, flexes proximal phalanges</td>
<td>L4, L5, S1</td>
</tr>
</tbody>
</table>


Author indicates the most important nerve roots, where applicable.

KEY CLINICAL CONCEPT DISORDERS OF NERVE, MUSCLE, AND NEUROMUSCULAR JUNCTION

A variety of disorders can affect the peripheral nervous system at multiple levels. This text focuses on neuroanatomical localization, so in this chapter and in Chapter 9 we concentrate mainly on localized disorders of the spinal nerve roots, nerve plexuses, or individual nerve branches. Here, we will place these disorders in the wider context of peripheral nervous system disease, so that a more complete differential diagnosis can be formulated.

Disorders of the peripheral nervous system can often be distinguished from central nervous system dysfunction by the anatomical pattern of sensory or motor deficits (see KCC 6.3, 7.3; Table 8.1). In addition, presence of lower motor neuron signs (see KCC 6.1) such as atrophy, fasciculations, or hyporeflexia suggests peripheral nervous system dysfunction, as do paraspinal signs in a peripheral nerve distribution (see KCC 7.1). When the location of lesions in the central versus peripheral nervous system remains uncertain based on the history and physical examination, diagnostic tests such as neuroimaging studies (Chapter 4), blood tests, CSF analysis, and electrophysiological studies (see KCC 9.2) can be helpful. Disorders of the peripheral nervous system can be produced by a large number of mechanical, toxic, metabolic, infectious, autoimmune, inflammatory, degenerative, and congenital causes that are beyond the scope of this text (see references for additional details).

We will now briefly discuss several common disorders of nerve, neuromuscular junction, and muscle.

**Common Neuropathies**

Neuropathy is a general term meaning nerve disorder. The site of pathology can be in the roots, myelin, or both, and can affect large-diameter fibers, small-diameter fibers, or both. Usually, neuropathies affect both sensory and motor fibers in the nerve, although one or the other may be preferentially involved. Damage can be reversible or permanent. The location of neuropathy...
can be focal (mononeuropathy), multifocal (mononeuropathy multiplex), or generalized (polyneuropathy). Neuropathy affecting the spinal nerve root is called radiculopathy, which will discuss in greater detail in KCC 8.3. Motor neuron disorders (see KCC 6.7) can also cause lower motor neuron-type weakness, but do not cause sensory involvement as is usually seen in neuropathies.

Important causes of neuropathy include diabetes; mechanical causes; infections disorders such as Lyme disease, HIV, CMV, varicella-zoster virus, or hepatitis B (see KCC 5.9); toxic; malnutrition; and immune disorders such as Guillain–Barré syndrome, among others.

**Diabetic neuropathy** is produced by a number of mechanisms, including compromise of the microvascular blood supply of the peripheral nerves. The most common pattern of diabetic neuropathy is distal symmetrical polyneuropathy, which results in a characteristic glove and stocking pattern of sensory loss (see Figure 7.9D). Mononeuropathies are also relatively common in diabetes. Acute diabetic mononeuropathy can affect any cranial or spinal nerve, but is most common in CN III and the femoral and sciatic nerves. Onset is usually fairly sudden, and sensorimotor deficits in the nerve distribution may be accompanied by painful paresthesias. There is often partial or complete recovery over the course of weeks to months after onset.

Mechanical causes of nerve injury include extrinsic compression, traction, laceration, or entrapment by intrinsic structures such as bone or connective tissue. Mild mechanical disruption of a nerve causes neurapraxia in which there is temporary impairment of nerve conduction, which usually resolves within hours to weeks. More severe injury can interrupt the axons, leading to Wallerian degeneration (degeneration of axons and myelin) distal to the site of injury. Axonal damage to the distal extremities is often referred to as proximal or the complex regional pain syndrome causalgia (also called reflex sympathetic dystrophy or sympathetically mediated pain). In some instances, when peripheral nerves are severed or otherwise disrupted, they can be reinnervated surgically. In addition, some entrapment syndromes may be amenable to surgical decompression. Painful paresthesias associated with neuropathies of all causes are often treated with medications such as tricyclic antidepressants and anticonvulsants. Common mechanical neuropathies are discussed further in KCC 8.5 and 9.1.

**Guillain–Barré syndrome**, also known as acute inflammatory demyelinating polyneuropathy (AIDP), is an important form of neuropathy caused by immune-mediated demyelination of peripheral nerves. Onset typically occurs 1 to 2 weeks following a viral illness, Campylobacter jejuni enteritis, HIV infection, or other infections. Presentation is with progressive weakness, areflexia, and tingling paresthesias of the hands and feet with motor involvement typically much more severe than sensory involvement. Symptoms usually reach their worst point 1 to 3 weeks after onset; recovery occurs over several months. Diagnosis is based on typical clinical presentation, CSF demonstrating elevated protein without a significantly elevated white blood cell count, and EMG/nerve conduction studies compatible with demyelination (see KCC 9.2). In recovery, patients are typically treated with plasmapheresis or intravenous immunoglobulin therapy. In severe cases, patients require intubation and mechanical ventilation. Autonomic dysfunctions can be prominent in some cases, requiring careful monitoring. With good supportive care, the majority of patients experience complete recovery, although about 20% of patients have some residual weakness 1 year after onset.

**Common Disorders of the Neuromuscular Junction**

Impaired neuromuscular transmission can lead to motor weakness without sensory deficits. Causes include myasthenia gravis, neuromuscular blocking agents and other drugs, Lambert–Eaton myasthenic syndrome (usually paraneoplastic), and botulism.

**Myasthenia gravis** is an immune-mediated disorder in which there are circulating antibodies against the postsynaptic nicotinic acetylcholine receptors of the neuromuscular junction of skeletal muscle cells. The disorder can sometimes be accompanied by other autoimmune phenomena such as hyperthyroidism, lupus, rheumatoid arthritis, and vitiligo. Myasthenia gravis has a bimodal age-related onset, with onset in the second or third decades more common in women and onset in the sixth or seventh decades more common in men. The prevalence is 50 to 125 cases per million. Clinical features include generalized symmetrical weakness, especially of proximal limb muscles, neck muscles, the diaphragm, and eye muscles. Involvement of bulbar muscles can cause dysphonia, a nasal-sounding voice, and dysphagia (see KCC 12.8). Reflexes and sensory exam are normal. Characteristically, weakness becomes more severe with repeated use of a muscle, or during the course of the day. About 15% of cases have weakness involving only the extracocular muscles and eyelids, a condition called ocular myasthenia.

Diagnosis of myasthenia gravis is based on clinical features, and several diagnostic tests, including the Tensilon test, repetitive nerve stimulation, measurement of anti-acetylcholine antibodies, single fiber EMG, and chest CT or MRI. In the Tension test, a short-acting acetylcholinesterase inhibitor (edrophonium) is administered while observing clinical effects on involved muscles. This test should be performed where cardiac monitoring is available, as edrophonium can cause cardiac bradycardia or tachyarrhythmias. The patient is then given an intravenous test dose of 1 to 2 mg of edrophonium, an acetylcholinesterase inhibitor with onset of action within about 30 seconds and duration of about 5 minutes. If there are no adverse effects, the patient is then given 5 mg of edrophonium while carefully testing use or several weak muscles for transient improvement. In equivocal cases, intermediate-acting acetylcholinesterase inhibitors such as neostigmine can be useful. Compound motor action potential measurement (see KCC 9.2) associated with repetitive nerve stimulation at a rate of 3 per second often produces a characteristic decrement in amplitude in myasthenia and is considered positive if there is a decrement greater than 10%. Single-fiber EMG is more sensitive (about 90%), but is not specific for myasthenia.

**Anti-acetylcholine receptor antibodies** are positive in about 85% of cases, but in only about 50% of cases of ocular myasthenia. About 12% of patients with myasthenia have thymomas, a tumor of the thymus gland, and many others have thymic hyperplasia, so CT or MRI of the chest should be performed. In addition, testing for associated conditions such as thyroid disease and other immune disorders is appropriate.

Treatment of myasthenia is with anticholinesterase medications and immunotherapy. **Pyridostigmine** (Mestinon) is a long-acting cholinesterase inhibitor, with onset of action beginning about 30 minutes after oral administration, and duration of about 2 hours. Patients' doses are individually titrated, but should not ordinarily exceed 120 mg every 3 hours, since excess anticholinesterase can actually worsen weakness. Most patients in the age range of adolescence to 60 years are treated surgically with thymectomy (whether a thymoma is present or not), as this usually leads to improvement by unclear mechanisms, likely involving a reduced autoimmune response. Use of thymectomy outside this age range, or in patients with ocular myasthenia is more controversial, but has been used in some cases as well. Thymectomy should be
TABLE 8.4 Common Causes of Radiculopathy

<table>
<thead>
<tr>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disc herniation</td>
</tr>
<tr>
<td>Osteophytes</td>
</tr>
<tr>
<td>Spinal stenosis</td>
</tr>
<tr>
<td>Trauma</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>Epidermal abscess</td>
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<tr>
<td>Epidermal metastases</td>
</tr>
<tr>
<td>Mesial gangliosclerosis</td>
</tr>
<tr>
<td>Cancer (e.g., breast, lung, bowel)</td>
</tr>
<tr>
<td>Guillain-Barré syndrome</td>
</tr>
<tr>
<td>Herpes zoster (shingles)</td>
</tr>
<tr>
<td>Lyme disease</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
</tr>
<tr>
<td>Idiopathic neuritis</td>
</tr>
</tbody>
</table>

The straight-leg raising test can be helpful in the diagnosis of mechanical nerve root compression in the lumbar region (Figure 8.5A). In this test, the patient lies supine, and the examiner slowly elevates the patient's leg at an increasing angle to the table while keeping the leg straight at the knee joint. This provokes traction on the nerve roots, and the test is considered positive if it reproduces the patient's typical radicular pain and paresthesias. A response of less than 10° or more than 60° of straight-leg raising is probably not caused by root compression. In the crossed straight-leg raising test, elevating the asymptomatic leg causes typical symptoms in the symptomatic leg. The crossed straight-leg raising test has a specificity of 90% for lumbar nerve root compression. Radicular symptoms may also be increased by the Valsalva maneuver (e.g., coughing, straining, sneezing). In cervical radiculopathy, radicular symptoms may be increased by flexing or turning of the head toward the affected side, likely because of increased narrowing of the intervertebral foramina by these movements. Pain on percussion of the spine (Figure 8.5B) may indicate metastatic disease, epidural abscess, osteomyelitis, or other disorders of the vertebral bones, although this sign is often absent in these conditions.

Back pain that is persistent, progressively worsens, or occurs in an older individual, in a patient with prior history of neoplastic disease, or where there is a possibility of epidural abscess, should always be evaluated with a neuroimaging study. An MRI of the spine is usually the test of choice (see Chapter 4). It is important, however, to carefully interpret the MRI in the context of the history and physical examination, since incidental disc bulges and other degenerative changes of the spine are common findings even in individuals without symptoms. In some cases, CT myelography (Chapter 4) can help to define abnormalities that are not well visualized on MRI. When diagnostic uncertainty remains, EMG and nerve conduction studies (see KCC9.2) may be helpful.

Other causes of radiculopathy are listed in Table 8.4. Spinal stenosis, meaning "narrowing of the spinal canal," can arise congenitally, or gradually as a result of degenerative processes, or by a combination of both factors. Lumbosacral stenosis may result in neurogenic claudication, in which bilateral leg pain and weakness occur with ambulation. Cervical stenosis can cause a mixture of radicular and long tract signs. Trauma produces radiculopathy through compression, traction, or avulsion of nerve roots off the spinal cord. Diabetic neuropathy can occasionally involve nerve roots, particularly at thoracic levels producing abdominal pain. Epidural metastases most commonly occur in the vertebral bodies, but they can extend laterally to compress nerve roots. Syphilis of cancer cells such as adenocarcinoma, lymphoma, medulloblastoma, and glioblastoma within the cerebrospinal fluid can involve the nerve roots. Many causes of radiculopathy are similar to those causing neuropathy in general (see Chapter 8.1) but may have an increased tendency to involve the nerve roots. For example, some autoimmune disorders, such as Guillain-Barré syndrome, have a predilection for nerve roots. Reactivation of latent varicella-zoster virus (chickenpox virus) in dorsal root ganglia produces the painful blistersing lesions of herpes zoster or "shingles." These occur in a dermatomal distribution, associated with sensory, and less commonly motor, loss in the affected nerve roots. Herpes zoster is most common in thoracic dermatomes (but can occur anywhere). Treatment with oral antiviral agents such as acyclovir or famciclovir can shorten the duration of blistersing lesions. Severe pain can persist after the blistering eruption, referred to as postherpetic neuralgia. When herpes zoster occurs in the ophthalmic division of the trigeminal nerve, it can threaten vision, and it is usually treated with intravenous acyclovir. Lyme disease, a tick-borne illness caused by the spirochete Borrelia burgdorferi, can cause radiculopathies. Cytomegalovirus polyradiculopathy can be seen in patients with HIV infection, most commonly in the lumbar spinal roots. A mild form of radiculopathy can also be caused by HIV itself. Dumbbell-shaped nerve sheath tumors, such as schwannomas and neurofibromas, can occasionally occur in a neural foramen, producing radiculopathy.

Simplification: Three Nerve Roots to Remember in the Arm

For practical purposes, the most clinically important nerve roots in the arm are C5, C6, and C7. It is important to be familiar with the reflexes and the motor and sensory functions associated with these nerve roots, as summarized in Figure 8.6 and Table 8.5. When examining patients, it is helpful to have remembered at least one muscle that gets its major innervation from each of these three nerve roots. In addition to the nerve roots listed in Table 8.5, it is also worth knowing that C8 radiculopathy accounts for about 6% of cervical radiculopathies, is usually caused by C7-T1 disc herniation, and is associated with weakness of the intrinsic hand muscles and decreased sensation in the fourth and fifth digits and the medial forearm. About 20% of all cervical radiculopathies involve two or more cervical levels.

Simplification: Three Nerve Roots to Remember in the Leg

The most clinically important nerve roots in the leg are L4, L5, and S1. Reflexes and the motor and sensory functions associated with L4, L5, and S1 are summarized in Figure 8.7 and Table 8.6. As with the cervical nerve roots, it is helpful, when examining patients, to have remembered at least one muscle that gets its major innervation from each of these nerve roots.
TABLE 8.5 Three Important Nerve Roots in the Arm

<table>
<thead>
<tr>
<th>NERVE ROOT</th>
<th>MAIN WEAKNESSa</th>
<th>REFLEX DECREASEDb</th>
<th>REGION OF SENSORY ABNORMALITYb</th>
<th>USUAL DISC INVOLVED</th>
<th>APPROXIMATE PERCENTAGE OF CERVICAL RADICULOPATHIES</th>
</tr>
</thead>
<tbody>
<tr>
<td>C5</td>
<td>Deltoid, infraspinatus, biceps</td>
<td>Biceps, pectoralis</td>
<td>Shoulder, upper arm</td>
<td>C4-C5</td>
<td>7%</td>
</tr>
<tr>
<td>C6</td>
<td>Wrist extension, biceps</td>
<td>Biceps, brachioradialis</td>
<td>First and second fingers, forearm</td>
<td>C5-C6</td>
<td>18%</td>
</tr>
<tr>
<td>C7</td>
<td>Triceps</td>
<td>Triceps</td>
<td>Third finger</td>
<td>C6-C7</td>
<td>48%</td>
</tr>
</tbody>
</table>

aSee Figure 8.6.
bSee Figure 8.6.

KEY CLINICAL CONCEPT

CAUDA EQUINA SYNDROME

Impaired function of multiple nerve roots L1, L2 is called cauda equina syndrome. If the deficits begin at the L2 roots and below, there may be no obvious leg weakness. Sensory loss in an S2 to S5 distribution (see Figure 8.4) is sometimes called saddle anesthesia. Involvement of the S2, S3, and S4 nerve roots can produce a distended atonic bladder with urinary retention or overflow incontinence. In cauda equina syndrome, continuous nerve root pain passes just below the intervertebral foramen. An anterior approach can also be made in the cervical spine, in which an incision is made in the anterior neck and the dissection is carried down to the vertebral bodies. The anterior approach provides direct access to the discs without traversing the spinal canal, and also allows mechanical fusion of adjacent vertebral bodies, usually using a bone graft.

CLINICAL CASES

CASE 8.1 UNILATERAL NECK PAIN AND TINGLING NUMBNESS IN THE THUMB AND INDEX FINGER

CHIEF COMPLAINT

A 30-year-old man came to his physician's office because of 4 weeks of left-sided neck and arm pain and tingling.

HISTORY

Previous history was unremarkable except for minor sports injuries. These included a skiing accident 2 years ago in which he struck the left side of his neck and had local pain lasting about 3 weeks, and a backward fall during a softball game 1 year ago in which he struck his occiput without loss of consciousness but had some confusion for about 30 minutes. Four weeks ago he awoke one morning with severe left neck and shoulder pain with tingling radiating down into the first and second fingers of the left hand (thumb and index finger). The symptoms improved slightly after a few days but then recurred about 4 days ago, making sleep difficult. Over the counter pain medications helped but did not eliminate the pain. He did not notice any weakness, numbness, change in bowel or bladder function (see KCC 7.5), or hermit's sign (see KCC 7.1). PHYSICAL EXAMINATION


Neurologic exam:
OCULAR NERVES: Intact.
MOTOR: Normal tone. S5 power throughout, except for 4/5 power in the left biceps, brachioradialis, and wrist extensors.
REFLEXES:
2 0 6 9
COORDINATION: Normal on finger-to-nose and heel-to-toe testing.
SENSORY: Intact light touch, vibration, and joint position sense. Mildly decreased pinprick sensation in the left first and second fingers. Two-point discrimination 4-5 mm in the left index finger, compared to 3 mm in the right index finger (using a ruler and the ends of a paper clip).
LOCALIZATION AND DIFFERENTIAL DIAGNOSIS

On the basis of the symptoms and signs shown in bold above, where is the lesion? What is the most likely diagnosis?
CASE 8.2 UNILATERAL OCCIPITAL AND NECK PAIN

MINCASE
A 74-year-old man with a past history of bladder carcinoma developed left-sided occipital and neck pain over the course of 2 weeks. Exam was normal except for questionable altered sensation over the left occipital area. Head CT and cervical X-rays were normal. A bone scan and MRI of the cervical spine were therefore done.

LOCALIZATION AND DIFFERENTIAL DIAGNOSIS
On the basis of the symptoms and signs shown in bold above, where is the lesion? What is the most likely diagnosis?

Discussion
The key symptoms and signs in this case are:
• Pain and sensory changes over the left occipital area

The combination of pain and sensory loss in this territory suggests a peripheral nerve lesion. Sensation in the occipital scalp is provided by C2 (Figure 8.4), which gives rise to the greater and lesser occipital nerves.

The most likely clinical localization is a left C2 nerve root or left occipital nerve. Given the patient's history of bladder cancer, the most possible diagnosis is epidermal metastasis compressing the left C2 nerve root, or left occipital nerves. Less likely possibilities include degenerative disease of the spine, or other diagnoses listed in Table 8.4.

Clinical Course and Neuroimaging
A cervical spine MRI (Figure 8.9) was done, revealing a left cervical mass involving C2. The patient had a CT-guided needle biopsy of the mass, and pathology revealed metastatic transitional cell bladder carcinoma. Radiation therapy was instituted, but the patient gradually deteriorated and was ultimately referred for hospice care.

CASE 8.3 UNILATERAL SHOULDER PAIN AND WEAKNESS

MINCASE
A 50-year-old man with a past history of multiple high school and college football injuries was in a motor vehicle accident and developed left shoulder pain and numbness that occasionally radiated down the left arm into the thumb and was increased by neck extension. Exam was normal except for 4/5 deltoid power on the left and decreased pinprick sensation in the left shoulder.

LOCALIZATION AND DIFFERENTIAL DIAGNOSIS
On the basis of the symptoms and signs shown in bold above, where is the lesion? What is the most likely diagnosis?

Discussion
The key symptoms and signs in this case are:
• Left shoulder pain and decreased sensation
• Left deltoid weakness

Sensation to the shoulder and motor innervation of the deltoid muscle is provided by the axillary nerve, which gets its predominant supply from the C5 nerve root (see Table 8.1; Figure 8.6). The most likely diagnosis is therefore a left C5 radiculopathy caused by C4-C5 disc herniation or osteophytes. Other, less likely causes of a C5 radiculopathy are listed in Table 8.4. An ancillary neuropathy should also be considered (see Table 9.3). In addition, another diagnosis to be considered is rotator cuff tear, an injury to tendons and ligaments that can cause weakness of abduction and external rotation at the shoulder. However, such an injury would not explain this patient's sensory changes.

Clinical Course
The patient underwent a cervical spine MRI, which demonstrated bony osteophytes (see Table 8.3) causing narrowing of the intervertebral neural foramina at C4-C5 (not shown). He was taken to the operating room for laminectomy and decompression of the neural foramina (see KCC.8.5) and had a good postoperative recovery.
CASE 8.1 UNILATERAL NECK PAIN AND TINGLING NUMBNESS IN THE THUMB AND INDEX FINGER

Figure 8.8 Herniated C5-C6 Intervertebral Disc Obliterating Left C6 Neural (Intervertebral) Foramen Mri of the cervical spine. (A) Sagittal T1-weighted image showing herniated C5-C6 intervertebral disc. (B) Axial T2-weighted image at level of herniated C5-C6 intervertebral disc showing that the disc obliterates the left C6 neural foramen.

Discussion
The key symptoms and signs in this case are:
- Blistering rash and decreased pinprick sensation in the left shoulder and arm.
- Weak left deltoid, arm external rotation, biceps, and brachioradialis, with absent left biceps and brachioradialis reflexes.

The herpetic skin lesions, together with sensory loss in a left C5-C6 distribution, make the most likely diagnosis herpes zoster of the left C5 and C6 nerve roots (see KCC 8.3). Although more common in thoracic dermatomes, herpes zoster can occur in other dermatomes as well, and can occasionally cause weakness. The muscle weakness and reflex loss in this patient are also consistent with C5 and C6 involvement, although C5 seems to be more severely affected, since wrist extension (C6) was not weak (see Tables 8.1 and 8.5; Figure 8.6).

Clinical Course
A lumbar puncture was done. The cerebrospinal fluid (CSF) was normal except for the presence of 224 white blood cells per cubic millimeter (normal is 0-5; see KCC 5.9 and 5.10; Table 5.7) with 89% lymphocytes. Viral cultures from CSF and from the skin lesions were negative; however, a polymerase chain reaction (PCR) test on CSF was positive for varicella-zoster virus. The patient was treated with intravenous, and later oral, acyclovir. A cervical spine MRI was negative, as was careful examination for cranial nerve involvement. When the patient was seen 3 months later in follow-up, the rash had resolved, and the pain and weakness in his left arm were improving but were still a significant problem.
CASE 8.2: UNILATERAL OCCIPITAL AND NECK PAIN

Figure 8.9 Metastatic Bladder Carcinoma Encasing Left C2 Nerve Root
Axial T1-weighted MRI of the cervical spine.

Case 8.6 Unilateral neck pain, hand weakness, and numbness in the ring and little fingers

MINICASE
A 34-year-old cardiothoracic surgeon developed left neck and shoulder pain, with numbness and tingling radiating down the ulnar aspect of his arm into the fourth and fifth fingers. On exam he had some weakness of the intrinsic muscles of the left hand, and decreased sensation to pinprick and light touch over the left fourth and fifth fingers (Figure 8.12). The remainder of the exam was normal.

LOCALIZATION AND DIFFERENTIAL DIAGNOSIS
On the basis of the symptoms and signs shown in bold above, where is the lesion? What is the most likely diagnosis?

Discussion
The key symptoms and signs in this case are:
- Weakness of the intrinsic muscles of the left hand
- Left neck and shoulder pain, with paresthesias and decreased sensation in the left fourth and fifth fingers

It would have been helpful for localization if additional details of the motor exam had been provided. Weakness of hand intrinsic muscles (thenaroids, interossei) can...
be caused by lesions of the ulnar nerve, median nerve, lower trunk of the brachial plexus (see Chapter 9), C5, or C7 nerve roots (see Table 8.1). In addition, the distribution of abnormal sensation in this patient is consistent with a lesion of the ulnar nerve, lower trunk of the brachial plexus (C5, T1; see Chapter 9), or C5 nerve root (see Figure 8.4). Neck and shoulder pain suggests a radiculopathy. Therefore, a left C8 radiculopathy caused by leftward C7-T1 disc herniation is the most likely diagnosis (see also Table 8.4); however, an ulnar neuropathy or lower brachial plexus lesion should also be considered.

**Clinical Course**

An MRI showed a C7-T1 disc herniation (see Figure 8.8 for a similar scan at a different level). At the time of laminectomy, some free disc fragments were found compressing the left C8 nerve root and were removed. Postoperatively, the patient's pain was resolved, and his hand strength recovered fully.

**CASE 8.7 PAIN AND NUMBNESS IN THE MEDIAL ARM**

**MINICASE**

A 66-year-old executive had been suffering for 2 years with pain and numbness in his left shoulder and medial arm. Exam was notable for decreased sensation to light touch in the left medial arm and forearm (Figure 8.13), and was otherwise unremarkable. Several MRIs and a CT myelogram were done suggesting possible neural compression at multiple levels, including C5-C7, C6-T1, and T1-T2.

**LOCALIZATION AND DIFFERENTIAL DIAGNOSIS**

On the basis of the symptoms and signs shown in bold above, where is the lesion? What is the most likely diagnosis?

![Figure 8.13 Region of Decreased Sensation](image)

**Discussion**

The key symptoms and signs in this case are:

- Left shoulder pain, with decreased sensation in medial arm and forearm

This patient had sensory changes in the left T1 dermatome (see Figure 8.4). Thoracic radiculopathy is uncommon, but can occasionally be seen as a result of disc herniation, or other disorders listed in Table 8.4. It should be noted that this patient had sensory findings only, with no motor involvement (see Table 8.1), which can occur with incomplete nerve root lesions (see KCC 8.3).

**Clinical Course**

Because the imaging studies did not provide a definite level, yet he had refractory pain, the patient was taken to the operating room for laminectomy and exploration of the left C7, C8, and T1 nerve roots. At the time of surgery the left T1 nerve root was found to be compressed by T1-T2 disc fragments, which were removed. This case illustrates that MRI or CT findings suggesting nerve root compression need to be interpreted in the context of clinical symptoms and signs, since asymptomatic radiological abnormalities are common. Postoperatively, the patient's pain improved markedly.

**CASE 8.8 LOW BACK PAIN RADIATING TO THE SOLE OF THE FOOT AND THE SMALL TOE**

**CHEF COMPLAINT**

Following an accident, a 38-year-old man developed difficulty walking, and low back pain radiating to the lateral sole of his left foot.

**HISTORY**

The patient was working on a road when he was injured by an explosion. He suffered severe burns requiring plastic surgery. In addition, he experienced low back pain with numbness and "pins and needles" running down his left leg into the sole and lateral aspect of the left foot, including the small toe. He had some trouble walking, mostly because of pain, but also noticed difficulty standing on his toes with the left foot. He denied changes in bowel, bladder, or erectile function.

**PHYSICAL EXAMINATION**

Vital signs: T = 98°F, P = 80, BP = 112/80.

Neck: Supple.

Lungs: Clear.

Heart: Regular rate with no murmurs, gallops, or rubs.

Abdomen: Normal bowel sounds; soft.

Extremities: Normal.

Dermatologic: Multiple scars on face and arms.

Neurologic exam:

- Cranial nerves: Intact.
- Motor: S5 power throughout, except for 4/5 power in the left gastrocnemius and hamstrings (semimembranosus, semitendinosus, and biceps femoris).

![Figure 8.14 Region of Decreased Sensation](image)

**Discussion**

The key symptoms and signs in this case are:

- Weakness of the left gastrocnemius and hamstrings, with absent left Achilles tendon reflex
- Paresthesias and decreased sensation in the left lateral calf, lateral foot including the small toe, and sole

The weakness, reflex loss, and sensory changes in this patient are consistent with a left S1 radiculopathy (see Tables 8.1, 8.6; Figures 8.4, 8.7). The most likely diagnosis is a left posterolateral L5-S1 disc herniation compromising the left S1 nerve root (see also Table 8.4 for other possibilities).

**COORDINATION:** Normal on finger-to-nose testing.

**Sensation:** Intact except for decreased light touch and pinprick sensation in the left lateral calf, left lateral foot including the small toe, and sole of the left foot (Figure 8.14).

**LOCALIZATION AND DIFFERENTIAL DIAGNOSIS**

On the basis of the symptoms and signs shown in bold above, where is the lesion? What is the most likely diagnosis?
Clinical Course and Neuroimaging

A spine MRI was performed and showed a left L5-S1 disc herniation (Figures 8.15, 8.16). The patient's symptoms did not improve, and he was therefore taken to the operating room for a laminectomy, which revealed a herniated L5-S1 disc with a free disc fragment compressing the left S1 nerve root in the lateral recess. The fragment was removed, and the patient did well until 1 year later, when he had recurrent pain in the same distribution and mild paresthesia. Repeat MRI showed scar tissue surrounding the left S1 nerve root. This could not be treated surgically, and he was therefore treated with pain medications and local steroid injections with only partial relief.

Related Case. Figure 8.17 (page 332) shows an example from a different patient of a myelogram (see Chapter 4) demonstrating bilateral L5 nerve root compression by a herniated L4-L5 disc.

CASE 8.9 UNILATERAL THIGH WEAKNESS WITH PAIN RADIATING TO THE ANTERIOR SHIN

MINICASE
A 76-year-old man suffered for 1 year with relentless pain and numbness radiating from his right buttock down the anterior thigh into the shin. Exam was notable for 4/5 right quadriceps strength, 4/5 right iliopsoas strength, absent right patellar reflex, and decreased pinprick sensation in the right shin and medial calf (Figure 8.18).

LOCALIZATION AND DIFFERENTIAL DIAGNOSIS
On the basis of the symptoms and signs shown in bold above, where is the lesion? What is the most likely diagnosis?

Discussion
The key symptoms and signs in this case are:
- Weakness of the right quadriceps and iliopsoas, with absent right patellar reflex
- Paresthesias and decreased sensation in the anterior thigh, shin, and medial calf

The patient's symptoms of weakness, reflex loss, and sensory changes is compatible with a right femoral neuropathy or L4 radiculopathy (see Table 8.2, 8.6, Figures 8.4, 8.7; see also Table 9.3). Lesions of the femoral nerve can sometimes be distinguished from an L4 radiculopathy by testing for weakness of thigh adduction, which may be present in L4 radiculopathy but not femoral neuropathy (see Table 8.1). Unfortunately, thigh adduction testing was not documented in this patient. An L2 or L3 radiculopathy could also be considered in this patient; however, these radiculopathies do not usually produce sensory changes extending below the knee, and they are also much less common than an L4 radiculopathy. The most likely diagnosis is therefore right femoral neuropathy or right posteroslateral L3-L4 disc herniation compressing the right L4 nerve root (see also Table 8.1 for other possibilities).

Clinical Course
Interestingly, rather than an L3-L4 posteroslateral disc herniation, this patient's MRI (not shown) revealed a herniated right L4-L5 disc extending far upward and laterally to compress the right L4 nerve root (review Figure 8.3C). Following laminectomy and removal of the herniated disc material, the patient had complete resolution of the pain, and his right leg strength improved.

CASE 8.10 LOW BACK PAIN RADIATING TO THE BIG TOE

MINICASE
A 57-year-old man with low back pain for over 20 years tripped over a door ledge and had a sudden increase in right-sided low back pain radiating down his leg to the right big toe. He had some difficulty walking because of the pain, causing him to visit the emergency room several times over the next 3 months, where his exam was notable for 3/5 power in the right extensor hallucis longus and tibialis anterior, 4/5 power in the right foot invertors and evertors, normal reflexes, and decreased pinprick sensation in the right anterolateral calf and dorsum of the foot (Figure 8.19). Straight-leg raising (see Figure 8.5A) beyond 30° on the left side had no effect, but on the right side reproduced the patient's usual pain.

LOCALIZATION AND DIFFERENTIAL DIAGNOSIS
On the basis of the symptoms and signs shown in bold above, where is the lesion? What is the most likely diagnosis?

Discussion
The key symptoms and signs in this case are:
- Weakness of the right extensor hallucis longus, tibialis anterior, and right foot invertors and evertors
- Pain radiating to the right big toe reproduced by straight-leg raising, with decreased sensation in the anterolateral calf and dorsum of the foot

This patient has typical radicular pain, sensory loss, and weakness compatible with a right L5 radiculopathy (see Tables 8.1, 8.6, Figures 8.4, 8.7). A peroneal nerve palsy (see Tables 8.1, 9.3) can also produce similar decreased sensation and foot drop but does not cause painful paresthesias with straight-leg raising. In addition, lesions of the peroneal nerve can sometimes be distinguished from an L5 radiculopathy by testing for weakness of foot inversion which may be present in L5 radiculopathy, but not in peroneal nerve palsy (see Table 8.1).

The most likely diagnosis is therefore right posteroslateral L4-L5 disc herniation compressing the right L5 nerve root (see also Table 8.4 for other possibilities).

Clinical Course
An MRI showed a herniated L4-L5 disc compressing the right L5 nerve root (see Figure 8.6E for a similar scan at a different level). Surgery was discussed with the patient; however, he was lost to follow-up.
CASE 8.8 LOW BACK PAIN RADIATING TO THE SOLE OF THE FOOT AND THE SMALL TOE

Figure 8.15  L5-S1 Posterolateral Disc Herniation
Compressing Left S1 Nerve Root In the Lateral Recess
T1-weighted MRI of the spine. (A) Parasagittal view slightly to the left of midline, showing herniated L5-S1 intervertebral
nerve roots (white arrow) in spinal canal.

Figure 8.16  Axial Sections Showing Posterolateral Disc Herniation Compressing Left S1 Nerve Root In the Lateral Recess
T1 weighted MRI of the spine. (A) Mid-sagittal view showing herniated L5-S1 intervertebral disc (as in Figure 8.15A), with levels of axial sections in B-E indicated. Sections B-E proceed from medial to lateral. (B) Axial section at level of L5 vertebral body showing L5 nerve root exiting lateral recess. (C) Axial section at level of L5-S1 intervertebral disc (as in Figure 8.15A). (D) Axial section at level of L5-S1 intervertebral disc showing herniation of disc into left lateral recess compressing left S1 nerve root (compare to Figure 8.8). (E) Axial section at level of S1 body showing S1 nerve roots in lateral recess below the level of compression.
CASE 8.11 SADDLE ANESTHESIA WITH LOSS OF SPHINCTERIC AND ERECTILE FUNCTION

CHIEF COMPLAINT
A 39-year-old man came to the emergency room with 10 days of bilateral gluteal pain, numbness, and sphincteric dysfunction.

HISTORY
Ten days prior to admission the patient was doing heavy labor with concrete when he coughed and felt a sudden "pop" followed by sharp pain in the gluteal region bilaterally. The pain was only partly relieved by over-the-counter pain medications. During the following days he noticed that he had no erections, even upon awakening. In addition, he noticed a loss of sensation over his genitals and buttocks. When he sat down it felt as though he was "on air" because he could not feel the seat. He also became constipated and did not have any bowel movements for 10 days, despite frequent attempts. Urination was also difficult, and when he felt discomfort from bladder distention, he applied pressure over his lower abdomen to initiate flow. Because of increasing problems with urinary retention, he finally came to the emergency room.

PHYSICAL EXAMINATION
Vital signs: T = 98.6°F, P = 60, BP = 130/80, R = 16.
Neck: Supple with no bruits.
Lungs: Clear.
Heart: Regular rate with no murmur, gallops, or rubs.
Abdomen: Normal bowel sounds; soft, firm, distended bladder palpable in lower abdomen above pubic bone.
Extremities: No edema.
Rectal: Rectal tone flaccid.
Neurologic exam:
Mental Status: Alert and oriented x3. Normal language.
Splanchnic Nerves: intact II-XII.

Discussion
The key symptoms and signs in this case are:
- Pain in the gluteal region bilaterally with loss of sensation in a saddle distribution over the genitals and buttocks
- Constipation, urinary retention, loss of erections, loss of rectal tone, no anal wink, and loss of bulbocavernous reflex

Impaired bowel, bladder, and sexual function can be caused by bilateral lesions of the cerebral hemispheres, spinal cord, conus medullaris, cauda equina, or peripheral nerves (see KCC 7.5). The intact cremasteric reflex suggests that function of the L1-L2 nerve roots is preserved (see Table 3.7), and the normal lower extremity strength suggests preserved function down through S1. Meanwhile, the region of pain and sensory loss is in the bilateral S2 through S5 dermatomes (Figure 8.4), suggesting a lesion of the lower cauda equina or conus medullaris.

The most likely clinical localization is cauda equina S2 through S5 roots, or conus medullaris.

Given the sudden onset of symptoms, a central disc herniation is likely as the diagnosis. Since the lowest nerve roots are located more medially in the cauda equina (see Figure 8.3C), a central disc herniation tends to compress the lower nerve roots. For other, less likely causes of cauda equina syndrome in this patient, see KCC 8.4. Possible lesions of the conus medullaris include intrinsic tumors such as ependymomas, or astrocytomas, metastatic lesions, demyelinating processes, and sarcoidosis.

Clinical Course and Neuroimaging
The patient immediately underwent a spinal CT/myelogram (Figure 8.21), which showed an L5-S1 central disc herniation compressing the cauda equina. An urgent laminectomy was therefore performed. A large mass of disc mater-
CASE 8.11 SADDLE ANESTHESIA WITH LOSS OF SPHINCTERIC AND ERECTILE FUNCTION

Figure 8.21 Large Posterior L5-S1 Disc Herniation Compressing Cauda Equina. Spiral CT myelogram (see Chapter 4). Sections A-C proceed from rostral to caudal. (A) Section at level of L4-L5 intervertebral disc showing normal-contrast agent-filled CSF space and cauda equina at this level. (B) Massive L5-S1 intervertebral disc herniation obliterating spinal canal at level of cauda equina. (C) Section at level of S1 vertebral body showing normal-appearing nerve roots, spinal canal, and other structures. Compare to Figure 8.3C.

(A)

(B)

(C)

(CASE 8.11 (CONTINUED))

(a) was found compressing the thecal sac from the anterior aspect at the L5-S1 intervertebral level. Following decompression the patient's pain improved, and he regained some gluteal sensation; however, he still had urinary retention and required intermittent catheterization at the end of his 11-day hospital stay.

Additional Cases

Related cases can be found in other chapters for the following topics: peripheral nerve disorders (Cases 9.1–9.11); distal symmetric polyneuropathy (Cases 6.5, 10.3); and cranial neuropathy (Cases 12.2–12.7, 13.1–13.3, 13.5). Other relevant cases can be found using the Case Index.

Brief Anatomical Study Guide

1. In this chapter we have discussed the segmental innervation of the body provided by dorsal sensory and ventral motor nerve roots that exit the spinal cord at cervical, thoracic, lumbar, and sacral levels (see Figure 8.1A) and fuse to form mixed spinal nerves (see Figure 8.1B). Because the vertebral bones outgrow the spinal cord during development, the lower roots continue below the L1 or L2 vertebral bones as the cauda equina (see Figure 8.1). The sensory regions innervated by nerve roots are called dermatomes (see Figure 8.4), and motor territories of nerve roots are called myotomes.

2. The most common cause of nerve root dysfunction, or radiculopathy, is intervertebral disc herniation at the cervical or lumbosacral
Brief Anatomical Study Guide (continued)

levels (see Figures 8.2, 8.3). The nerve root involved usually corresponds to the vertebral body below the level of the herniated disc. For example, an L5-S1 disc herniation usually causes an L1 radiculopathy. The three most clinically relevant arm and leg nerve roots are C5, C6, and C7, and L4, L5, and S1, respectively. A summary of the sensory and motor functions of these nerve roots is provided in Tables 8.5 and 8.6, and Figures 8.6 and 8.7.

References

General References
Add to the Examination of the Peripheral Nervous System. 1986. Baillière Tindall on behalf of the Contributors of Brain, London.

Back Pain

Cervical Radiculopathy

Thoracic Radiculopathy


Lumbosacral Radiculopathy

Cauda Equina Syndrome
Major Plexuses and Peripheral Nerves

A 3-week-old infant was not moving her left arm normally. She was a large baby and had endured significant traction on her left shoulder during delivery. Her left arm had decreased tone and appeared internally rotated. She was able to extend her left arm at the elbow and could open and close her hand, but she could not abduct her left arm at the shoulder or flex it at the elbow. The left biceps reflex was absent. In this chapter, we will learn the sensory and motor functions of the major nerves in the arms and legs. As we shall see, this patient's symptoms are characteristic of injury to specific nerves.
ANATOMICAL AND CLINICAL REVIEW

In this chapter we will discuss the functions of the brachial plexus, lumbosacral plexus, and nerve branches that arise from them. Knowledge of the motor and sensory territories of the spinal nerve roots (see Chapter 8), major plexuses, and peripheral nerves can be very useful clinically in identifying specific nerve lesions and in distinguishing them from lesions of the central nervous system. Disorders specifically affecting motor neurons were discussed in Chapter 6 (see KCC 6.7). Nerve roots and radiculopathies were discussed in Chapter 3, where we also introduced peripheral nerve and neuromuscular disorders in general (KCC A.1). Here we will discuss the most important peripheral nerves in the upper and lower extremities, as well as common localized plexus and nerve syndromes.

Brachial Plexus and Lumbosacral Plexus

The brachial plexus is formed by nerve roots arising from the cervical enlargement at C5, C6, C7, C8, and T1 (Figure 9.3). These nerve roots provide the major sensory and motor innervation for the upper extremities. The nerves of the brachial plexus are so clinically important that it is worth committing the structure of the brachial plexus to memory. A simplified schematic can be helpful in this regard (Figure 9.2). The parts of the brachial plexus can be remembered by this mnemonic: Robert (roots) Taylor (trunks) Drinks (divisions) Cold (cocks) Beer (branches). It is also important to know the muscles innervated by each of the nerve branches (see Table 8.1). The five most clinically important nerve branches arising from the brachial plexus are the radial, median, ulnar, musculocutaneous, and axillary nerves (see the next section). A few more mnemonics may be helpful. The nerve branches of the posterior cord can be remembered with the mnemonic STAR (Axillary, Radial, Thoracodorsal, Subscapular). The muscles innervated by the musculocutaneous nerve are represented by the mnemonic BBC (Biceps, Brachialis, Concorchabialis). The lumbosacral plexus arises from L1, L2, L3, L4, L5, S1, S2, S3, and S4 at the lumbosacral enlargement and provides innervation to the lower extremities and pelvis (Figure 9.3). Once again, a simplified schematic may be helpful (Figure 9.4). The muscles innervated by each of the lumbosacral nerve branches should be reviewed (see Table 8.1). The most clinically important nerve branches arising from the lumbosacral plexus are the femoral, obturator, sciatic, tibial, and peroneal nerves, as will be described shortly. There is also a plexus formed by branches of CN XII and C1 through C5 called the cervical plexus, which supplies mainly the neck muscles. We will not discuss this plexus further, except to mention that the phrenic nerve, which supplies the diaphragm, arises from C3, C4, and C5.
<table>
<thead>
<tr>
<th>NERVE</th>
<th>MOTOR FUNCTIONS</th>
<th>REGION OF SENSORY LOSS WITH NEUROPATHY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radial nerve</td>
<td>Extension at all arm, wrist, and finger joints below the shoulder, forearm supination, thumb abduction in plane of palm</td>
<td>Posterior cutaneous nerve of arm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Posterior cutaneous nerve of forearm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dorsal digital nerves (radial)</td>
</tr>
<tr>
<td>Median nerve</td>
<td>Thumb flexion and opposition, flexion of digits 2 and 3, wrist flexion and abduction, forearm pronation</td>
<td>Median nerve</td>
</tr>
<tr>
<td>Ulnar nerve</td>
<td>Finger adduction and abduction other than thumb, thumb adduction, flexion of digits 4 and 5, wrist flexion and adduction</td>
<td>Ulnar nerve</td>
</tr>
<tr>
<td>Axillary nerve</td>
<td>Abduction of arm at shoulder beyond first IP</td>
<td>Axillary nerve</td>
</tr>
<tr>
<td>Musculocutaneous nerve</td>
<td>Flexion of arm at elbow, supination of forearm</td>
<td>Lateral cutaneous nerve of forearm</td>
</tr>
</tbody>
</table>

**Regions of sensory innervation by cutaneous nerve branches are shown in Figure 8.9. The actual area of sensory loss following a nerve injury is somewhat smaller than the territories shown because of overlap from adjacent nerves. This should be compared to the dermatomal sensory distribution of nerve roots shown in Figure 8.4.**

**REVIEW EXERCISES**

1. Practice drawing the simplified schematic of the brachial plexus shown in Figure 9.2.

2. Practice drawing the simplified schematic of the lumbo-sacral plexus shown in Figure 9.4.

**Simplification: Five Nerves to Remember in the Arm**

It is most clinically important to be familiar with the functions of the radial, median, ulnar, axillary, and musculocutaneous nerve in the arm. The motor and sensory functions of these nerves are summarized in Table 9.1, and are demonstrated on neuroexam.com Video 54 and 55. Additional details are found in Table 8.1. In general, the radial nerve is important for extension of all joints in the arm and hand, the median nerve is important for the thumb side of the hand and wrist, and the ulnar nerve is important for the pinky side of the hand and wrist. Note that (1) the sensory territories shown here are smaller in Figure 9.5 because adjacent nerves overlap somewhat, and (2) Table 9.1 shows regions of sensory loss with nerve injury rather than the whole region innervated by the nerve. Finger flexion is best tested at the distal interphalangeal joints (see neuroexam.com Video 55), where the flexor digitorum profundus (median nerve for digits 2 and 3; ulnar nerve for digits 4 and 5) acts without significant contributions from other muscles (Table 9.2).
TABLE 9.2 Muscles Contributing to Flexion and Extension at Finger Joints Other than the Thumb

<table>
<thead>
<tr>
<th>Flexion*</th>
<th>Extension*</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCP</td>
<td>PIP</td>
</tr>
<tr>
<td>Flexor digitorum profundus</td>
<td>X</td>
</tr>
<tr>
<td>Flexor digitorum superficialis</td>
<td>X</td>
</tr>
<tr>
<td>Flexor digitorum (fifth digit)</td>
<td>X</td>
</tr>
<tr>
<td>Lumbricals</td>
<td>X</td>
</tr>
<tr>
<td>Opponens pollicis</td>
<td>X</td>
</tr>
<tr>
<td>Extensor digiti quinti</td>
<td>X</td>
</tr>
<tr>
<td>Extensor indicis proprius</td>
<td>X</td>
</tr>
<tr>
<td>Extensor digiti minimi (fifth digit)</td>
<td>X</td>
</tr>
</tbody>
</table>

Note: Boldface indicates the most important muscles.
* MCP: metacarpophalangeal joint; PIP: proximal interphalangeal joint; DIP: distal interphalangeal joint.

Simplification: Three Nerves Acting on the Thumb

Different thumb muscles are innervated by the radial, ulnar, and median nerves. It is easiest to remember these by the mnemonic RUM (Radial, Ulnar, Median), as shown in Figure 9.6. Thumb abduction in the plane of the palm (abductor pollicis longus) is mediated by the Radial nerve, adduction (ad- ductor pollicis, and opposition (opponens pollicis) and flexion (flexor pollicis longus and superficial head of the flexor pollicis brevis) by the Median nerve. It should also be recalled that thumb abduction per- pendicular to the palm (see Table 3.6, neuromus. com Videos SS) is mediated by the abductor pollicis brevis, which is innervated by the median nerve after it passes through the carpal tunnel.

Intrinsic and Extrinsic Hand Muscles

The intrinsic hand muscles include the muscles of the thenar eminence at the base of the thumb (opponent pollicis, abductor pollicis brevis, flexor pollicis brevis, adductor pollicis), the muscles of the hypothenar eminence at the base of the pinky finger (opponens digitii minimi, abductor digitii minimi, flexor digitii minimi), the lumbricals, and the interossei. Intrinsic hand muscles are innervated by the ulnar nerve, except for the L0A (Lumbricals I and II, Opponens pollicis, Abductor pollicis brevis, Flexor pollicis brevis—superficial head) muscles, which are innervated by the median nerve after it passes through the carpal tunnel. All intrinsic hand muscles are supplied by C8 and T1 (see Table 8.1).

In addition to the intrinsic hand muscles, extrinsic muscles in the forearm are important for finger movements (see Table 8.1). Intrinsic and extrinsic muscles contributing to flexion and extension at finger joints other than the thumb are summarized in Table 9.2. As we have already mentioned, it should be clear from this table that the flexor digitorum profundus (median nerve for digits 2 and 3; ulnar nerve for digits 4 and 5) is best tested at the distal interphalangeal joints, since other muscles participate in flexion at the other joints. Similarly, the extensor digitorum (radial nerve and C7) is best tested at the metacarpophalangeal joints. See Tables 8.1 and 9.1 for guidelines contributing to finger adduction, abduction, and opposition. Note, for exam- ple, that the palmar interossei adduct the fingers, while the dorsal interossei abduct them.

TABLE 9.3 Important Nerves in the Leg

<table>
<thead>
<tr>
<th>Nerve</th>
<th>Motor Functions</th>
<th>Region of Sensory Loss with Neuropathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Femoral nerve</td>
<td>Leg flexion at the hip, leg extension at the knee</td>
<td>Femoral nerve</td>
</tr>
<tr>
<td>Obturator nerve</td>
<td>Adduction of the thigh</td>
<td>Obturator nerve</td>
</tr>
<tr>
<td>Sciatic nerve</td>
<td>Leg flexion at the knee (see also tibial and peroneal nerves below)</td>
<td>Common peroneal nerve</td>
</tr>
<tr>
<td>Tibial nerve</td>
<td>Foot plantar flexion and inversion, toe flexion</td>
<td>Posterior tibial nerve</td>
</tr>
<tr>
<td>Superficial peroneal nerve</td>
<td>Foot eversion</td>
<td>Superficial peroneal nerve</td>
</tr>
<tr>
<td>Deep peroneal nerve</td>
<td>Foot dorsiflexion, toe extension</td>
<td>Deep peroneal nerve</td>
</tr>
</tbody>
</table>

Simplification: Five Nerves to Remember in the Leg

It is most clinically important to be familiar with the functions of the femoral, ob- turator, sciatic, tibial, and peroneal nerves in the leg. The motor and sensory functions of these nerves are summarized in Table 9.3 and are demonstrated on neuromus. com Videos 56 and 57. Additional details are found in Table 8.1. Note again that the sensory territories shown here are smaller than in Figure 9.5, since here we are interested in regions of sensory loss. The tibial and common peroneal nerves are the two most important branches of the sciatic nerve. The ham- string muscles (semimembranosus, sem- ilunaris, and biceps femoris) are innervated by the sciatic nerve itself before it divides into the tibial and common peroneal nerves. The common peroneal nerve divides further to give rise to the superficial and deep peroneal nerves (see Figures 9.3, 9.4; Table 9.3).

REVIEW EXERCISES

1. Turn back to Tables 3.4-3.6 in Chapter 3, where we discussed strength and reflex testing (see also neuromus. com Videos 54-58). In these tables, cover all columns except for the left-most column. For each action or reflex, list the appropriate muscle, nerves, and nerve roots being tested (refer to Table 8.1).
2. In Tables 9.1 and 9.3, cover the columns showing the regions of sen- sory loss and sketch the region of sensory loss for each of the five nerves in the arm and the leg.
In Chapter 9, we introduced the general causes of neuropathy (see KCC 8.1). Here we focus on clinical localization of common mononeuropathies andplexus syndromes caused by mechanical factors or diabetes. Note that in some cases trauma to a limb produces nerve injury, with the exact mechanism of such injury remaining unclear.

Upper-Extremity Nerve Injuries

Brachial Plexus, Upper Trunk Injury (Erb-Duchenne Palsy). Common causes include traction on an infant's shoulder during a difficult delivery and motorcycle accidents. Damage to the upper trunk of the brachial plexus (see Figures 9.1, 9.2) causes loss of function in C5- and C6-innervated muscles, resulting in prominent weakness of the deltoid, biceps, infraspinatus, and wrist extensors (see Table 9.1). The arm assumes a characteristic "bellman's tip" or "waiter's tip" pose, held at the side, internally rotated, and with the wrist flexed (Figure 9.7). Finger and hand movements are relatively spared. Most infants recover fully, but prognosis depends on the severity of the injury. Surgical repair of the plexus is occasionally pursued. Differential diagnosis includes traumatic avulsion of the C5 and C6 nerve roots, or other causes of a C5 and C6 radiculopathy (see KCC 8.3).

Brachial Plexus, Lower Trunk Injury (Klumpke's Palsy). Common causes include upward traction produced by grasping a branch during a fall from a tree, thoracic outlet syndrome, and Pancoast's syndrome. Damage to the lower trunk of the brachial plexus (see Figures 9.1, 9.2) causes weakness of C8-T1-innervated muscles, resulting in hand and finger extension of the arm, which may also decrease brachial arterial pulses. EMG and X-rays (looking for a cervical rib or other bony abnormalities) are important diagnostically. Treatments include exercises to strengthen shoulder muscles and surgical decompression for well-documented refractory cases. Treatment for epineural cases has been a source of controversy.

In Pancoast's syndrome, an apical lung tumor (usually non-small cell carcinoma) extends into the lower brachial plexus. In addition to lower plexus signs (sometimes including Horner's syndrome), the recurrent laryngeal nerve is occasionally involved as it loops downward into the thorax, producing hoarseness (see KCC 12.8). Ultimately, the entire brachial plexus may be invaded, producing a thall, inessate upper extremity.

Axillary Neuropathy. Dislocation or fracture of the proximal humerus can compress the axillary nerve, causing deltoide weakness and numbness in the shoulder (see Table 9.1). Differential diagnosis includes CS radial neuropathy, although axillary neuropathy does not involve the biceps, while CS radiculopathy does.

Radial Neuropathy. Common causes include sleeping with the arm slung over a park bench ("Saturday night palsy"); compression of the axilla by intraperonasal crease ("crutch palsy"), or fracture of the humerus damaging the nerve as it travels in the spiral groove. There is weakness of all extensors of the arm, hand, and fingers below the shoulder, weakness of forearm supination, loss of the triceps reflex, and sensory loss in a radial nerve distribution (see Table 9.1). A wrist drop is often present (Figure 9.8A). The triceps may be spared, depending on how distal the lesion is in the arm. The posterior interosseous nerve is a purely motor branch of the radial nerve. Trauma or entrapment of the posterior interosseous nerve results in weakness of radial nerve-innervated muscles sparing the triceps (see Table 9.1) and with no sensory loss. Tight wrist bands or handcuffs can sometimes compress the superficial branch of the radial nerve, causing isolated sensory loss in the dorsal lateral hand.

Medial Neuropathy. Causes include sleeping with a lover's hand resting on the upper arm ("honeymooners' palsy"). Fractures of the humerus or distal radius can occasionally injure the median nerve. In addition, entrapment (see KCC 8.1) can occur as the nerve passes through the pronator teres muscle in the forearm. There is weakness of flexion and abduction, opposition of the thumb, and sensation of the third and fourth fingers, together with sensory loss in a median nerve distribution (see Table 9.1). In an attempt to make a fist, the hand may assume a "preacher's hand" or "orator's hand" pose (see Figure 9.8B).

Carpal Tunnel Syndrome. This common entrapment syndrome is caused by compression of the median nerve as it passes together with the tendons of the hand under the flexor retinaculum on the flexor surface of the wrist. It is most common in women over age 30 and can be associated with activities such as typing or housekeeping that can cause repetitive stress injuries, edema, and inflammation in the forearm. Other causes include pregnancy, oral contraceptives, hypothyroidism, arthritis, wrist fracture, acromegaly, uremia, diabetes, and amyloidosis. Recall that after the median nerve passes through the carpal tunnel, it innervates the LOAF (lumbricals 1 and 2, opponens pollicis, abductor pollicis brevis, flexor pollicis brevis—superficial head) muscles. The best test to look in suspected carpal tunnel syndrome is the abductor pollicis brevis, which abducts the thumb away from the midline of the palm (neurolog.com Video 50), although thumb flexion and opposition (see Figure 9.6) may also be weak. Symptoms often include sensory loss in the first, second, and third digits, as well as prominent paresthesias (see KCC 7.7) that are most bothersome at night and can sometimes radiate into the upper arm. Patients often report shaking the hand to try and relieve symptoms (flick sign). In advanced cases, thenar atrophy may be present. Wrist flexion, flexion of the second and third digits, and sensation over the thenar eminence are typically spared, since nerves providing these functions branch off proximal to the carpal tunnel.

Differential diagnosis of carpal tunnel syndrome includes radiculopathy of C6 and C7, or compression of the median nerve proximal to the carpal tunnel, although these conditions usually include more proximal symptoms. Tests to provoke paresthesias in a median nerve distribution may be helpful, but they are not very sensitive or specific. These include Tinel's sign, in which the median nerve is percussed in the carpal tunnel; and Phalen's sign, in which the dorsal surfaces of the hands are pressed together, fleeting the wrists for about 1 minute. Treatments include immobilization by a removable wrist splint, steroid injections, and surgical decompression of the carpal tunnel.

Ulnar Neuropathy. The medial epicondyle of the elbow carries the name "funny bone" because mild trauma to the ulnar nerve as it passes over the
elbow in the ulnar groove (between the olecranon and medial epicondyle) produces transient paresthesias (see KCC 7.1) in an ulnar distribution. A common cause of ulnar neuropathy is entrapment (see KCC 8.1) at the elbow in the cubital canal, which lies in the region of the ulnar groove. This condition is sometimes called tardy ulnar palsy; a delayed result of a postanesthetic degenerative, or congenital increased carrying angle at the elbow. The ulnar nerve can also be damaged acutely by fractures of the medial epicondyle, or it may be compressed by a habit of resting the elbows on a hard table.

Findings include weakness of wrist flexion and adduction, finger adduction and abduction, and flexion of the fourth and fifth digits, together with sensory loss and paresthesias in an ulnar distribution (Table 9.1). As with most neuropathies, motor findings may be absent in mild cases. Severe cases may include atrophy and fasciculations in the hypothenar eminence. Because of weakness ulnaris at the fourth and fifth digits, these fingers may assume a characteristic "ulnar claw" posture (see Figure 9.9C). Differential diagnosis includes C8 and T1 radiculopathy, Pancoast's syndrome, thoracic outlet syndrome, or other lesions of the brachial plexus (see Table 9.2). Unlike ulnar neuropathy, these conditions sometimes produce a Horner's syndrome, sensory changes in the T1 dermatome of the upper arm (see Figure 8.6), or involvement of hand muscles innervated by the median nerve. Entrapment in the cubital canal at the elbow can be treated surgically by translocation of the ulnar nerve to the flexor side of the elbow.

Compression of the ulnar nerve at the hand as it passes over the hamate bone in Guyan's canal can occur from prolonged leaning forward while cycling. The result is weakness of finger adduction and abduction without sensory loss because the cutaneous branches of the ulnar nerve are given off more proximally. Combination of chronic median and ulnar nerve lesions leads to thenar and hypothenar atrophy with loss of thumb opposition, residual in a "stilisa hand" or "monkey's paw" (see Figure 9.8D).

Lower-Extremity Nerve Injuries

Femoral Neuropathy. The femoral nerve can occasionally be injured during pelvic surgery or compressed by a retroperitoneal hematoma or pelvic mass. Abnormalities include weakness of thigh flexion and knee extension, loss of the patellar reflex, and sensory loss in the anterior thigh (Table 9.3). Differential diagnosis includes L3 or L4 radiculopathy, L3 or L4 radiculopathy, however, may include weakness of hip adduction (obturator nerve), whereas this feature is associated with femoral neuropathy (see Table 8.1).

Sciatic Neuropathy. Causes of sciatic neuropathy include posterior hip dislocation, acetabular fracture, and intramuscular injection placed too medially and inferriorly in the buttocks. There is weakness of all foot and ankle muscles and of knee flexion and of the Achilles tendon reflex, and sensory loss in the foot and lateral leg below the knee (Table 9.3). Differential diagnosis includes lesions in the foot area of the motor cortex (see KCC 6.3; Figure 6.14).

The term "sciatica" is vague and refers to all disorders causing painful paresthesias in a sciatic distribution. The most common cause is compression of lumbosacral roots by disc material and osteophytes (see KCC 8.3). Rarely, the sciatic nerve may be compressed more distally by muscular or skeletal elements.

Peroneal Nerve Palsy. As the common peroneal nerve passes around the fibular head near the skin surface, it is vulnerable to laceration, stretch injury by

foot-ease, foot inversion, or compression by tight stockings, a cast, crossed legs, or trauma. In peroneal nerve palsy, there is "foot drop" with weakness of foot dorsiflexion and eversion, and sensory loss over the dorsolateral foot and shin. Most patients recover spontaneously when the mechanical cause is removed. A foot brace may improve function if foot drop is significant. Differential diagnosis includes L5 radiculopathy. However, L5 radiculopathy includes weakness of foot dorsiflexion, eversion, and inversion, while in peroneal palsy, foot inversion is normally spared because this function can be carried out by the tibialis posterior (innervated by the tibial nerve) (Table 9.3; see also Table 8.1).

Meralgia Paresthetica. The lateral femoral cutaneous nerve (which originates in L2 and L3; Figures 9.9 and 9.4) may be compressed by the inguinal ligament or fascia lata producing paresthesias and loss of sensation in the lateral thigh (Figure 9.5). This entrapment syndrome includes no motor involvement or reflex changes. Common causes include obesity, pregnancy, weight loss, or heavy equipment belt, and symptoms may be worse after prolonged walking, standing, or sitting. Differential diagnosis includes L2 or L3 radiculopathy, although unlike meralgia paresthetica, these conditions usually include motor changes or decreased patellar reflex. Symptoms most often resolve spontaneously or by avoidance of mechanical precipitants; however, surgical decompression is occasionally attempted in refractory cases.

Morton's Metatarsalgia. Tight-fitting shoes can compress the digital nerves, especially of the third and fourth toes, producing patches of numbness and paresthesias.

In conclusion, familiarity with the patterns of sensory and motor loss in the common plexus and in the nerve syndromes discussed in this section, as well as those seen in radiculopathies (see KCC 8.5) and other disorders of nerves, muscles, and the neuromuscular function (see KCC 8.1), can greatly aid in localizing neurological deficits and in distinguishing disorders of the peripheral and central divisions of the nervous system. When the diagnosis remains uncertain, electrodiagnostic tests can often be helpful, as discussed in the next section.
A compound motor action potential (CMAP) of the ulnar nerve was recorded in this normal example at several stimulus locations. (A) Stimulation of the ulnar nerve at the wrist, and recording of CMAP from the abductor digiti quinti in the hypothenar eminence. (B) Ulnar nerve stimulation just proximal to the ulnar groove. (C) Ulnar nerve stimulation just distal to the ulnar groove. (D) CMAP recordings for different stimulation sites. For each trace, the distance from the recording electrode (in centimeters) and the latency to CMAP onset (in milliseconds) are indicated to the left. Conduction velocities between adjacent stimulation sites (in meters per second) were calculated by dividing the distance between the two stimulation sites by the difference in motor latencies for the two sites. (After Rajbux KS, Thompson LL, 1989. The Electromyographer's Handbook, 2nd Ed. Little, Brown, Boston.)

KCC 8.1). In addition, there are standard values for SNAP amplitudes. Decreased SNAP amplitudes suggest that conduction in some axons of the nerve has been interrupted, as is the case in axonal damage.

CMAP studies can be used to evaluate the function of the neuromuscular junction by the use of repetitive stimulation. Slow repetitive stimulation (2-3 Hz) depolarizes presynaptic terminals of acetylcholine; faster repetitive stimulation (35 Hz) increases presynaptic calcium, facilitating neurotransmitter release. Under normal conditions, repetitive stimulation does not significantly affect CMAP amplitude because there is a "safety factor," meaning that every presynaptic action potential results in a postsynaptic potential well above the threshold needed to produce a muscle cell action potential. Under pathologic conditions, however, failures in neuromuscular transmission occur. Therefore, for example in myasthenia gravis (see KCC 8.1), in which there is a decrease in postsynaptic acetylcholine receptors on muscle cells, slow repetitive stimulation results in a gradual decrement in CMAP amplitude. Decrements of >10% is considered abnormal. In Lambert-Eaton myasthenic syndrome, in which there is decreased presynaptic neurotransmitter release, fast repetitive stimulation (or active volitional muscle contraction) causes CMAPs to increment in amplitude from an abnormally low starting point.

Electromyography (EMG), an electrode is inserted directly into a muscle, and motor unit action potentials (MUPs) are recorded from muscle cells. The EMG pattern provides information useful in distinguishing weakness caused by neuropathic disorders (nerve or motor disease) from that caused by myopathic disorders (muscle disease). In neuropathic disorders, increased spontaneous activity (fibrillation potentials and positive sharp waves) often is recorded on EMG, and is sometimes also visible on physical examination as fasciculations (see KCC 6.1). Fasciculations and other forms of spontaneous activity occur due to chronic denervation of muscle cells. Denervation also causes adjacent motor axons to sprout and reinnervate a larger region, resulting in abnormally large motor units (a motor unit consists of all the muscle cells innervated by a single motor neuron axon). Therefore, with neuropathic disorders, MUPs are of abnormally large amplitude and duration. Reduced MUP amplitude and duration suggests a myopathic disorder is present.

When a muscle is voluntarily contracted, the EMG normally shows a pattern of continuous firing of motor units referred to as a normal recruitment pattern. In neuropathic disorders, the recruitment pattern has normal amplitude but shows interrupted firing, since some motor units are not successfully activated. This phenomenon is referred to as decreased, reduced, or incomplete recruitment. In myopathic disorders, the recruitment patterns is continuous or even increased (since more motor units need to be activated for a given force), but the amplitude is often decreased.

**CLINICAL CASES**

**CASE 9.1 COMPLETE PARALYSIS AND LOSS OF SENSATION IN ONE ARM**

**CHIEF COMPLAINT**

A 68-year-old man with a history of lung cancer gradually developed severe pain, weakness, and numbness in his right arm.

**HISTORY**

The patient smoked for 34 years. Two years ago he was diagnosed with lung cancer and underwent a right upper-lobe lung resection followed by radiation and chemotherapy. Six months ago he developed shooting pain and swelling of the right arm. He gradually lost all strength and sensation in the entire right arm up to the shoulder but continued to have severe burning pain. Past medical history was notable for right eye surgery following an assault with a baseball bat 20 years ago.

**PHYSICAL EXAMINATION**

Vital signs: T = 99.4F, P = 110, BP = 130/80. Weak: Supine; no tenderness. Lungs: Clear. Heart: Regular rate with no murmurs, gallops, or rubs. Abdomen: Normal bowel sounds; soft, no masses. Extremities: Right arm swollen, with two firm 5 cm discolored masses—one in the right axilla and one in the upper right chest wall. Also marked clubbing of the fingers bilaterally. Neurologic exam:

- **MENTAL STATUS:** Alert and oriented × 3.
- **Cranial nerves:** Intact, except for the right eye, which had an irregular pupil and diminished vision in both the lateral and medial fields.
- **Motor:** Normal tone except for the right arm, which was flaccid, 5/5 power throughout, except for 0/5 power in the right shoulder, arm, and hand.

**REFLEXES:**

<table>
<thead>
<tr>
<th>Reflex</th>
<th>Right</th>
<th>Left</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biceps</td>
<td>2+</td>
<td>2+</td>
</tr>
<tr>
<td>Brachioradialis</td>
<td>2+</td>
<td>2+</td>
</tr>
<tr>
<td>Triceps</td>
<td>2+</td>
<td>2+</td>
</tr>
<tr>
<td>Radial</td>
<td>2+</td>
<td>2+</td>
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<tr>
<td>Ulnar</td>
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<td>2+</td>
</tr>
<tr>
<td>Median</td>
<td>2+</td>
<td>2+</td>
</tr>
<tr>
<td>Forearm extension</td>
<td>2+</td>
<td>2+</td>
</tr>
<tr>
<td>Forearm flexion</td>
<td>2+</td>
<td>2+</td>
</tr>
<tr>
<td>Shoulder abduction</td>
<td>2+</td>
<td>2+</td>
</tr>
<tr>
<td>Shoulder adduction</td>
<td>2+</td>
<td>2+</td>
</tr>
</tbody>
</table>

**Impression:** Acute flaccid paralysis without sensory deficit.
CASE 9.1 (CONTINUED)

sensory: Absent light touch, pinprick, and vibration sense in the entire right arm up to the deltoid (Figure 9.10). Sensation otherwise normal.

LOCALIZATION AND DIFFERENTIAL DIAGNOSIS
1. On the basis of the symptoms and signs shown in bold above, where is the lesion?
2. What is the most likely diagnosis?
3. This patient had an abnormal right eye due to prior trauma. If his right eye had been normal previously, what additional finding might be present on exam that would help with the localization?

Discussion
1. The key symptoms and signs in this case are:
   - Paralysis, with decreased tone and absent reflexes in the entire right arm and hand
   - Absent light touch, pinprick, and vibration sense in the entire right arm up to the deltoid
   - Pain and swelling in the right arm

   Weakness in one arm can be caused by peripheral nerve lesions or by lesions in the arm region of the motor cortex (see KCC 6.3; Figure 6.14E). However, it is unlikely that a cortical lesion would produce complete paralysis and sensory loss in the entire arm, ending sharply at the shoulder, with no face or leg weakness at all. In addition, no single peripheral nerve lesion could produce this pattern. Therefore, the lesion must involve the entire right brachial plexus, or all right-sided nerve roots from C5 through T1.

2. The history of right apical lung tumor supports the possibility of a lesion invading the right brachial plexus from below (see the description of Parinaud’s syndrome in KCC 9.1), as does the presence of swelling in the arm, suggesting obstruction of venous return.

3. A lesion of the proximal portion of the lower brachial plexus involving the T1 nerve root can cause a Horner’s syndrome (see Figures 6.13, 13.10; KCC 13.5). This condition could be difficult to appreciate in this patient because of his prior history of right eye trauma.

Clinical Course and Neuroimaging
A brachial plexus MRI (Figure 9.11) showed extensive invasion of the apical lung mass into the region of the right brachial plexus. The cancer in this patient, unfortunately, was no longer amenable to treatment. However, his pain was managed by a multidisciplinary team using oral, intravenous, and epidural medications to provide adequate pain relief.

CASE 9.2 A NEWBORN WITH WEAKNESS IN ONE ARM

MINICASE
A 2-week-old infant girl was brought to the pediatrician because of left arm weakness. She was born at 42 weeks (2 weeks past the due date) weighing 10 pounds 11 ounces, and the delivery was complicated by shoulder dystocia (difficulty delivering the shoulder) resulting in significant traction on the left neck and shoulder during delivery. Left arm weakness was noted at birth and improved slightly but was still present at the appointment. Exam was normal except for the left upper extremity, which had decreased tone and lay internally rotated at the infant's side with decreased spontaneous movements. She did not abduct the left arm or flex it at the elbow, but did have spontaneous opening and closing of the hand with normal grip strength, normal elbow extension, and some wrist flexion. The left biceps reflex was absent, and other reflexes were 2/4 throughout.

LOCALIZATION AND DIFFERENTIAL DIAGNOSIS
On the basis of the symptoms and signs shown in bold above, where is the lesion? What is the most likely diagnosis?

Discussion
The key symptoms and signs in this case are:
- Weakness of left arm external rotation, abduction, and elbow flexion, with decreased tone and absent biceps reflex

The patient has typical findings consistent with a left brachial plexus upper trunk injury (Erb-Duchenne palsy), affecting C5 and C6 innervated muscles, caused by left shoulder traction at birth (KCC 9.1).

Clinical Course
A physical therapy program was initiated to preserve range of motion during recovery. At age 7 weeks the patient was able to lift her arm off the table and had some external rotation of the arm, as well as slight spontaneous elbow flexion. The left biceps reflex was still absent. By age 4 months she was able to reach for objects well with either hand, although she preferred to use her right hand, and she had 4+/5 left biceps strength when pulled to a seated position. Continued improvement was anticipated.

CASE 9.3 A BLOW TO THE MEDIAL ARM CAUSING HAND WEAKNESS AND NUMBNESS

MINICASE
A 38-year-old alcoholic man was seen to fall, catching his right arm on a garbage can. He was brought to the emergency room. He had an abrasion and tenderness of the right upper medial arm. Neurologic exam was normal except for 4+/5 strength of right thumb opposition, second and third finger flexors, and wrist flexion and abduction. There was also decreased pinprick and light touch sense along the lateral surface of the right hand and first, second, and third fingers (Figure 9.12).

LOCALIZATION AND DIFFERENTIAL DIAGNOSIS
On the basis of the symptoms and signs shown in bold above, where is the lesion? What is the most likely diagnosis?
Discussion

The key symptoms and signs in this case are:
- Weakness of right thumb opposition, second and third finger flexion, and wrist flexion and abduction
- Decreased pinprick and light touch sense along the lateral surface of the right distal forearm, hand, and first, second, and third fingers
- Abrasion and tenderness of the right upper medial arm

The pattern of weakness and sensory loss in this patient is consistent with a median nerve injury (Table 9.1; Figure 9.5; see also Table 8.3). The most likely cause is compression of the nerve in the upper medial arm, as evidenced by the tenderness in this area and the mechanism of injury.

Clinical Course

X-rays of the right arm revealed no fractures. The patient was discharged from the emergency room and did not return for follow-up.

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CASE 9.1 COMPLETE PARALYSIS AND LOSS OF SENSATION IN ONE ARM

Figure 9.11 Right Apical Lung Cancer Extending into the Region of the Brachial Plexus T1-weighted coronal MRI scan of the chest.

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CASE 9.4 NOCTURNAL PAIN AND TINGLING IN THE THUMB, POINTER, AND MIDDLE FINGER

MINICASE

A 28-year-old man who works in a cola factory developed pain and tingling in his right thumb, index, and middle fingers over the past 2 months that occasionally radiates into the right arm and forearm. His symptoms are worse at night or when the arm is relaxed. He has also noticed some decreased sensation of the fingertips of the same fingers while buttoning his shirt. Exam was notable only for obesity and 4/5 weakness of the right opponens pollicis and decreased pinprick sensation in the palmar aspect of the right first, second, and third fingers, sparing the thenar area (Figure 9.13). Tinel's and Phalen's signs were not present.

LOCALIZATION AND DIFFERENTIAL DIAGNOSIS

On the basis of the symptoms and signs shown in bold above, where is the lesion? What is the most likely diagnosis?

---

CASE 9.5 HAND AND WRIST WEAKNESS AFTER A FALL

MINICASE

A 20-year-old male waiter tripped while working at a restaurant and broke his fall by extending his left hand onto a table. That night he had pain in his left arm that resolved by the next day, but he then noticed weakness of the left hand and wrist and came to the emergency room. Exam was normal except for 3/5 strength in the left wrist extensors, finger extensors, and thumb abduction in the plane of the palm, and 4/5 strength in forearm supination. Strength in all other muscles was intact, as was sensation.

LOCALIZATION AND DIFFERENTIAL DIAGNOSIS

On the basis of the symptoms and signs shown in bold above, where is the lesion? What is the most likely diagnosis?
Discussion
The key symptoms and signs in this case are:

- Weakness of left forearm supination, wrist extensors, finger extensors, and abduction of the thumb in the plane of the palm

These muscles are all supplied by the radial nerve (Table 9.1; see also Table 8.1). In particular, the fact that the tripeas was spared and that there was no sensory loss suggest a lesion of the posterior interosseous nerve, a purely motor branch of the radial nerve. The posterior interosseous branch of the radial nerve was apparently injured during the fall, with the exact mechanism being unclear (see KCC 9.1).

Clinical Course
X-rays of the left arm did not reveal a fracture. The patient was given a splint to avoid developing contracture deformities and was followed by an occupational therapist as his strength gradually recovered. An EMG done 2 months after the injury was consistent with a lesion of the left radial nerve distal to the fibers innervating the tripeas. By 4 months after the injury, strength had returned to 4/5 in the affected muscles and was continuing to improve gradually. (Note: In posterior interosseous nerve injuries, the extensor carpi radialis is usually spared, so extension of the wrist in the radial direction is preserved. This was not tested for in this case.)

CASE 9.6 NUMBNESS AND TINGLING IN THE PINKY AND RING FINGER

MINICASE
A 32-year-old computer programmer developed 2 months of worsening tingling and numbness in his left fifth digit; in the medial aspect of his left fourth digit, and along the medial surface of his left hand and forearm. The symptoms were worse upon awakening in the morning and were exacerbated after resting his elbows on a hard surface. Exam was normal except for 4/5 strength in left fifth finger abduction, and decreased pinprick sensation in the left fifth digit and the medial half of the left fourth digit (Figure 9.14). Symptoms were not worsened by arm abduction plus elevation.

LOCALIZATION AND DIFFERENTIAL DIAGNOSIS
On the basis of the symptoms and signs shown in bold above, where is the lesion? What is the most likely diagnosis?

Figure 9.14 Region of Sensory Loss

Discussion
The key symptoms and signs in this case are:

- Weakness of left fifth finger abduction
- Paresthesias and decreased pinprick sensation in the left fifth digit and the medial half of the left fourth digit

The sensory and motor deficits in this patient could be caused by mild dysfunction in the ulnar nerve, the brachial plexus lower trunk (e.g., thoracic outlet syndrome), the brachial plexus medial cord, or the C8 or T1 nerve roots (Table 9.1; KCC 9.1; see also Table 8.1). The fact that the symptoms are worse after pressure on the elbow, are not accompanied by neck pain (common in cervical radiculopathy; see KCC 8.3), and are not exacerbated by arm abduction plus elevation (characteristic of thoracic outlet syndrome) suggests, but does not prove, that the ulnar nerve is the culprit.

Clinical Course
Nerve conduction studies (see KCC 9.2; Figure 9.9) were normal except in the ulnar nerves. To measure conduction velocity in the ulnar nerve, a recording electrode was placed on the skin over the biceps of the abductor digit minimi muscle, and a stimulating electrode was placed on the skin at various points on the arm over the course of the ulnar nerve. When a stimulus was given to the nerve, a compound motor action potential (CMAP) could be recorded over the muscle. Distal conduction velocity in this patient was normal when the ulnar nerve was stimulated below the medial epicondyle of the elbow, but was decreased when the ulnar nerve was stimulated just above the elbow, suggesting a conduction problem at the elbow.

The nerve conduction studies showed that both ulnar nerves were affected, although only the left one had produced symptoms. Nerve conduction studies of the median nerves were normal bilaterally. The patient was given elbow pads to wear while sleeping or while working at the computer; and he was instructed to avoid resting on his elbows. Two months later his paresthesias had improved markedly; strength in his finger abductors was normal, and he had only mildly decreased sensation in a left ulnar distribution.

CASE 9.7 UNILATERAL THIGH PAIN, WEAKNESS, AND NUMBNESS IN A DIABETIC

MINICASE
A 45-year-old man spent several weeks in the intensive care unit for diabetic ketoacidosis and severe bilateral pneumonia. When he finally stabilized and was transferred to a regular hospital floor, he noticed weakness and numbness in the left leg, with numbness and tingling over the anterior thigh down to the medial calf above the foot. A neurology consult was called, and on exam he had 4/5 strength in the left iliopsoas and quadriceps, with preserved strength in all other muscle groups, including the thigh adductors. There was decreased pinprick sensation in the left anterior thigh and medial calf (Figure 9.15). Reflexes were normal and symmetrical except for an absent left patellar reflex.

LOCALIZATION AND DIFFERENTIAL DIAGNOSIS
On the basis of the symptoms and signs shown in bold above, where is the lesion? What is the most likely diagnosis?

Figure 9.15 Region of Sensory Loss

Discussion
The key symptoms and signs in this case are:

- Weakness of the left iliopsoas and quadriceps with absent patellar reflex
- Paresthesias and decreased pinprick sensation in the left anterior thigh and medial calf

 syllable, the brachial plexus medial cord, or the C8 or T1 nerve roots (Table 9.1; KCC 9.1; see also Table 8.1). The fact that the symptoms are worse after pressure on the elbow, are not accompanied by neck pain (common in cervical radiculopathy; see KCC 8.3), and are not exacerbated by arm abduction plus elevation (characteristic of thoracic outlet syndrome) suggests, but does not prove, that the ulnar nerve is the culprit.

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The nerve conduction studies showed that both ulnar nerves were affected, although only the left one had produced symptoms. Nerve conduction studies of the median nerves were normal bilaterally. The patient was given elbow pads to wear while sleeping or while working at the computer; and he was instructed to avoid resting on his elbows. Two months later his paresthesias had improved markedly; strength in his finger abductors was normal, and he had only mildly decreased sensation in a left ulnar distribution.

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LOCALIZATION AND DIFFERENTIAL DIAGNOSIS
On the basis of the symptoms and signs shown in bold above, where is the lesion? What is the most likely diagnosis?

Figure 9.15 Region of Sensory Loss

Discussion
The key symptoms and signs in this case are:

- Weakness of the left iliopsoas and quadriceps with absent patellar reflex
- Paresthesias and decreased pinprick sensation in the left anterior thigh and medial calf
The pattern of weakness, reflex loss, and sensory changes in this patient could be caused by an L4 radiculopathy or a femoral neuropathy (Table 9.3; see also Tables 8.1, 8.6; Figure 8.4). The fact that thigh adduction is spared suggests a femoral neuropathy, since L4 contributes significantly to both the obturator and femoral nerves. The most likely diagnosis is left femoral neuropathy caused by diabetes (see KCC 8.1, 9.1). Less likely, insertion of a femoral vein catheter during the patient's stay in the intensive care unit may have caused an undetected hematoma compressing the femoral nerve. Compare this case to Case 8.9.

Clinical Course

The patient gradually recovered strength in the left leg. When seen 3 years later, he had 5/5 power in all muscle groups, but he had persistent sensory loss in a left femoral nerve distribution and an absent left patellar reflex.

CASE 9.8 TINGLING AND PARALYSIS OF THE FOOT AFTER A FALL

CHIEF COMPLAINT
A 35-year-old woman presented to the emergency room after a fall with tingling and paralysis of the right foot.

HISTORY
Two days ago the patient slipped on a wet floor in the supermarket and fell backward, landing on her back. She initially noticed no symptoms, but she woke up at 3:00 am to feed her 2-month-old baby and was unable to move her right foot. She also had a tingling sensation in her right lateral lower leg and foot. These symptoms did not resolve over the next 2 days, so she came to the emergency room. There was no back pain, and there were no bowel or bladder symptoms.

PHYSICAL EXAMINATION
Vital signs: T = 98°F, P = 84, BP = 136/68.
Neck: Supple with no bruits.
Lungs: Clear.
Heart: Regular rate.
Abdomen: Soft.
Extremities: Normal.
Back and spine: No tenderness.
Rectal: Normal tone with no masses.
Neurologic exam: MENTAL STATUS: Alert and oriented x 3. Fluent speech.
CRANIAL NERVES: Intact.
MOTOR: No drift. Normal tone, except for diminished tone in the right foot, 5/5 power throughout, except for 0/5 power in the right tibialis anterior, extensor hallucis longus, foot inverters, foot everters, and gastrocnemius, and 3/5 power in the right hamstrings.

REFLEXES:

COORDINATION: Normal on finger-to-nose testing.
Gait: Falling movements of the right foot while raising it off the floor with each step.
Sensory: Decreased light touch, pinprick, vibration, and joint position sense in the right lateral calf and in the entire right foot (Figure 9.16). Sensation otherwise normal.

LOCALIZATION AND DIFFERENTIAL DIAGNOSIS
On the basis of the symptoms and signs shown in bold above, where is the lesion? What is the most likely diagnosis?

Figure 9.16 Region of Sensory Loss

CASE 9.9 A LEG INJURY RESULTING IN FOOT DROP

MINICASE
A 27-year-old man slipped on a wet tile floor and twisted his right foot toward the left, resulting in acute foot pain, followed by weakness. He was seen in the emergency room and had 0/5 power in his right tibialis anterior and extensor hallucis longus, and 3/5 power in his right foot everters. Power was otherwise 5/5, including the right foot inverters and gastrocnemius. He had decreased sensation to pinprick on the dorsum of the right foot, which was especially pronounced in the web space between the first and second toes (Figure 9.18).

LOCALIZATION AND DIFFERENTIAL DIAGNOSIS
On the basis of the symptoms and signs shown in bold above, where is the lesion? What is the most likely diagnosis?
Discussion

The key symptoms and signs in this case are:
- Weakness in the right tibialis anterior and extensor hallucis longus; moderate weakness of the right foot evectors
- Decreased sensation to pinprick on the dorsum of the right foot, especially between the first and second toes

The pattern of weakness and sensory loss is consistent with injury to the common peroneal nerve (see Table 9.3; KCC 9.1; see also Table 8.1), which most likely occurred during the fall. Note that the deep peroneal nerve (tibialis anterior, extensor hallucis longus, sensation between first and second toes) appears to be more severely involved in this patient than the superficial peroneal nerve (foot eversion, sensation on dorsal foot and lateral shin). In addition, this should be distinguished from an L5 radiculopathy, in which there may also be weakness of foot inversion (compare to Case 9.10).

Clinical Course

An EMG (see KCC 9.2) 2 days after the injury showed abnormally low recruitment of motor unit action potentials in the right tibialis anterior, extensor hallucis longus, extensor digitorum brevis, and peroneus muscles, suggesting a neuropathic process. Motor nerve conduction studies showed decreased amplitudes when the right peroneal nerve was stimulated just above the fibular neck, and normal amplitudes when stimulated just below the fibular neck, suggesting nerve injury at the fibular neck. The patient gradually improved over the following months.

CASE 9.8 TINGLING AND PARALYSIS OF THE FOOT AFTER A FALL

Figure 9.17 Abnormal Bright Signal in the Right Sciatic Nerve, Compatible with Sciatic Neuropathy MRI of the lumbar plexus. (A) Coronal T2-weighted MRI showing the plane of section for B. (B) Axial T2-weighted section, showing abnormal bright signal in the right sciatic nerve as it passes dorsal to the femur.

CASE 9.9 (CONTINUED)

Figure 9.18 Bright Signal in Sciatic Nerve

CASE 9.10 LATERAL THIGH PAIN AND NUMBNESS AFTER PREGNANCY

MINICASE

two days after giving birth, a 24-year-old woman developed burning pain and numbness in the right lateral thigh, which was worsened by walking. Exam was normal except for a patch of decreased sensation to light touch, pinprick, and cold on the right lateral thigh (Figure 9.19). Specifically, reflexes and motor strength were normal.

LOCALIZATION AND DIFFERENTIAL DIAGNOSIS

On the basis of the symptoms and signs shown in bold above, where is the lesion? What is the most likely diagnosis?

Discussion

The key symptoms and signs in this case are:
- Pain, paresthesias, and decreased sensation to light touch, pinprick, and cold on the right lateral thigh

A purely sensory disorder affecting the lateral thigh is consistent with dysfunction of the lateral femoral cutaneous nerve, or femoral paresthesia (Figure 9.5, KCC 9.1). An L2 or L3 radiculopathy could be considered; however, there were no motor or reflex abnormalities or back pain to support this possibility.

Clinical Course

The patient was reassured that her symptoms were caused by injury to a sensory nerve that would likely improve with time. Her symptoms gradually resolved over the following 5 months and required no specific treatment.
CASE 9.11 DYSARTHRIA, PTOSIS, AND DECREASED EXERCISE TOLERANCE

CHIEF COMPLAINT
A 35-year-old woman saw a neurologist because of worsening dysarthria and muscle fatigue.

HISTORY
The patient worked as a nurse and over the course of four months she noticed that at the end of her shift, she had profound difficulty enunciating her words. This was most apparent at the end of her workday. Also, toward the end of her workday she had difficulty producing a full smile. Her symptoms disappeared with rest. She also noticed some mild neck discomfort and felt that it was difficult at times to hold her head up. In addition, she had reduced exercise tolerance, becoming short of breath sooner than previously when using the treadmill at her gym.

PHYSICAL EXAMINATION
Vital signs: T = 98°F, P = 80, BP = 90/70.
Neck: Supple, no bruits.
Lungs: Clear.
Heart: Regular rate.
Abdomen: Soft.
Extremities: Normal.
Neurologic exam:

DIAGNOSIS: Vascular lesions intact visual fields and acuity. Pupils equal and reactive to light and accommodation. Extracephalic movements intact with no nystagmus. On prolonged upgaze she developed ptosis of the left eyelid. Facial sensation was intact. Face movements were symmetrical. Hearing was normal. Palate elevation was normal and tongue was midline. While reading a long passage aloud, her speech gradually became dysarthric.

Motor: Normal tone. No fasciculations or tremor. 5/5 strength throughout.

Sensory: Normal pinprick, temperature, vibration, and joint position sense. No extinction.

LOCALIZATION AND DIFFERENTIAL DIAGNOSIS
1. Based on the symptoms and signs shown in bold above, where is the lesion?
2. What is the most likely diagnosis?

Discussion
The key symptoms and signs in this case are:
- Dysarthria, worse at the end of prolonged speech
- Difficulty producing a full smile at the end of the day
- Ptosis of the left eye on prolonged upgaze
- Difficulty holding head up at the end of the day
- Reduced strength and shortness of breath on treadmill

1. Dysarthria can be caused by cranial nerve or upper motor neuron disorders (see KCC 12.9), as well as facial weakness due to damage (see Figure 12.13). Ptosis can result from disorders of CN III supplying the levator palpebrae superioris, or from Horner's syndrome (see KCC 13.6). Weakness of the neck muscles, legs, and respiratory muscles, likewise, can have central or peripheral causes. However, the weakness in these multiple locations, in the absence of any sensory findings, would be unusual for a neuropathy. In addition, there are no upper motor neuron signs to suggest a multifocal disorder affecting the central nervous system. Therefore, a peripheral disorder affecting the neuromuscular junction or muscles involved in speech, eyelid elevation, respiratory muscles, and proximal respiratory, neck, and leg muscles is most likely.

2. This pattern of weakness with no sensory loss and intact reflexes, together with the fact that the weakness was worse toward the end of the day or with repeated use of the muscles, is most suggestive of myasthenia gravis (see KCC 8.1.1). Other possible causes of diffuse, slowly progressive weakness without sensory loss, reflex loss, or upper motor neuron signs include Lambert-Eaton syndrome and myopathic disorders (see KCC 8.1).

Diagnostic Studies and Clinical Course
The neurologist performed a Tensilon test (see KCC 8.1) by evaluating the patient's ability to read a long passage aloud. Her dysarthria was markedly reduced after administration of Tensilon, so the test was considered positive. Acetylcholine receptor antibodies were also positive at 1.73 nmol/L (normal is less than 0.3 nmol/L). Repetitive stimulation (see KCC 9.2) of the ulnar nerve at 5 per second produced a 23% decrement of the CMAP amplitude recorded over the abductor digiti minimi muscle (Figure 9.20). Decrements of greater than 10% is considered abnormal and supports the diagnosis of myasthenia gravis (see KCC 9.2). Pulmonary function tests were normal. The patient underwent a chest CT, which revealed a 7 x 5 cm lobulated mass in the right anterior mediastinum extending over to the right side of the pericardium, consistent with a thymoma (see KCC 8.1). She was treated with the anti-inflammatory medication prednisolone (Medrol) and underwent surgical resection of the thymic mass, which confirmed histologically to be a thymoma. Following surgery, her dysarthria and fatigue resolved completely, and she had a normal neurologic exam, including no dysarthria and no ptosis, even after prolonged upgaze.

Additional Cases
Related cases can be found in other chapters for the following topics: radiculopathy (Cases 8.1-8.11); distal symmetric polyneuropathy (Cases 6.5, 10.3); and cranial neuropathy (Cases 12.2-12.7, 13.1-13.3, 13.13). Other relevant cases can be found using the Case Index.

Brief Anatomical Study Guide
1. The brachial plexus arises from C5 through T1 (see Figure 9.2), while the lumbar plexus arises from L1 through S4 (see Figure 9.4).
2. The most clinically important nerves in the upper extremity are the radial, median, ulnar, axillary, and musculocutaneous nerves; the sensory and motor functions of these nerves are summarized in Table 9.1.
3. The most important nerves in the lower extremity are the femoral, obturator, sciatic, tibial, and peroneal nerves; the sensory and motor functions of these nerves are summarized in Table 9.3.

References
General References

Additional Cases
Related cases can be found in other chapters for the following topics: radiculopathy (Cases 8.1-8.11); distal symmetric polyneuropathy (Cases 6.5, 10.3); and cranial neuropathy (Cases 12.2-12.7, 13.1-13.3, 13.13). Other relevant cases can be found using the Case Index.

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2. The most clinically important nerves in the upper extremity are the radial, median, ulnar, axillary, and musculocutaneous nerves; the sensory and motor functions of these nerves are summarized in Table 9.1.
3. The most important nerves in the lower extremity are the femoral, obturator, sciatic, tibial, and peroneal nerves; the sensory and motor functions of these nerves are summarized in Table 9.3.

References
General References
CASE 9.11 DYSARTHRIA, PHTOSIS, AND DECREASED EXERCISE TOLERANCE

Figure 9.20 Decrement on Repetitive Stimulation
Repetitive stimulation testing was performed by stimulating the ulnar nerve of the right arm and recording the CMAP over the right abductor digitorum minimi muscle (see Figure 9.8). Stimulation was repeated at 1 per second for a total of 5 stimuli. Successive stimuli are shown displaced sequentially to the right (3 ms displacement per stimulus) to allow comparison of amplitudes of successive CMAs. The first CMAP in the series is displayed farthest to the left and the 5th CMAP is displayed farthest to the right. There was a decrement in CMAP amplitude of 23%.


Upper Extremity

Brachial Plexus

Median Nerve

Radial Nerve
Ulnar Nerve

Sciatic Nerve
Peroneal Nerve
Meralgia Paresthetica
CHAPTER 10

Cerebral Hemispheres and Vascular Supply

A 45-year-old man with a history of cigarette smoking and hypertension staggered into a diner grunting incoherently, then tripped and fell to the floor. The manager called an ambulance, and in the emergency room the patient was found to have severe right face and arm weakness. Six days later, he was still able to utter only a few barely articulate words, but he could follow many simple commands and answered yes/no questions appropriately. Each area of the cerebral cortex belongs to a specific vascular “territory,” and this patient’s symptoms are typical of cortical damage to one such territory. To diagnose and treat patients with these disorders, we must learn about the local functions of different parts of the cerebrum and their associated blood supply, which are the focus of this chapter.
ANATOMICAL AND CLINICAL REVIEW

The cerebral hemispheres are what we usually envision when we think of the human brain. In this chapter we will review the functional anatomy of the cerebral hemispheres by studying their blood supply and the clinical-anatomical correlations that can be made when the blood supply is transiently or permanently disrupted. The blood supply and functional anatomy of the brainstem and cerebellum will be discussed in Chapters 14 and 15; the spinal cord blood supply was discussed in Chapter 6. Understanding the blood supply of the brain provides a useful review of regional brain anatomy, since blood vessel territories typically overlap several spatially adjacent functional systems. In addition, knowledge of blood vessel territories is clinically useful, since it enables the localization of common stroke syndromes on clinical grounds, allowing proper diagnostic and therapeutic interventions to be promptly initiated.

Review of Main Functional Areas of Cerebral Cortex

We will now briefly review the main functional areas of the cerebral cortex that are commonly affected by cerebral infarctions (Figure 10.1). Additional details can be found in other chapters discussing motor, somatosensory, visual, and association cortex at greater length (see Chapters 2, 6, 7, 11, and 19.). Recall that the face and hand areas of the sensorimotor homunculi are on the lateral convexity, while the leg areas are in the two hemispheric fissures (see Figure 6.2). In the dominant hemisphere, upper left hemisphere, Broca's area lies in the inferior frontal gyrus, just anterior to the articulatory areas of the primary motor cortex, a location well suited for planning the articulatory program (Figure 10.1A; see also Figure 19.2, KCC 19.4). Meanwhile, Wernicke's area lies in the superior temporal gyrus, adjacent to the primary auditory cortex (see also Figure 12.16), and is involved in language processing. Association cortex in the non-dominant, usually right, hemisphere is important for attention to the contralateral body and space, especially the right parietal lobe. Primary visual cortex for the contralateral visual hemifield lies along the calcineurine fissure of the occipital lobe (Figure 10.1B; see also Figure 11.15). The optic radiations, while matter pathways carrying visual information from the thalamus to the visual cortex, pass under the parietal and temporal cortex; they can be damaged in infarcts of these lobes, causing contralateral visual field deficits.

Circle of Willis: Anterior and Posterior Circulations

The arterial supply to the cerebral hemispheres is derived from the anterior circulation provided by the bilateral paired internal carotid arteries, as well as by the posterior circulation provided by the bilateral vertebral arteries (Figure 10.2). The anterior circulation arises from the common carotid arteries originating at the aorta or brachiocephalic arteries (see Figure 4.20A). At the carotid bifurcation, the common carotid splits forming the internal carotid and external carotid arteries (see Figure 4.19). The vertebral arteries, which supply the posterior circulation, arise from the subclavian arteries (see Figure 4.20B) and then ascend (see Figure 4.19) through foramina in the transverse processes of the cervical vertebrae (foramina transversaria; see Figure 10.26) before entering the foramen magnum and joining to form the basilar artery. These anterior and posterior circulations meet in an anastomotic ring called the circle of Willis, from which all major cerebral vessels arise (Figure 10.3). The circle of Willis provides abundant opportunities for collateral flow; however, a complete ring is present in only approximately 5% of individuals. The main arteries supplying the cerebral hemispheres are the anterior, middle, and posterior cerebral arteries. The anterior cerebral arteries (ACAs) and middle cerebral arteries (MCAs) are the terminal branches of the internal carotid arteries. The anterior cerebral arteries anastomose anteriorly at the anterior communicating artery (AComm). The anterior and posterior circulations are linked to each other via the posterior communicating arteries (PComm's), which connect the internal carotids to the posterior cerebral arteries, thereby joining the anterior
and posterior circulations. The posterior cerebral arteries (PCAs) arise from the top of the basilar artery, which in turn is formed by the convergence of the two vertebral arteries. In addition to the posterior cerebral arteries, several branches to the brainstem and cerebellum arise from the verteobasilar system, as we will discuss in Chapters 14 and 15.

The internal carotid artery has several named segments during its course (see Figure 10.2). These can be well visualized in the angiograms in Figures 4.16A,C and 4.18B. First comes the relatively vertical cervical segment in the neck, followed by a sharp horizontal bend as the internal carotid enters the temporal bone as the petrous segment. Next comes the cavernous segment as the internal carotid begins its S-shaped turn, also known as the carotid siphon, within the cavernous sinus (see Figure 13.11). It then passes the anterior clinoid process (see Figure 5.2B) to pierce the dura and bends posteriorly to enter the subarachnoid space as the supracavernous, or intracavernous, segment (see Figure 4.16C). Although there are several smaller branches, the main branches of the supracavernous internal carotid artery can be remembered by the mnemonic OPAAM (if you can remember “OPAAM”), which stands for the Ophthalmic, Posterior communicating, Anterior choroidal, Anterior cerebral, and Middle cerebral arteries. The ophthalmic artery usually arises from the bend in the internal carotid just after it enters the dura (see Figure 4.16A,C). The ophthalmic artery enters the optic foramen with the optic nerve and provides the main blood supply to the retina.

Sometimes, in an alternative nomenclature, the terms A1, M1, and P1 are used for the initial segments of the ACA, MCA, and PCA, respectively, and second- and third-order branches are referred to as A2, A3, etc.
Figure 10.5 Regions of Cortex Supplied by the Anterior Cerebral Artery (ACA), Middle Cerebral Artery (MCA), and Posterior Cerebral Arteries (PCA) (A) Lateral view. (B) Medial view. (C) Interior view.

Vascular Territories of the Deep Cerebral Structures

The most important penetrating vessels at the base of the brain are the lentiform and calcarine arteries. These small vessels arise from the internal carotid and middle cerebral arteries, respectively, to supply the basal ganglia and internal capsule. The internal carotid artery supplies the anterior perforated substance, the anterior perforated substance, and the thalamus. The middle cerebral artery supplies the lateral geniculate nucleus and the posterior limb of the internal capsule. The posterior cerebral artery supplies the thalamus and the posterior limb of the internal capsule. The deep penetrating arteries that arise from the middle cerebral artery include the thalamoperforating arteries, which supply the thalamus and the posterior choroidal arteries, which supply the middle cerebral artery and the thalamus. The superficial and deep territories of the main cerebral arteries are summarized in the coronal and axial sections in Figure 10.9.

Figure 10.7 Lenticulostriate Arteries

Coronal section showing the lenticulostriate arteries arising from the proximal middle cerebral artery and supplying the basal ganglia and internal capsule. The recurrent artery of Heubner arises from the anterior cerebral artery.
Figure 10.8 Blood Supply to Deep Cerebral Structures

(A) Blood vessels supplying the basal ganglia and thalamus.

(B) Blood supply to the internal capsule and globus pallidus.

Figure 10.9 Summary of Superficial and Deep Blood Supply to the Cerebral Hemispheres

(A) Coronal section.

(B) Axial section.
Recognition of the classic syndromes produced by infarcts of the middle cerebral artery (MCA), anterior cerebral artery (ACA), and posterior cerebral artery (PCA) territories remains a cornerstone of neurologic assessment and continues to play an important role in evaluating patients with acute stroke. We discuss localization of these syndromes here; stroke pathophysiology and clinical management are discussed in KCC 10.3 and 10.4.

**Middle Cerebral Artery (MCA)**

Infarcts and ischemic events are more common in the middle cerebral artery than in the anterior or posterior cerebral arteries, at least in part, because of the relatively large territory supplied by the middle cerebral artery. MCA infarcts occur in three general regions (see Figures 10.6, 10.7, and 10.9):

1. Superior division
2. Inferior division
3. Deep territory

Proximal MCA occlusions affecting all three of these regions are called MCA stem infarcts. The most common deficits seen with infarcts of left or right MCA territories are summarized in Table 10.1. Knowledge of the deficits associated with each of these territories is clinically useful since MCA infarcts are relatively common. Deficits such as aphasia, hemineglect, hemianopia, and face-arm or face-arm-leg sensory/motor loss are described further in KCC 6.3, 7.3, 11.2, 19.6, 19.5, and 19.9. Large MCA territory infarcts

---

**TABLE 10.1 Major Clinical Syndromes of the MCA, ACA, and PCA Territories**

<table>
<thead>
<tr>
<th>LOCATION OF INFARCT</th>
<th>AFFECTED TERRITORY</th>
<th>DEFICITS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left MCA superior division</td>
<td>Right face and arm weakness of the upper motor neuron type, and a nonfluent, or Broca’s, aphasia. In some cases there may also be some right face and arm cortical-type sensory loss.</td>
<td></td>
</tr>
<tr>
<td>Left MCA inferior division</td>
<td>Flaccid, or Wernicke’s, aphasia and a right visual field deficit. There may also be some right face and arm cortical-type sensory loss. Motor findings are usually absent, and patients may initially seem confused or dizzy, but otherwise intact, unless carefully examined. Some mild right-sided weakness may be present, especially at the onset of symptoms.</td>
<td></td>
</tr>
<tr>
<td>Left MCA deep territory</td>
<td>Right pure motor hemiparesis of the upper motor neuron type. Larger infarcts may produce “cortical” deficits as well, such as aphasia.</td>
<td></td>
</tr>
<tr>
<td>Left MCA stem</td>
<td>Combination of the above, with right hemiplegia, right hemianesthesia, right homonymous hemianopia, and global aphasia. There is often a left gaze preference, especially at the onset, caused by damage to left hemisphere cortical areas important for driving the eyes to the right.</td>
<td></td>
</tr>
<tr>
<td>Right MCA superior division</td>
<td>Left face and arm weakness of the upper motor neuron type. Left hemineglect is present to a variable extent. In some cases there may also be some left face and arm cortical-type sensory loss.</td>
<td></td>
</tr>
<tr>
<td>Right MCA inferior division</td>
<td>Profound left hemineglect. Left visual field and somatosensory deficits are often present; however, these may be difficult to test convincingly because of the neglect. Motor neglect with decreased voluntary or spontaneous initiation of movements on the left side can also occur. However, even patients with left motor neglect usually have normal strength on the left side, as evidenced by occasional spontaneous movements or purposeful withdrawal from pain. Some mild right-sided weakness may be present. There is often a right gaze preference, especially at onset.</td>
<td></td>
</tr>
<tr>
<td>Right MCA deep territory</td>
<td>Left pure motor hemiparesis of the upper motor neuron type. Larger infarcts may produce “cortical” deficits as well, such as left hemineglect.</td>
<td></td>
</tr>
<tr>
<td>Right MCA stem</td>
<td>Combination of the above, with left hemiplegia, left hemianesthesia, left homonymous hemianopia, and profound left hemineglect. There is usually a right gaze preference, especially at the onset, caused by damage to right hemisphere cortical areas important for driving the eyes to the left.</td>
<td></td>
</tr>
<tr>
<td>Left ACA</td>
<td>Right leg weakness of the upper motor neuron type and right leg cortical-type sensory loss. Grasp reflex, frontal lobe behavioral abnormalities, and transcortical aphasia can also be seen. Larger infarcts may cause right hemiplegia.</td>
<td></td>
</tr>
<tr>
<td>Right ACA</td>
<td>Left leg weakness of the upper motor neuron type and left leg cortical-type sensory loss. Grasp reflex, frontal lobe behavioral abnormalities, and left hemineglect can also be seen. Larger infarcts may cause left hemiplegia.</td>
<td></td>
</tr>
<tr>
<td>Left PCA</td>
<td>Right homonymous hemianopia. Extension to the splenium of the corpus callosum can cause alesia without aphasia. Larger infarcts including the thalamus and internal capsule may cause aphasia, right hemisensory loss, and right hemiparesis.</td>
<td></td>
</tr>
<tr>
<td>Right PCA</td>
<td>Left homonymous hemianopia. Larger infarcts including the thalamus and internal capsule may cause left hemisensory loss and left hemiparesis.</td>
<td></td>
</tr>
</tbody>
</table>

*Compare regions of infarcts to Figure 10.1.*
often have a gaze preference towards the side of the lesion (see Figure 13.15) especially in the acute period, shortly after onset.

Other combinations not listed in Table 10.1, such as superior plus inferior division infarcts sparing deep territories, or superior division plus deep territories, can occasionally occur. In addition, there are sometimes partial or overlapping syndromes. Smaller cortical infarcts can also occur within one territory, producing more focal deficits, such as homoparesis (see KCC 6.3; Figure 6.14E, F).

Small deep infarcts involving penetrating branches of the MCA or other vessels are called lacunes, as we will discuss in KCC 10.4. Certain characteristic lacunar syndromes (see Table 10.3) can often be distinguished on clinical grounds from infarcts involving large blood vessel territories (see Table 10.1).

**Anterior Cerebral Artery (ACA)**

ACA infarcts typically produce contralateral lower extremity cortical-type sensory loss (see KCC 7.3) and weakness of the upper motor neuron type. There may also be a variable degree of frontal lobe dysfunction depending, in part, on the size of the infarct. Such dysfunction may include a gait apraxia, affect, apraxia, and incontinence (see KCC 19.11). Sometimes damage to the supplementary motor area and other regions in the frontal lobe leads to an unusual "alien hand syndrome" characterized by semilateral movements of the contralateral arm that are not under voluntary control.

**Posterior Cerebral Artery (PCA)**

PCA infarcts typically cause a contralateral homonymous hemianopia (see Table 10.1, Figure 11.15). Smaller infarcts that do not involve the whole PCA territory may cause smaller homonymous visual field defects. Sometimes the small penetrating vessels that come off the proximal PCA are involved, leading to infarcts in the thalamus or posterior limb of the internal capsule. The result can be a contralateral sensory loss, contralateral hemiparesis, or even homonymous aphasia (see KCC 19.6). If the infarct is in the dominant hemisphere, the motor areas of the cortex or the superior division of the internal capsule can produce alexia without agraphia (see KCC 10.7).

Small perforating vessels arising from the proximal PCAs at the top of the basilar artery (see Figure 4.17B) supply the midbrain. Vascular syndromes of this region of the brainstem will be discussed in Chapter 14 (see KCC 14.3).

### REVIEW EXERCISE

Cover all but the left-most column in Table 10.1. For each vessel territory, describe the regions of the brain involved (see Figures 10.5, 10.9) and the expected deficits (see Figure 10.1).

### KEY CLINICAL CONCEPT

**WATERSHED INFARCTS**

When a cerebral artery is occluded, ischemia or infarction occurs in the territory supplied by that vessel, with regions near other vessels relatively spared. In contrast, when the blood supply to two adjacent cerebral arteries is compromised, the regions between the two vessels may be more susceptible to ischemia and infarction. These regions between cerebral arteries are called **watershed zones** (Figure 10.10). Bilateral watershed infarcts in both the ACA-MCA and MCA-PCA watershed zones can occur with severe drops in systemic blood pressure. A sudden occlusion of an internal carotid artery or a drop in blood pressure in a patient with carotid stenosis (KCC 10.5) can cause an ACA-MCA watershed infarct, since these vessels are both fed by the carotid system (see Figure 10.2).

Watershed infarcts can produce proximal arm and leg weakness ("arm in the barrel" syndrome) because the regions of homunculus involved often include the trunk and proximal limbs (see Figure 10.1A). In the dominant hemisphere, watershed infarcts can cause transcortical aphasia syndromes (see KCC 19.6). MCA-PCA watershed infarcts can cause disturbances of higher-order visual processing (see KCC 19.12). In addition to watershed infarcts between the superficial territories of different cerebral vessels, watershed infarcts can also occasionally occur between the superficial and deep territories of the MCA (see Figure 10.9).

### 10.2 Transient neurologic episodes are a common diagnostic problem. Symptoms and signs may be positive or negative, and they can be motor, somatosensory, visual, auditory, olfactory, kinesthetic, emotional, or cognitive in nature. Some causes of transient neurologic episodes are listed in Table 10.2. Of these, the most common causes are transient ischemic attacks, migraines, seizures, and other non-neurologic conditions such as cardiac arrhythmia or hypoglycemia. In this chapter we will be concerned primarily with transient neurologic episodes caused by cerebrovascular disease. A transient ischemic attack, or TIA, is classically defined as a neurologic deficit lasting less than 24 hours, caused by temporary brain ischemia. This concept has been revised in recent years for several reasons. First, although some transient ischemic deficits last longer, the more typical duration for a TIA is about 10 minutes. Second, improved imaging technology and animal studies suggest that ischemic deficits lasting more than about 10 minutes probably produce at least some permanent cell death in the involved region of the brain. In TIA lasting more than an hour, in fact, are usually small infarcts. On the other hand, despite the appearance of a small infarct on an MRI scan, complete functional recovery can sometimes occur within 1 day. The concept of a TIA remains useful, at the very least, as an important warning sign for a potentially larger ischemic injury to the brain. Several mechanisms for TIA's have been proposed, each of which may occur in different situations. One possibility is that an embolus temporarily occludes the blood vessel but then dissolves, allowing return of blood flow...
TABLE 10.2 Differential Diagnosis of Transient Neurologic Episodes

<table>
<thead>
<tr>
<th>CATEGORY</th>
<th>EXAMPLES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Structural/mechanical</td>
<td>Intermittent compression of spinal cord or peripheral nerve; Chialt</td>
</tr>
<tr>
<td>Vascular</td>
<td>malformation; phlebothrombosis</td>
</tr>
<tr>
<td>Epileptic seizures</td>
<td></td>
</tr>
<tr>
<td>CSF flow-related</td>
<td>Colloid cyst of the third ventricle</td>
</tr>
<tr>
<td>Genetic</td>
<td></td>
</tr>
<tr>
<td>Toxic/metabolic</td>
<td>Hypokalemic or hyperkalemic periodic paralysis; epileptic status</td>
</tr>
<tr>
<td>Infectious/Inflammatory</td>
<td>Medication-related; toxic exposure; hypoglycemia; carcinoid;</td>
</tr>
<tr>
<td>Movement disorders</td>
<td>Encephalitis; multiple sclerosis</td>
</tr>
<tr>
<td>Psychogenic</td>
<td>Chorea; dystonia; tic disorders</td>
</tr>
<tr>
<td>Other</td>
<td>Panic attacks; dissociative disorders; somatization</td>
</tr>
<tr>
<td>Other non-neurologic</td>
<td>Retinal detachment; shoulder dislocations; angina; cardiac arrhythmias;</td>
</tr>
<tr>
<td></td>
<td>hypotension; hypoglycemia; peripheral vascular disease; breath-holding</td>
</tr>
<tr>
<td></td>
<td>spells</td>
</tr>
</tbody>
</table>

*Following format of Figure 1.1.

Before permanent damage occurs. Other possibilities include in situ thrombus formation on the blood vessel wall and/or vasospasm leading to temporary narrowing at the blood vessel lumen.

Transit loss of consciousness without other focal features is a special case of transient neurologic dysfunction. The most common cause by far is cardiac syncope including vasovagal transient episodes of hypotension ("fainting"). Other causes include angina, peripheral vascular disease, and other non-neurologic causes. Neurologic causes are responsible for less than 5% to 10% of cases of syncope, and include seizures (see KCC 18.2), other causes of coma listed in Table 14.4, and rarely, TIA of the posterior circulation affecting the brain or reticular activating systems (see KCC 14.3).

STROKE Stroke is the third leading cause of death in the United States and a major cause of permanent disability. Recent improvements in the acute diagnostic and therapeutic management of stroke have made it clear that stroke should be treated as an emergency along similar lines to those currently used for cardiac emergencies. Stroke refers to both hemorrhagic events, such as intracerebral or subarachnoid hemorrhage, and to ischemic infarction of the brain. Sometimes ischemic strokes can cause blood vessels to become fragile and rupture, leading to secondary hemorrhagic conversion. Ischemic stroke is discussed in this section, and nontraumatic intracranial hemorrhage is discussed in KCC 5.6.

Mechanisms of Ischemic Stroke

Ischemic stroke occurs when there is inadequate blood supply to a region of the brain for enough time to cause injury (death) of brain tissue. There are numerous mechanisms for ischemic stroke. In clinical practice, a distinction is often made between embolic and thrombotic strokes. In an embolic infarct a piece of material (usually a blood clot) is formed in one place and then embolizes through the bloodstream to suddenly lodge in and occlude a blood vessel supplying the brain. In thrombotic infarcts a blood clot is formed locally on the blood vessel wall, usually at the site of an underlying atherosclerotic plaque, causing the vessel to occlude. Embolic infarcts are considered to occur suddenly with minimal deficits at onset, whereas thrombotic infarcts may have a more stuttering course. In reality, this distinction is not often easy to make on clinical grounds alone.

Another important distinction is between large-vessel and small-vessel infarcts. Large-vessel infarcts involve the major blood vessels on the surface of the brain, such as the middle cerebral artery and its main branches (see KCC 10.5). Large-vessel infarcts are most often caused by emboli, although thromboemboli can also occasionally occur, especially in large proximal vessels such as the vertebral, basilar (see KCC 14.3), and carotid arteries. Small-vessel infarcts involve the small penetrating vessels that supply deep structures in the cerebral hemispheres. These include the basal ganglia, thalamus, and internal capsule (see Figures 10.7, 10.8), while in the brainstem these include the medial portions of the midbrain, pons, and medulla (see Figures 14.18, 14.20). Small-vessel infarcts are sometimes also called lacunar infarcts because they resemble small lakes or cavities when the brain is examined on pathologic section.

In embolic infarcts, the goal is to detect the source of the embolus and then to try to stop the stroke before it occurs. Emboli are most commonly composed of thrombotic material (blood clot). In cardioembolic infarcts, the embolus originates in the heart. Cardioembolic infarcts occur in conditions such as atrial fibrillation, in which thrombi form in the fibrillating left atrial appendage; myocardial infarction, in which thrombi form on hypokalemic or diabetic regions of infarcted myocardium; and valvular disease or mechanical protheses, in which thrombi form on the valve leaflets or prosthetic parts.

Artery-to-artery emboli can also occur. These include emboli arising from a stenosed segment of the internal carotid artery (KCC 10.5), vertebral arteries, or an occluded basilar artery. Dissection of the carotid or vertebral arteries (KCC 10.6) often results in thrombus formation, which can embolize to the brain. In addition, atherosclerotic disease of the aortic arch is increasingly being recognized as an important potential source of artery-to-artery thromboembolic material. Occasionally, a patient with more than one cause of embolism can develop a thromboembolus formed in the venous system to bypass the lungs and pass directly from the right side of the heart, reaching the brain.

Aside from thrombus, emboli composed of other materials can less commonly lead to stroke. Examples include air emboli in deep-sea divers or iatrogenic introduction of air into the circulation; septic emboli in bacterial endocarditis, which can lead to mycotic aneurysms and hemorrhage; fat or cholesterol emboli in trauma to long bones or to arterial walls; proteinaceous emboli in marantic endocarditis; disc emboli in cervical trauma; amniotic fluid emboli during childbirth; platelet aggregates; and foreign materials introduced into the circulation (such as talc or other contaminants of illicit intravenous drugs).

Lacunar infarcts are usually associated with small-vessel disease caused by chronic hypertension. In hypertension, small penetrating vessels become occluded by a pathologic process known as lipohyalinosis. Small vessels can also be occluded by atherosclerotic disease, in situ thrombosis, or small emboli. Abnormalities of the parent vessel wall such as thrombosis, atheroma formation, or dissection can occlude the openings to one or more small vessels. Numerous characteristic lacunar syndromes have been described and most of the common ones are listed in Table 10.3. The clinical features of these lacunar syndromes can help localize infarcts and can help distinguish them from large vessel infarcts (see Table 10.1).

In ataxic hemiparesis, the ataxia (see KCC 15.2) is caused by damage to proprioceptive or cerebellar circuitry rather than by damage to the cerebellum itself.
Thalamic lacunes can cause contralateral somatosensory deficits (see KCC 7.3; Figure 7.9A), sometimes followed by a thalamic pain syndrome. Basal ganglia lacunes can occasionally cause movement disorders such as hemiballismus (see KCC 16.1). For additional details on less common lacunar syndromes, see the references at the end of this chapter.

Cortical vs. subcortical lesions can sometimes be differentiated clinically based on the absence or presence of so-called cortical signs, including aphasia (see KCC 15.6), neglect (see KCC 19.5), homonymous visual field defects (see KCC 11.2), and cortical sensory loss (see KCC 7.3). However, each of these defects can be seen in some cases of subcortical lesions as well. Presence of a typical lacunar syndrome (Table 10.3), such as pure motor hemiparesis, suggests that a subcortical lesion is present. Clinical differentiation between hemispheric vs. brainstem lesions will be discussed in KCC 14.3.

In addition to focal neurologic deficits (see KCC 10.1, 10.2, 11.3, and 14.3), ischemic stroke can be associated with headache, or less commonly, seizures. Headache (see KCC 5.1) occurs in 25% to 30% of ischemic strokes. When headache is unilateral, it is more commonly on the side of the infarct, although exceptions do occur. Headache may be more common for posterior than for anterior circulation infarcts, and is often seen in diastole of the carotid or vertebral arteries (see KCC 10.6). Seizures (see KCC 18.2) occur in 10% to 15% of stroke patients, occasionally as the presenting abnormality.

**TABLE 10.3 Common Lacunar Syndromes**

<table>
<thead>
<tr>
<th>SYNDROME</th>
<th>CLINICAL FEATURES</th>
<th>POSSIBLE LOCATIONS FOR INFARCT</th>
<th>POSSIBLE VESSELS INVOLVED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pure motor hemiparesis or</td>
<td>Unilateral face, arm, and leg upper motor neuron-type</td>
<td>Posterior limit of internal</td>
<td>Lenticulostriate arteries (common), anterior choroidal artery, or perfering branches of posterior cerebral artery</td>
</tr>
<tr>
<td>dysarthria hemiparesis</td>
<td>weakness, with dysarthria</td>
<td>capsule (common)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ventral pons (common)</td>
<td>Ventral penetrating branches of basilar artery</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Corona radiata</td>
<td>Small middle cerebral artery branches</td>
</tr>
<tr>
<td>Ataxic hemiparesis</td>
<td>Same as pure motor hemiparesis, but with ataxia on one</td>
<td>Same as pure motor hemiparesis</td>
<td>Same as pure motor hemiparesis</td>
</tr>
<tr>
<td>(thalamic lacune)</td>
<td>same side as weakness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pure sensory stroke</td>
<td>Sensory loss to all primary modalities in the</td>
<td>Posterior lateral nucleus of the thalamus (VPL)</td>
<td>Thalamo-perforator branches of the posterior central arteries</td>
</tr>
<tr>
<td>(thalamic lacune)</td>
<td>contralateral face and body</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensory-motor stroke</td>
<td>Combination of thalamic lacune and pure motor</td>
<td>Posterior limit of the internal</td>
<td>Thalamo-perforator branches of the posterior central arteries</td>
</tr>
<tr>
<td>(thalamo-occipital lacune)</td>
<td>hemiparesis</td>
<td>capsule, and either thalamic</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>VPL or thalamic somatosensory</td>
<td>Lenticulostriate arteries, anterior choroidal, thalamo-perforator, or Teuber’s arteries</td>
</tr>
<tr>
<td>Basal ganglia lacune</td>
<td>Usually asymptomatic, but may cause hemiballismus (see</td>
<td>Caudate, putamen, globus</td>
<td></td>
</tr>
<tr>
<td></td>
<td>KCC 16.1)</td>
<td>pallidus, or subthalamic nuclei</td>
<td></td>
</tr>
</tbody>
</table>

Is summarized:
- Emboli usually cause large-vessel infarcts involving cerebral (or less commonly) corticospinal cortices, with sudden onset of maximal deficits.
- Lacunes are small-vessel infarcts usually seen in chronic hypertension, commonly affecting the deep white matter and nuclei of the cerebral hemispheres and brainstem.
- Thrombosis occasionally occurs in large proximal vessels such as vertebral, basilar, and carotid arteries and may also contribute to lacunar infarction.

**Stroke Risk Factors**

Certain patients are at increased risk for vascular disease, including ischemic stroke. When the history is being taken, patients should be asked if they have the following common vascular risk factors: hypertension, diabetes, hypercholesterolemia, cigarette smoking, family history, or prior history of stroke or other vascular disease (Table 10.4). In addition, certain cardiac disorders are important risk factors for stroke, especially atrial fibrillation, mechanical valves or other valvular abnormalities, patent foramen ovale (mentioned in the section on cardioembolic stroke), and annuloplasty or artificial heart valves for mitral valve disease (Table 10.5).

Less commonly, several other systemic medical conditions may affect the coagulation pathways or work through other mechanisms to increase both thrombotic and embolic infarcts (Table 10.3). Those that coagulate platelets also increase the risk for venous thrombosis (see KCC 10.7).

Ischemic stroke is relatively uncommon in young individuals because the cumulative effects of the major stroke risk factors (see Table 10.4) tend to women with age. When stroke does occur in a young patient, conditions such as arterial dissection (see KCC 10.6), patent foramen ovale, or the disorders listed in Table 10.5 should be considered in addition to the usual causes.

**Treatment and Diagnostic Workup of Ischemic Stroke and TIA**

There is a growing movement to treat stroke or TIA as an acute medical emergency or brain attack, similar to heart attack. Prompt medical attention allows early therapeutic interventions that improve outcome. When the history and exam suggest a possible ischemic event, an imaging study of the brain should be done immediately to rule out hemorrhage. In most emergency rooms, CT scans can be performed more quickly than MRI scans, and a CT will suffice for this purpose. Remember that an infarct will often not be visible on the initial CT scan, especially if it is done within a few hours of symptom onset; however, a hemorrhage will almost always be visible (see Chapter 4). Meanwhile, routine blood chemistries, cell counts, and coagulation studies should be sent. Specialized coagulation studies can be sent when clinically appropriate (Table 10.5), such as in a young individual with no known vascular risk factor.

Once a hemorrhage has been ruled out by CT, many physicians treat patients with thrombolytic agents, such as tissue plasminogen activator (t-PA), in acute ischemic stroke. This treatment has been demonstrated to be effective, and it improves the chances of a good functional outcome if given within 3 hours of stroke onset; however, it does carry some increased risk of intracranial hemorrhage. In patients with stroke who are not eligible for t-PA, or in patients who have had a TIA, heparin anticoagulation is often used while further diagnostic studies are being performed. As with t-PA, it is essential to rule out the presence of intracranial hemorrhage before administering this treatment. There is some controversy over the use of heparin in acute stroke, and further studies will be needed to investigate its safety and efficacy.

Other acute interventions being investigated include intra-arterial thrombolysis. This is performed by catheterization of the occluded vessel

**TABLE 10.4 Common Stroke Risk Factors**

<table>
<thead>
<tr>
<th>Risk Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
</tr>
<tr>
<td>Cigarette smoking</td>
</tr>
<tr>
<td>Positive family history</td>
</tr>
<tr>
<td>Cardiac disease (valvular disease, atrial fibrillation, patent foramen ovale, low ejection fraction)</td>
</tr>
<tr>
<td>Prior history of stroke or other vascular disease</td>
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**TABLE 10.5 Medical Conditions Leading to Hypercoagulability**

<table>
<thead>
<tr>
<th>Condition</th>
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<tbody>
<tr>
<td>Protein S deficiency</td>
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<tr>
<td>Protein C deficiency</td>
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<tr>
<td>Antithrombin III deficiency</td>
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<tr>
<td>Other hereditary coagulation factor disorders</td>
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<tr>
<td>Dehydration</td>
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<tr>
<td>Adrenocarcinoma</td>
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<tr>
<td>Surgery, trauma, childbirth</td>
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<tr>
<td>Disseminated intravascular coagulation</td>
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<tr>
<td>Antiphospholipid antibody syndromes</td>
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<tr>
<td>Vasculitis (effects on vessel wall in addition to hypercoagulability)</td>
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<tr>
<td>Temporal arteritis</td>
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<tr>
<td>Primary central nervous system vasculitis (granulomatous angitis)</td>
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<tr>
<td>Systemic lupus erythematosus</td>
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<tr>
<td>Polyarteritis nodosa</td>
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<tr>
<td>Wegener's granulomatosis</td>
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<tr>
<td>Other chronic systemic disorders</td>
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<tr>
<td>Infections</td>
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<tr>
<td>Neoplasm</td>
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<tr>
<td>Sickle cell disease</td>
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<tr>
<td>Polycythemia</td>
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<tr>
<td>Leukemia</td>
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<tr>
<td>Glucose intolerance</td>
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<tr>
<td>Homocysteinemia (increases risk of atherosclerosis)</td>
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(see Figure 4.9), which allows direct administration of the thrombolytic agent to the thrombus. In addition, several compounds are being tested that may preserve brain tissue before irreversible cell damage occurs, such as atorvastatin, calcium channel blockers, and glutamate receptor antagonists. Angioplasty and stenting of stenosed vertebral, carotid, and intracranial vessels are being tried against the lines of similar procedures in coronary arteries. Finally, hyperglycemia should be corrected in acute stroke because it can worsen hemorrhagic lesions by increasing local tissue acidosis and blood-brain barrier permeability.

Patients are best managed in an inpatient setting, and some studies suggest improved outcomes with specialized stroke units. The diagnostic evaluation begins with the patient's history and examination, including questions about stroke risk factors (see Table 10.4), and continues with certain diagnostic tests, which we will now discuss. Blood flow in the major cranial and neck vessels should be assessed with Doppler ultrasound and/or magnetic resonance angiography (MRA; see Figures 4.18, 4.19). This is particularly important in suspected internal carotid artery stenosis, since carotid endarterectomy may be required (see KCC 10.5). Conventional angiography may be needed in cases where the degree of stenosis is uncertain based on these tests.

The possibility of a cardioembolic source should be investigated with an electrocardiogram to look for evidence of cardiac ischemia or arrhythmias, and an echocardiogram to look for structural abnormalities or thrombus. Some practitioners perform a 24-hour Holter monitor test to look for arrhythmias, although the diagnostic yield of this test may be low if used in all patients. Studies have shown that patients with atrial fibrillation are at increased risk of embolic stroke, and that this risk is significantly reduced from the top of the thrombus treated with Coumadin oral anticoagulation. As already mentioned, young patients with stroke or other patients with suggestive history should also be evaluated for the less common conditions listed in Table 10.5.

In patients with large MCA infarcts, there may be substantial edema and mass effect, which can sometimes lead to herniation (see KCC 5.4) and death.

One therapeutic measure that is being investigated for such patients is hemi-infarctectomy, in which a portion of skull is temporarily removed over the region of swelling and is later replaced after the danger of herniation has passed.

Because stroke often occurs in conjunction with other serious medical disorders, a multidisciplinary treatment approach is appropriate. Careful attention to medical complications, high-quality nursing care, and a comprehensive rehabilitation program can substantially reduce morbidity and mortality.

Preventive measures are most important in reducing the incidence of stroke. Modifiable risk factors such as hypertension, smoking, and hypercholesterolemia should be addressed. In addition, antithrombotic drugs such as aspirin have been shown to reduce the risk of ischemic stroke recurrence.

KEY CLINICAL CONCEPT
CAROTID STENOSIS

10.5 Atherosclerotic disease commonly leads to stenosis of the internal carotid artery just beyond the carotid bifurcation (see Figures 4.18, 10). Thrombi formed on a stenotic internal carotid artery can embolize distally, giving rise to TIAs or infarcts of various carotid branches, especially the MCA, ACA, and Ophthalmic artery. Carotid stenosis is thus associated with MCA territory symptoms such as contralateral face-arm or face-arm-leg weakness, contralateral sensory changes, contralateral visual field defects, aphasia, or neglect. In addition, there may be ophthalmic artery symptoms such as ipsilateral monocular visual loss (see KCC 11.3), and ACA territory symptoms such as contralateral leg weakness.

Carotid stenosis can sometimes be detected on physical examination as a whooshing sound, or bruit, that continues into diastole and is best heard with the bell of the stethoscope applied lightly just below the angle of the jaw (see neuroxcom.com Video 2). The severity of carotid stenosis can usually be estimated noninvasively with Doppler ultrasound and MRA, although conventional angiography remains gold standard. Recent studies have demonstrated an important role for carotid endarterectomy in symptomatic carotid stenosis. In this procedure the carotid artery is exposed surgically and temporarily clamped. A longitudinal incision is made in the artery, and atheromatous material is washed out from the internal carotid lumen, eliminating the stenosis. Carotid endarterectomy has been compared prospectively with medical therapy in patients who had a stroke or TIA on the side of a >70% stenosis of the internal carotid artery. Over 2 years of follow-up in one major trial (the North American Symptomatic Carotid Endarterectomy Trial), the rate of stroke on the side of the stenosis was 26% in the medically treated group, compared to 9% in the group that underwent endarterectomy. Studies have also suggested that in less severe (50% to 70%) carotid stenosis with symptoms or severe carotid stenosis even without symptoms, outcome may be improved by surgery, although the data is less convincing than in symptomatic carotid stenosis.

Carotid endarterectomy may be performed in patients who have ipsilateral amaurosis fugax, in patients with transient ischemic attacks, or in patients with recent symptoms who have an asymptomatic carotid stenosis of >70%.

10.6 Head or neck trauma, and sometimes even minor events such as a coughing sneeze, can cause a small tear to form on the inner surface of the carotid or vertebral arteries. This may allow blood to burst into the vessel wall, producing a dissection. A flap then protrudes into the vessel lumen, under which thrombus forms that can embolize distally. Patients with a dissection may describe feeling of pressure or tingling in the neck, and may report a pop at the onset. In carotid dissection, the patient may hear a turbulent sound with each heartbeat and have an ipsilateral Horner's syndrome (see KCC 13.5) and pain over the eye. In vertebral dissection, there is often posterior neck and occipital pain. TIAs or infarcts occur in the anterior circulation with carotid dissection, and in the posterior circulation with vertebral dissection. There may be a delay of hours to up to several weeks between onset of dissection and ischemic events. Dissection is usually treated with intravenous heparin antiocoagulation followed by oral Coumadin anticoagulation to prevent thromboembolic events. The required duration of therapy has not been studied, but most practitioners continue anticoagulation for several months and perform follow-up MRAs to ensure adequate vessel wall antiocoagulation. Sometimes dissection, particularly of the vertebral artery, leads to formation of a pseudoaneurysm that may rarely rupture, causing subarachnoid hemorrhage.

KEY CLINICAL CONCEPT
DISSECTION OF THE CAROTID OR VERTEBRAL ARTERIES
Venous Drainage of the Cerebral Hemispheres

Like the arterial system, the venous drainage of the brain has superficial and deep territories. The superficial veins drain mainly into the superior sagittal sinus and the cavernous sinus, while the deep veins drain into the great vein of Galen (Figure 10.11). Ultimately, nearly all venous drainage for the brain reaches the internal jugular veins. As we discussed in Chapter 5, the major cerebral venous sinuses lie enclosed within folds of the two layers of dura (see Figure 5.1).

The superior sagittal sinus sweeps back and drains into the two transverse sinuses (Figure 10.11A,B). Each of these sinuses turns downward to become a sigmoid sinus that exits the skull through the jugular foramen, draining the internal jugular vein. The cavernous sinus is a plexus of veins located on either side of the sella turcica that surrounds portions of the internal carotid artery and cranial nerves III, IV, V, and VI (see also Figure 13.11). The cavernous sinus drains via the superior petrosal sinus into the transverse sinus, and via the inferior petrosal sinus into the internal jugular vein (see Figure 10.11A,B). The deep structures drain into the internal cerebral veins (see Figure 4.7), the basal veins of Rosenthal, and other veins to reach the great cerebral vein of Galen (see Figure 10.11B,D). The great vein of Galen enters the dura of the tentorium and is joined by the inferior sagittal sinus to form the straight sinus, or sinus rectus (see Figure 10.11B; also see Figure 4.15A).

The confluence of the sinuses, also known as the torcular Herophili (or more simply as the torcula), occurs where the superior sagittal, straight, and occipital sinuses join together and are drained by the transverse sinuses (see Figure 10.11A,B). The torcula is often shaped in such a manner that most blood from the superior sagittal sinus enters the right transverse sinus, while most blood from the straight sinus enters the left transverse sinus.

Although cortical veins are highly variable, a few major, fairly constant veins include the inferior anastomotic vein of Labbe, which drains into the transverse sinus, the superior anastomotic vein of Trolard, which drains into the superior sagittal sinus, and the superficial middle cerebral vein, which drains into the cavernous sinus (see Figure 10.11C). The anterior cerebral veins and deep middle cerebral veins drain into the basal veins of Rosenthal, which then join the internal cerebral veins to form the great vein of Galen (see Figure 10.11D).

10.2 Sagittal sinus thrombosis is often associated with one of the hypercoagulable states listed in Table 10.5. It occurs with increased frequency in pregnant women and within the first few weeks post partum. Obstruction of venous drainage usually causes elevated intracranial pressure (see KCC 5.3). Back pressure in cortical veins can cause para-sagittal hemorrhages. In addition, the increased venous pressure can decrease cerebral perfusion, leading to infarcts. Seizures are common. Patients often have headaches and papilledema, and they may have depressed level of consciousness. The superior sagittal sinus can normally be seen as a triangular region on axial CT and MRI scan images (see Figures 4.12, 4.13). The sinus normally fills with intravenous contrast (see Figure 4.4), but in sagittal sinus thrombosis there may be a central, darker-filling defect, called the empty delta sign. More subtle radiological signs of sagittal sinus thrombosis include increased density of the sagittal sinus on CT due to conglobate blood (see Table 4.1), or increased T1 signal on MRI (see Table 4.4). In suspected sagittal sinus thrombosis, regardless of whether these subtle radiological findings are present, a more definitive study should be performed, such as magnetic resonance venography (MRV) or a conventional angiogram. Treatment usually involves anticoagulation therapy; although this is controversial when hemorrhage has occurred. Seizures (see KCC 18.2) and elevated intracranial pressure (see KCC 5.3) should be treated as well when present.

Thrombosis can also occur less commonly in the deep cerebral veins or in a major cortical vein, leading to infarcts or hemorrhage in the territories of these vessels.
CASE 10.1 SUDDEN-ONSET WORST HEADACHE OF LIFE

MINICASE
A 68-year-old man suddenly developed "the worst headache of my life." He had a history of severe diffuse arteriosclerosis, including coronary artery disease and peripheral vascular disease requiring multiple bypass operations. He was also a heavy smoker for over 40 years. On the morning of admission he was walking in the hallway at home, and at 10:00 am he suddenly developed an explosive headache worse than anything he had ever experienced. The headache began in the bifrontal area and over the next few minutes spread all over his head and down his neck.

He denied nausea, vomiting, loss of consciousness, or vision changes. Examination was unremarkable except for mild nuchal rigidity.

LOCALIZATION AND DIFFERENTIAL DIAGNOSIS
1. What diagnosis should be suspected in cases with this kind of clinical presentation (see Chapter 5)?
2. What is the most common cause of this disorder, and what vessels are most commonly affected?
3. What is the significance of the nuchal rigidity?
4. What tests should be performed?

Discussion
1. Sudden onset of severe headache that is worse than any experienced previously should be considered a subarachnoid hemorrhage until proven otherwise (see KCC 5.1, 5.6).
2. In about 80% of cases, spontaneous subarachnoid hemorrhage is caused by rupture of an aneurysm in the subarachnoid space. The most common locations for aneurysms are the origin of the anterior communicating artery, posterior communicating artery, or bifurcation points of the middle cerebral artery (see Figure 5.20).
3. Nuchal rigidity is often a sign of meningeal irritation (see Table 5.5) caused by inflammation, infection, or hemorrhage in the subarachnoid space.
4. In suspected subarachnoid hemorrhage an emergency head CT should be performed. Rarely, the CT is negative in subarachnoid hemorrhage, so if the clinical situation suggests subarachnoid hemorrhage, a lumbar puncture should then be performed (see KCC 5.10). Lumbar puncture should not be performed if the CT is positive, especially since lumbar puncture can occasionally cause aneurysm rupture by increasing the pressure across the wall of the aneurysm. If the patient is a candidate for surgery, once the diagnosis of subarachnoid hemorrhage has been confirmed, an angiogram should be performed to localize the aneurysm so that it can promptly be treated surgically.

Neuroradiology
The patient underwent an emergency head CT (Figure 10.12A), which demonstrated regions of hyperdensity in the subarachnoid space consistent with diffuse subarachnoid hemorrhage layering in the interhemispheric fissure, in the Sylvian fissures, and around the brainstem. In addition, the lateral ventricles appeared mildly dilated, compatible with hydrocephalus. This can occur from impaired CSF flow in the subarachnoid space because of the hemorrhage (see KCC 5.7). Next the patient was taken for an angiogram (see Figure 10.12B-D).
1. What blood vessel was injected with contrast dye to produce the images in Figure 10.12B-D? Cover the labels on Figure 10.12 and identify the internal carotid, anterior cerebral, and middle cerebral arteries (including the lenticonvex arteries). Note the presence of a sacular aneurysm measuring approximately 1 cm in diameter.
2. What is the site of origin of the aneurysm?

CEREBRAL HEMISPHERES AND VASCULAR SUPPLY

CASE 10.2 LEFT LEG WEAKNESS AND LEFT ALIEN HAND SYNDROME

CHIEF COMPLAINT
A 67-year-old woman suddenly developed left leg weakness and difficulty using her left hand.

HISTORY
Past history was notable for hypertension, peripheral vascular disease, and smoking one pack per day for 40 years. On the morning of admission, after finishing breakfast the patient tried to stand up and suddenly found she could not support her weight. She fell against a door, scrapping her left side, but managed to reach a telephone and call an ambulance.

PHYSICAL EXAMINATION
Vital signs: T = 98°F, P = 76, BP = 140/90, R = 14.
Neck: Supple with no bruits.
Lungs: Clear.
Heart: Regular rate.
Abdomen: Soft.
Extremities: A few abrasions present on the left arm and leg.
Neurologic exam:
MENTAL STATUS: Alert and oriented x 3. The patient seemed unaware at times of any weakness on her left side and did not complain about her abrasions. Language was fluent.
CN I - CN VI: Normal, except for a minimally decreased left nasociliary fold and mild dysartria.
MOTOR: Power 5/5 throughout, except for 1/5 to 2/5 strength in the left leg, both proximally and distally, and 4/5 strength in the proximal left arm.

COORDINATION AND GAIT: Not tested. SENSORY: There was inconsistent decreased response to pinprick on the left side.

CLINICAL COURSE
The patient's weakness temporarily worsened, so that by 2 days after admission she had 0/5 strength in both the left leg and arm. She also had extensor on the left side to double simultaneous tactile stimulation. One month later the patient had recovered 3/5 strength in the left leg but continued to have 0/5 strength in the left leg. Interestingly, she felt that her left arm was "out of control." Her left arm would occasionally grab onto things without her being aware of it, and she then had to use her right arm to release its grasp. She could not localize her left arm in space and had difficulty using the left hand to perform voluntary activities, with marked motor impersistence. When distracted, however, she could use both hands to perform certain automatic overlearned behaviors, such as folding a piece of paper in half.

LOCALIZATION AND DIFFERENTIAL DIAGNOSIS
1. On the basis of the symptoms and signs shown in bold above, where is the lesion?
2. What is the most likely diagnosis, and what are some other possibilities?
Discussion

1. The key symptoms and signs in this case are:
   - Profound weakness of the left leg, with mild weakness of the left arm and face, mild dysarthria, left leg hyperreflexia, and Babinski's sign
   - Left grasp reflex and motor impersistence
   - Left arm "out of control"
   - Unawareness of left-sided weakness and abrasions, decreased response to pinprick on the left, tactile extinction on the left

   Upper motor neuron-type weakness of the left leg could be caused by a lesion in the right primary motor cortex area, or the left thalamocortical spinal cord (see KCC. 63, Figure 6.14P). However, since there was also mild dysarthria and some left face and arm weakness, there must also have been some mild involvement of corticobulbar and corticospinal fibers for the face and arm, ruling out a spinal cord lesion. A grasp reflex and motor impersistence suggest a frontal lobe lesion (see KCC 19.11). The unusual behavior of her left arm is compatible with an alien hand syndrome (see KCC 10.11), sometimes seen in lesions of the supplementary motor area (see Figure 6.14). Anosognosia and contralateral neglect (see KCC 19.10) can be seen in nondominant (usually right) hemisphere lesions, especially in the parietal lobes, but sometimes also in the frontal lobes. In addition, some of the patient's apparent left-sided weakness may have been due to left motor neglect rather than to actual weakness, as suggested by her preserved ability to use her left hand well at times.

   The most likely clinical localization is right primary motor cortex foot area, supplementary motor area, and other adjacent regions of the right frontal or parietal lobes.

2. Given the sudden onset of the deficits, together with the patient's age, history of hypertension, smoking, and peripheral vascular disease, the most likely diagnosis is an embolic stroke (KCC 10.4). An infant of the right medial frontal lobe including foot motor cortex and supplementary motor area would be caused by occlusion of the right anterior cerebral artery (KCC 10.1). Another, less likely cause of a lesion in the cortex in this setting would be a hemorrhage. Since the deficits improved over time, a tumor or infection is unlikely as the cause.

Neuroimaging

A head CT scan done shortly after admission suggested probable right anterior cerebral artery infarct. Follow-up head CT scan 1 month after admission (Figure 10.13) confirmed the presence of a hypodense area on the anterior medial aspect of the right hemisphere consistent with a right anterior cerebral artery infarct (compare to Figures 10.4, 10.5, and 10.9).

CASE 10.3 DECREASED VISION ON ONE SIDE

CHIEF COMPLAINT

A 63-year-old woman went to an ophthalmologist because of episodes of decreased vision in her "right eye" and headaches.

HISTORY

Past medical history was notable for diabetes, elevated cholesterol, and coronary artery disease. About 5 or 6 weeks ago the patient began having episodes of sudden "blurry wavy" appearance of her vision.

She believed this was mostly in the right eye, but she did not try looking with one eye at a time. The episodes would last 15 to 20 minutes, occurring three to four times per week, and were accompanied by a severe left retro-orbital headache. She was able to recognize faces during the episodes but had difficulty reading. She denied any other symptoms. Two days ago an episode began that resulted in persistent decreased vision on the right.

CASE 10.3 (CONTINUED)

PHYSICAL EXAMINATION

Vital signs: T = 98.6°F, P = 84, BP = 180/78, R = 20.

Neck: Supple with no bruits.

Lungs: Clear.

Heart: Regular rate with no murmurs.

Abdomen: Soft, nontender.

Neurologic exam:


Cranial nerves: Pupils 3 mm, constriction to 2 mm bilaterally. Normal fundus. Visual acuity 20/30 right eye, 20/25 left eye. Visual field testing (see KCC 11.2) revealed a homonymous hemianopia (Figure 10.14). Extraocular movements intact. Facial sensation intact to light touch and pinprick.


LOCALIZATION AND DIFFERENTIAL DIAGNOSIS

On the basis of the symptoms and signs shown in bold above, where is the lesion? What is the most likely diagnosis, and are there any other possibilities?

Figure 10.14: Automated Visual Field Mapping Showing Right Homonymous Hemianopia. See KCC 11.2 for discussion of automated visual field mapping.

Discussion

The key symptoms and signs in this case are:

- Right homonymous hemianopia
- Left retro-orbital headache

As we will discuss in Chapter 11, a right homonymous hemianopia can be caused by a lesion in the left hemisphere visual pathways anywhere from the left optic tract to the left primary visual cortex (see Figure 11.15). The transitory episodes of 15 to 20 minutes of decreased right-sided vision occurring...
over several weeks, followed by a persistent deficit, are suggestive of TIA's (see KCC 10.3) preceding a cerebral infarct (see KCC 10.4). In addition, the patient's age and history of diabetes, hypercholesterolemia, and coronary artery disease raise the suspicion for cerebrovascular disease as the cause. Following the visual pathways from front to back, the optic tract and lateral geniculate nucleus of the thalamus are supplied by multiple small vessels. Infarcts of the optic tract are rare, and infarcts of the lateral geniculate nucleus are usually accompanied by damage to the adjacent internal capsule, causing central, hemiparesis. Infarcts of the entire optic radiation can occur, with large MCA infarcts causing a hemianopsia; however, this would also result in a contralateral hemiplegia and other deficits. Thus, the most common cause of hemianopsia without other deficits is infarction of the primary visual cortex, caused by occlusion of the posterior cerebral artery. The patient's left retro-ocular headache is also consistent with left PCA disease (see KCC 10.4). Occasionally, proximal PCA occlusion can involve small penetrating vessels (see Figures 10.8, 10.9), resulting in infarction of the thalamus or internal capsule as well. However, this patient did not have somatosensory or motor deficits, so the most proximal segment of the PCA must be spared. Other, less likely diagnoses in this setting include hemorrhage, tumor, abscess, or demyelination in the left occipital cortex.

The most likely clinical manifestation and diagnosis is: Left primary visual cortex lesion caused by left posterior cerebral artery infarct.

Note that the patient described her vision loss as occurring in the right eye. It is common for patients to describe a visual field defect in this manner even though the defect involves the visual fields of both eyes.

Clinical Course and Neuroimaging

An initial CT scan suggested left PCA infarct, and a follow-up head MRI scan a few days later (Figure 10.15) confirmed the presence of a left PCA infarct involving the left primary visual cortex. Note the presence of T2 bright signal in Figure 10.15A, consistent with increased water content from edema and necrosis. In addition, on the T1-weighted images (see Figure 10.15C) there were some bright areas consistent with methemoglobin (see Table 4.4) resulting from petechial hemorrhagic conversion. A more significant hemorrhage would have resulted in more dramatic evidence of a frank hematoma seen on both T1- and T2-weighted images.

The patient was admitted to the hospital and placed on intravenous heparin anticoagulation while testing was done, including a cardiac Holter monitor, an echocardiogram, and Doppler studies of the neck vessels to look for a source for the embolus (see KCC 10.4). These tests were negative; however, a magnetic resonance angiogram revealed multiple stenoses of the cerebral vessels compatible with diffuse intracranial atherosclerotic disease. It was therefore felt that the patient most likely had an artery-to-artery embolus, or a PCA thrombosis caused by severe atherosclerotic disease, and she was treated with long-term oral anticoagulation. Her right hemianopsia did not improve, but over time she learned to adapt to her deficit with improved reading and extra caution to avoid bumping into objects on her right side.
CASE 10.2 LEFT LEG WEAKNESS AND LEFT ALIEN HAND SYNDROME

Figure 10.13 Right Anterior Cerebral Artery (ACA) Infarct (A, B) Axial CT images progressing from inferior to superior. The central sulcus was located by following it down from higher sections (not shown; compare to Figure 4.12).
CASE 10.3 DECREASED VISION ON ONE SIDE

Figure 10.15 Left Posterior Cerebral Artery (PCA) Infarct: MRI of the brain. (A,B) Axial T2-weighted images proceeding from inferior to superior. (C) Parasagittal T1-weighted image of left hemisphere showing bright areas consistent with perichelosal hemorrhage in the region of the PCA infarct. (D) Parasagittal T1-weighted image of normal right hemisphere from the same patient for comparison, showing locations of calcarine and parieto-occipital fissures.

CASE 10.3 (CONTINUED)
**CASE 10.4 TRANSIENT EPISODES OF LEFT EYE BLURRINESS OR RIGHT HAND WEAKNESS**

MINICASE
A 71-year-old right-handed man with a long history of cigarette smoking and hypertension had an episode 5 months before admission of right hand weakness and speech difficulty “mixing up words.” Since then, he has had several episodes, lasting a few minutes each, of dim blurry vision in the left eye. Finally, he fell on three separate occasions when his right leg suddenly gave out, most recently on the day of admission. Examination was normal except for a high-pitched bruit audible over the left carotid artery.

**LOCALIZATION AND DIFFERENTIAL DIAGNOSIS**
1. What is the most likely cause of this patient's transient neurologic episode? What are some other possibilities?
2. For each type of episode shown in bold above, identify a branch of the internal carotid artery that could be responsible for the patient's symptoms.

**Discussion**
1. Given the patient's age and history of smoking and hypertension, atherosclerotic cerebrovascular disease is likely. The episodes lasted for a few minutes each and fit with a vascular anatomical pattern (see the localization discussion that follows) suggesting TIA’s (see KCC 10.3). In addition, the left carotid bruit is a “smoking gun” that heightens the suspicion further for TIAs caused by left internal carotid stenosis. Other, less likely possibilities are listed in Table 10.2.

2. The three types of episodes in this case are:
   - Right hand weakness and speech difficulty “mixing up words”
   - Symptomatic branch of internal carotid = Left MCA superior division (see KCC 10.1)
   - Right leg weakness: Symptomatic branch of internal carotid = Left ACA (see KCC 10.1)
   - Decreased vision in the left eye: Symptomatic branch of internal carotid = Left ophthalmic artery (see KCC 10.5, 11.3)

   Interestingly, unlike the case in this patient, internal carotid stenosis often causes TIAs mainly in one carotid branch, resulting in recurrent, nearly stereotyped episodes. For example, a patient may have several episodes of contralateral hand weakness, numbness, and tingling, or several episodes of transient monocular visual loss.

**Clinical Course**
Carotid Doppler studies showed a very tight stenosis of the left internal carotid artery. This was confirmed by MRA. The patient underwent an endarterectomy of the left internal carotid artery. In this procedure the carotid is temporarily cross-clamped, an incision is made in the artery, atherosclerotic plaque is carefully shelled out, and the artery wall is then stitched back together (see KCC 10.5). A large atheromatous plaque was removed in this patient, and when it was examined histopathologically, it was found to have a residual lumen of only 0.1 cm in diameter. The patient did very well postoperatively, with no further episodes of weakness or vision changes.

**Related Cases**
Typical MRA findings in a different patient with critical stenosis of the right internal carotid artery are shown in Figure 10.16. This patient presented with two episodes, lasting 5 minutes each, of left hand numbness, tingling, and a feeling like it was not part of her body. A pathologic specimen from yet another patient removed at the time of carotid endarterectomy is shown in Figure 10.17.

**CASE 10.5 NONFLUENT APHASIA WITH RIGHT FACE AND ARM WEAKNESS**

**CHIEF COMPLAINT**
A 65-year-old man was brought to the emergency room because of right face and arm weakness and inability to speak.

**HISTORY**
The patient had a past history of alcohol use, cigarette smoking, and hypertension. He ate breakfast at the same diner every day but had not shown up there for 2 days. On the morning of admission, he staggered back into the diner grunting incoherently, tripped, and fell on the floor. The manager noticed that the patient was having trouble moving his right arm, so he called an ambulance.

**PHYSICAL EXAMINATION**

Lungs: Clear

Cardiac: Regular rate with no murmurs, S4 gallop

Abdomen: Soft, non-tender.

Extremities: No edema.

**Neurologic exam:**
- **MINIMAL STATUS:** Alert. Grunted only, producing no words. Followed no commands except to close eyes or open mouth. Overused gestures to raise arms or legs
- **Cranial nerves:** Pupils 3 mm, constricting to 2 mm bilaterally. Preserved blink to threat bilaterally. Extraocular movements intact. Decreased right nasolabial fold at rest, and decreased movements of right face, sparing forehead.

**Discussion**
1. The key symptoms and signs in this case are:
   - Decreased movements of right face (sparing forehead), profound right arm weakness, and mild right leg weakness
   - Nonfluent (Broca's) aphasia

   Unilateral face and arm weakness are usually caused by a lesion in the contralateral face and arm areas of the motor cortex (see KCC 6.3; Figure 16.14). In support of this, the pattern of facial weakness fits with an upper motor neuron lesion. Note that there was no hyperreflexia on the right side, but this is not unusual in an acute upper motor neuron lesion. The slight right arm flexion toward the painful stimulus likely represents a fragment of flexor posture (see Figure 3.5A). Another possible localization would be a deep lesion involving the internal capsule; however, the leg is only mildly involved, making this less likely. In addition, the Broca's aphasia in this patient is compatible with a lesion involving the left frontal cortex. Note that the patient initially had a global aphasia, which evolved to Broca's aphasia. This is a pattern commonly seen with large acute lesions involving Broca's area and adjacent regions of the left frontal lobe (see KCC 10.4). Note also that the intact visual fields are very helpful for ruling out a more posterior lesion.
The most likely clinical localization is left primary motor cortex face and arm areas, Broca’s area, and adjacent left frontal cortex.

2. The patient was not elderly; however, given the history of hypertension and cigarette smoking, and the anatomical distribution of his deficits, the most likely diagnosis is a left MCA superior division infarct (KCC 10.1). Other less likely diagnoses include a hemorrhage, tumor, or abscess affecting the left frontal lobe.

**Clinical Course**

A head CT done in the emergency room showed a left MCA superior division infarct that appeared more than 24 hours old. The patient was afebrile and placed on intravenous heparin anticoagulation while an embolic workup was done (see KCC 10.4). A brain MRI scan done 4 days after admission confirmed the left MCA superior division infarct (Figure 10.18). Note the presence of a T2 bright area consistent with increased water from edema and necrosis in the territory of the left MCA superior division (see Figures 10.5, 10.6, 10.9, KCC 10.1). The sulci appear effaced when compared to the same region in the opposite hemisphere, representing mass effect. The infarct can be seen to involve the left frontal operculum (Broca’s area) and the face and arm motor areas on the lateral convexity of the frontal lobe. However, the leg motor area, lying superiorly in the interhemispheric fissure, was spared, as was the posterior limb of the internal capsule (see Figures 10.1, 10.9B).

Carotid Doppler studies and magnetic resonance angiography showed no flow in a segment of the left internal carotid artery. Because of the critical importance of distinguishing carotid occlusion from a tight stenosis (see KCC 10.5), a conventional angiogram was performed that confirmed carotid occlusion (see Case 10.10 for angiographic findings in carotid occlusion). Thus, the patient most likely had an embolus that formed in the occluded left internal carotid and migrated upward to the left middle cerebral artery superior division. He was discharged on oral anticoagulation therapy to try and prevent further emboli. Note that embolic infarcts can also occur with carotid stenosis (rather than occlusion), in which case endarterectomy may be indicated (see KCC 10.5).

As already noted, the patient’s global aphasia quickly evolved into a Broca’s aphasia, but he continued to have some difficulty comprehending more complex commands. His right leg strength recovered fully, and his right arm strength also improved. By the sixth hospital day he was able to extend his fingers and move most muscles in the right arm against gravity but not against resistance.
CASE 10.6 TALKING RAGTIME

CHIEF COMPLAINT
A 64-year-old right-handed man with a history of schizophrenia suddenly began talking nonsense and repeating himself over and over again.

HISTORY
The patient had a history of chronic schizophrenia, with occasional auditory hallucinations and paranoid delusions treated with antipsychotic medications in the past. He also had hypertension and a recent episode of chest pain. On the day of admission he was last seen in his usual state of health at 12:00 noon. His wife went out shopping, and when she returned at 4:00 P.M., he was seated at the kitchen table saying meaningless syllables and irrelevant phrases over and over and would not respond to any of her questions. She also noticed that his right arm was hanging down at his side, and she called an ambulance.

PHYSICAL EXAMINATION
Neck: No bruits.
Lungs: Clear.
Heart: Regular rate with no murmur, gallops, or rubs.
Abdomen: Soft, nontender.
Extremities: Mild ankle edema.
Rectal: Normal.
Neurologic exam:
MENTAL STATUS: Alert, mildly agitated. Responded to all questions by saying only "Yup, yup" or "I don’t know" repeatedly. Followed no commands, named no objects, and could not repeat. Occasionally asked, "What time is it?" or repeated other irrelevant phonemes, such as "jillian" or "leat" multiple times. Did not follow written commands. Mimicked some gestures, but only when shown in the left visual field.
COORDINATION: Not tested.
Gait: Stood cautiously and took short tentative steps without support.
Sensory: Grasmed and withdrew in response to pinprick in all extremities. Grasmed more in response to pinprick on the left side than the right.
LOCALIZATION AND DIFFERENTIAL DIAGNOSIS
1. On the basis of the symptoms and signs shown in bold above, where is the lesion?
2. What is the most likely diagnosis, and what are some other possibilities?

Discussion
1. The key symptoms and signs in this case are:
   • Fluent aphasia with impaired comprehension and repetition
   • Blink to threat present only on the left
   • Greater grimace in response to pinprick on the left side than the right
   • Slightly increased tone in the right arm, with right Babinski’s sign

This patient had a Wernicke’s aphasia (see KCC 19.5), with fluent, meaningless speech, together with severely impaired comprehension and repetition. This syndrome suggests a lesion in the left temporoparietal cortex, including Wernicke’s area. The right visual field defect could also be explained by a lesion in this area if the optic radiations were involved (Figure 10.1A). Movements on the right side are relatively spared, suggesting that the primary motor cortex was not directly involved. However, the right sensory loss, mild right-sided upper motor neuron findings, and possible mild right neglect (as evidenced by the patient’s reluctance to use his right arm) suggest involvement of the left parietal lobe and left primary sensory cortex, with mild impingement on corticospinal tract fibers.
The most likely clinical localization is left temporo-parietal lobe, including Wernicke's area, optic radiations, and somatosensory cortex.

2. The anatomical distribution of the lesion fits with a left MCA anterior division infarct (KCC 10.1). This diagnosis is further supported by the patient's history of hypertension, and possible cardiac disease (chest pain). Other less likely possibilities include hemorrhage, abscess, or tumor in the left temporo-parietal region.

Interestingly, the patient had a history of schizophrenia, which can also cause nonsensical speech and disregard for verbal questions or commands. The other neurologic findings are not diagnostic of a neurologic rather than a psychiatric disorder in this case. However, in left MCA anterior division infarcts, sensory and motor deficits are often absent, making the diagnosis more difficult. Once again visual field testing is essential to detect possible lesions, although the results may be hard to interpret even with binocular threat if the patient is sufficiently agitated.

Clinical Course

Head CT in the emergency room showed a region of hypodensity in the left temporo-parietal lobes, and follow-up head CT 2 days after admission confirmed a left MCA anterior division infarct (Figure 10.19). Note the slight effacement in the region of hypodensity in the left temporal and parietal lobes. The stroke can be seen to include Wernicke's area (see Figure 10.1A), the optic radiations, and left parietal cortex, but to spare the precentral gyrus and internal capsule. Recall that the margin between the MCA superior and inferior divisions is somewhat variable in the parietal lobe. For example, in inferior division infarcts, often less of the parietal lobe is involved than in this case.

The patient was admitted for a workup, which revealed no embolic source. He was treated with intravenous and later, oral anticoagulation. By the second hospital day he had nearly normal movements on the right side and no longer had an upgoing toe on the right. His aphasia improved somewhat, with more varied and intermittently coherent spontaneous speech. He was fluent but continued to have severely impaired language comprehension and decreased vision on the right side.

case 10.7 Dysarthria and Hemiparesis

MINICASE

An 84-year-old woman with a history of hypertension and diabetes had two episodes of slurred speech and right-sided weakness on two consecutive days, and on the third day the developed persistent dysarthria and right hemiplegia. Exam was normal except for right facial weakness sparing the forehead, dysarthria, decreased right-sided tone, 5/5 power in the right arm and leg, and right upgoing plantar response.

Localzation and Differential Diagnosis

1. On the basis of the symptoms and signs shown in bold above, where is the lesion?
2. What is the most likely diagnosis, and what are some other possibilities?

Discussion

The key symptoms and signs in this case are:

- Dysarthria and right face, arm, and leg paralysis with a right Babinski's sign
- This patient has pure motor hemiplegia, without sensory abnormalities or cortical signs such as aphasia or neglect. This can be localized to the contralateral corticobulbar and corticospinal tracts, most commonly in the internal capsule or ventral pons (see KCC 6.3). Dysarthria is commonly present as well, giving rise to the term "dysarthria hemiparesis." In addition, the facial weakness is of the upper motor neuron type, since the forehead is spared. The right Babinski's sign also supports an upper motor neuron lesion.

The most likely clinical localization is left corticobulbar and corticospinal tracts in the internal capsule or ventral pons. Given the patient's age and the history of hypertension and diabetes, an ischemic infarct is the most likely diagnosis. Internal capsule infarcts are most commonly caused by occlusion of the lenticulostriate arteries, which arise from the proximal MCA and supply the deep MCA territories (Figures 4.16B, 10.7-10.9). Infarcts of this kind are often called lacunes (see KCC 10.4).

Other vessels that can cause internal capsule lacunes include the anterior choroidal artery and small perforating vessels from the proximal PCA. Infarcts in the ventral pons can be caused by occlusion of the small paramedian perforators arising from the basilar artery (see Figures 14.18-14.20). Aside from a lacunar infarct, other possibilities include hemorrhage, tumor, abscess, or demyelination in the left posterior limb of the internal capsule, ventral pons, corona radiata, or cerebral peduncle (compare to Cases 6.4 and 6.5).

Clinical Course and Neuroimaging

Head CT in the emergency room showed a hypodensity in the left internal capsule, which appeared more clearly on a follow-up head CT 10 days later (Figure 10.20). Note that lacunar infarcts are often smaller than the one seen in this case.

The patient was admitted to the hospital, and an MRI revealed bilateral severe scarring of the middle cerebral arteries. It was felt that thrombus or atheroma forming along the wall of the vessel might have occluded several lenticulostriate vessels coming off the proximal left middle cerebral artery (see Figures 4.16B, 10.7). She was then treated with anticoagulation with no further progression, but she continued to have severe right-sided weakness.

Case 10.8 Global Aphasia, Right Hemiplegia, and Hemianopia

Chief Complaint

A 65-year-old man was brought to the emergency room with sudden onset of inability to speak and right face, arm, and leg paralysis.

History

The patient was on vacation with his wife, and one morning at breakfast he dropped a pat of butter. He stood up to look for it and then suddenly began looking only to the left and slid back into his chair. He was unable to speak or follow commands and could not move his right arm or leg, his wife immediately called an ambulance. Past medical history was notable for hypertension and aortic valve replacement 7 years previously with a porcine valve. He was taking antihypertensive medications and aspirin.

Physical Examination

CASE 10.6 TALKING RAGTIME

Figure 10.19 Left Middle Cerebral Artery (MCA) Inferior Division Infarct
CT scan axial sections with A, B progressing from inferior to superior.

(A) Prefrontal lobe

Sylvian fissure

Thalamus

Left MCA inferior division infarct

Temporal lobe

Region of optic radiation

Anterior horn of lateral ventricle

(B) Superior frontal gyrus

Frontal lobe

Central sulcus

Precentral gyrus

Left MCA inferior division infarct

Parietal lobe

Fusiform gyrus

CASE 10.8 (CONTINUED)

Craniome: Pupils 3 mm, constriction to 2 mm bilaterally. Normal fundi. No blink to threat on the right. Left gaze preference. On visual tracking, eyes moved fully to the left but did not cross the midline to the right. Right corneal reflex was decreased. Right face had severely decreased movements, with relative sparing of the forehead. Gag reflex present.

Motor: No movement of the right arm, even in response to pain. Right leg with slight flexion only, moving toward painful stimulus. Left arm and leg with spontaneous purposeful movements. Able to raise left arm or leg off the bed.

Coordination and Gait: Not tested.

Sensory: No response to pain on right side except for weak flexion of right leg (see above). Grimace and purposeful withdrawal to pain on the left.

Localization and Differential Diagnosis
1. On the basis of the symptoms and signs shown in bold above, where is the lesion?
2. What is the most likely diagnosis, and what are some other possibilities?

Discussion
1. The key symptoms and signs in this case are:
   - Right face, arm, and leg paralysis, with right hyperreflexia and Babinski's sign
   - No response to pain on the right side except for weak flexion of the right leg
   - Global aphasia
   - No blink to threat on the right
   - Left gaze preference
   - Decreased right corneal reflex

This unfortunate man had the deficits of all three patients from Cases 10.5, 10.6, and 10.7 combined. Right hemiplegia with upper motor neuron signs can be caused by a large lesion affecting the entire left motor cortex, or by a lesion of the corticobulbar and corticospinal tracts (see KCC 6.3, Figure 6.4A,B). The slight flexion of the right leg into the painful stimulus seen in this patient is probably part of a reflex response such as triple flexion (see Figure 3.5C), which can be mediated by local spinal cord circuits. Loss of response to pain on the right side could be due partly to the hemiplegia; however, one would expect at least a grimace on the left face or uncomfortable movements of the left body if the painful stimulus were felt. Therefore, there is probably right hemisensory loss, caused by a large lesion of the left somatosensory cortex, by a lesion of the left thalamic somatosensory radiations, or by a lesion of the left thalamus (see KCC 7.3; Figure 7.9A). Decreased corneal reflex (see KCC 12.4) can be produced by damage to ipsilateral brainstem or cranial nerves V or VII. However, it can also be seen in contralateral supratentorial lesions of the somatosensory pathways. Global aphasia (see KCC 19.6) can be caused by large dominant-hemisphere lesions. Note that the ability to follow simple motor commands such as "close your eyes" is sometimes preserved even in global aphasia. Loss of blink to threat on the right can be caused by a lesion of the left optic tract, thalamus, optic radiations, or visual cortex (see Figure 11.15). An (ipsilateral gaze preference (see KCC 13.15) can also be seen with large cortical lesions, in which there is loss of the ability to drive the eyes toward the side opposite the lesion.

The most likely clinical localization is a large lesion affecting the entire left cerebral cortex, or a left hemisphere lesion involving a large region of cortex plus all subcortical pathways.
2. The patient's age and history of hypertension and cardiac disease suggest possible cerebrovascular disease. A left MCA stem infarct could produce all of the deficits described above (see Table 10.1). Other possibilities include massive left hemisphere hemorrhage or, less likely given the time course, an aneurysm or tumor.

**Clinical Course**

Initial head CT within a few hours of onset was negative, except for a hypodensity in the proximal left MCA, consistent with a blood clot. An EEG revealed atrial fibrillation, suggesting that an embolus had formed in the left atrium and traveled to the left MCA stem. Thrombolysis and other acute interventions were not available at the time this patient was admitted. A repeat head CT 1 day after admission again showed a hypodensity in the left MCA stem, but also showed a massive area of hypodensity consistent with infarction of the entire left MCA territory (Figure 10.21). Note that the infarct involved both the superficial and the deep MCA territories (compare to Figures 10.8 and 10.9), while sparing the thalamus, inferior temporal lobe, and medial occipitotemporal cortex (PICA territory), in addition to the medial frontotemporal cortex (ACA territory). Note also that the sulci over the left hemisphere appear effaced, and there is considerable left-to-right shift under the falx in the region of the midline, and deformation of the midbrain in the region of the tentorium, suggesting incipient uncal herniation (see KCC 5.4).

Three days after admission the patient became increasingly somnolent, and a repeat CT scan showed increased swelling of the left hemisphere, with about 1 cm of left-to-right midline shift and some effacement of the basilar cisterns. The patient was intubated and treated with intravenous mannitol in an attempt to decrease brain swelling by osmotic diuresis (see KCC 5.3). However, by the fourth hospital day the patient was unresponsive, exhibiting bilateral extensor posturing of the arms and legs (see Figure 3.5B). The family had a living will written previously by the patient stating that he did not want extreme measures to be taken to sustain his life if he had an illness with poor prognosis for good functional recovery. He was therefore extubated and given pain medications, and he died the next day with his family at the bedside.

**CASE 10.9 LEFT FACE AND ARM WEAKNESS**

**MINICASE**

A 91-year-old right-handed woman with a history of paroxysmal atrial fibrillation called her daughter one morning because she was unable to get her arm through the left sleeve of her dress. The patient's speech sounded slightly slurred over the telephone, so her daughter called an ambulance. Examination was notable for left facial weakness sparing the forehead, mild dysarthria, left arm pronator drift, 4/5 strength in the left arm, and brisk 3+ reflexes in the left arm compared to 2+ reflexes in the right arm. In addition, there was occasional extinction on the left side to double simultaneous visual or tactile stimulation. The patient was brought to the hospital on the left arm and brisk 3+ reflexes in the left arm compared to 2+ reflexes in the right arm. In addition, there was occasional extinction on the left side to double simultaneous visual or tactile stimulation. The remainder of the examination was essentially normal, including intact visual fields and normal leg strength.

**LOCALIZATION AND DIFFERENTIAL DIAGNOSIS**

1. On the basis of the symptoms and signs shown in bold above, where is the lesion?
2. What is the most likely diagnosis, and what are some other possibilities?

**Discussion**

1. The key symptoms and signs in this case are:
   - Left facial weakness sparing the forehead, left arm weakness, and hypertonia
   - Mild dysarthria

**CASE 10.7 DYSPHARIA AND HEMIPARESIS**

**Figure 10.20** Left Middle Cerebral Artery (MCA) Deep Territory Infarct. Head CT scan axial section showing "giant" lobe in the left genu and posterior limb of the internal capsule, probably caused by occlusion of lenticulostriate arteries.
CASE 10.8 GLOBAL APHASIA, RIGHT HEMIPLEGIA, AND HEMIANOPIA

Figure 10.21 Left Middle Cerebral Artery (MCA) Stem Infarct, Causing Significant Mass Effect
Head CT scan axial sections, with A-C progressing from inferior to superior.

(A) Precentral gyrus

(B) Anterior cingulate
gyrus

CASE 10.8 (CONTINUED)

(C) Superior frontal gyrus

CASE 10.10 LEFT HEMINEGLIGENCE

MINICASE
A 61-year-old left-handed security guard had an episode of left-hand tingling lasting less than an hour that was reported to medical staff by a friend. The next day he was at the grocery store buying a lottery ticket and reportedly slumped briefly to the floor. He denied that anything was wrong but said, "They called an ambulance because they said I had a stroke." On examination he was unaware of having any deficits and wanted to go home. He had profound left visual neglect, describing only the curtains to the far right in a picture of a complex visual scene and reading only the right two words on each line of a magazine article. When trying to write, he moved the pen in the air off to the right of the page. He had no blink to threat on the left, a marked right gaze preference, and mildly decreased left nasolabial fold. Spontaneous movements were decreased on the left side, but with provocation he was able to achieve 4/5 strength in the left arm and leg. He was able to feel touch on the left side but had extinction on the left to double simultaneous tactile stimulation. Reflexes were slightly brisker on the left.

LOCALIZATION AND DIFFERENTIAL DIAGNOSIS
1. What is the significance of the transient episode of hand tingling?
2. On the basis of the symptoms and signs shown in bold above, where is the lesion?
3. What is the most likely diagnosis, and what are some other possibilities?

Discussion
1. The key symptoms and signs in this case are:
   - Anosognosia, left visual neglect, extinction on the left to double simultaneous tactile stimulation, moving the hand to the right of the page, and decreased spontaneous movements on the left side
   - Right gaze preference
CEREBRAL HEMISPHERES AND VASCULAR SUPPLY

CASE 10.11 LEFT HEMINEGLIGENCE, HEMIPLEGIA, AND HEMIANOPIA

MINICASE
A 62-year-old right-handed woman with a history of hypertension, hyperthyroidism, and atraumatic fractures awoke one morning with pain behind her right eye. She tried to walk to the bathroom but fell at the doorway. Her family found her unable to move her left side, and as they called the ambulance she kept repeating "Do not call anyone" because she believed nothing was wrong. On exam, when shown her left hand and asked what it was, she replied, "Someone’s hand." When asked whose hand it was, she replied, "The doctor’s." She had no blink to threat on the left and no voluntary gaze to the left past the midline, and there was marked weakness of the lower portion of the left face. Strength was 0/5 in the left arm and leg, the left plantar response was upgoing, and there was no response to pinprick on the left side.

LOCALIZATION AND DIFFERENTIAL DIAGNOSIS
1. On the basis of the symptoms and signs shown in bold above, where is the lesion?
2. What is the most likely diagnosis, and what are some other possibilities?

Discussion
1. The key symptoms and signs in this case are:
   - Anosognosia, hemisomatognosia
   - Left face, arm, and leg plegia with left Babinski’s sign
   - No blink to threat on the left
   - No voluntary gaze to the left past the midline
   - No response to pinprick on the left side

   This patient clearly has a large lesion of the right hemisphere, including the entire corticobulbar and corticospinal systems, the retinofugal visual pathways, the somatosensory pathways, and the pathways responsible for personal awareness and for directing gaze into the contralateral homolateral field. This is similar to Case 10.8, but since the right hemisphere is involved, instead of aphasia the patient has loss of awareness of illness and of her entire left body. She has all the deficits of Case 10.9 and 10.10, plus a left hemiplegia and hemisensory loss. In summary, she must have a large lesion affecting the entire right cerebral cortex and/or all right hemisphere subcortical pathways.

2. Given her age, the sudden onset of deficits, and the history of hypertension and atraumatic fracture, the most likely diagnosis is a right MCA stem infarct (see Table 10.1). A large right hemisphere hemisomatognosia is also possible. Less likely, given the time course, is a large abscess or tumor.

Initial Clinical Course
The patient was admitted and initially given intravenous heparin anticoagulation. Head CT on admission was compatible with early right MCA stem infarct, and this was confirmed by MRI and MRA. Two days after admission, the patient became increasingly difficult to arouse, and she eventually developed a dilated right pupil with flexor posturing in the right arm and an upgoing toe on the right side.

1. What clinical syndrome do the new findings in bold constitute, and what is its localization?
2. What are some possible causes in this patient?

Discussion
1. The combination of impaired consciousness, dilated right pupil, and new right corticospinal findings is compatible with right uncus transtentorial herniation (see KCC 5.4). These three findings would be caused by compression of the midbrain reticular activating system, right CN III, and left cerebral peduncle, respectively.

Clinical Course and Neuroimaging

Head CT on the day of admission showed a mild hydrocephalus in the right tempoparietal area. Follow-up head CT 10 days later confirmed right MCA inferior division infarct that appeared very similar to Figure 10.19 (Case 10.6), except on the other side of the brain. Carotid Doppler studies and an MRA suggested occlusion versus critical stenoses of the right carotid artery (see KCC 10.5), so a conventional cerebral angiogram was done (see Chapter 4). Injection of the right carotid showed occlusion of the right common carotid artery (Figure 10.22A). Injection of the left carotid resulted in cross-filling to the right ACA and right MCA via the anterior communicating artery (Figure 10.22B). Therefore, the patient most likely had a right carotid occlusion, possibly on the day prior to admission, followed by thrombotic formation in the carotid, with embolization to the right MCA inferior division. This is similar to the cause of the infarct in Case 10.5, and should be contrasted with the case of carotid stenosis seen in Case 10.4.

The patient was treated with intravenous and, later, oral anticoagulation to try and reduce the risk of further emboli from his carotid. By 3 days after admission he was able to look voluntarily to the left, strength was normal on the left side when he was motivated, and reflexes were symmetrical. He still had decreased blink to threat on the left, and occasional (1/3 trials) left extention on double simultaneous tactile stimulation. Coma was eventually stopped, and in follow-up 1 year later the patient had a normal exam except for a left visual field cut (not precisely mapped out by the examiner).

- No blink to threat on the left
- Decreased spontaneous movements on the left side, with mildly decreased left nasolabial fold, and slightly brisker reflexes on the left

The transient episode of hand tingling occurring the day before the onset of a fixed deficit is suggestive of a TIA forensic an ischemic stroke. Left hand tingling could be caused by compromised flow in the right middle cerebral artery, most commonly from a cardiogenic embolus, or from a right carotid stenosis. Other possible causes of transient ischemic symptoms are summarized in Table 10.2.

2. This patient exhibits several forms of neglect (see Chapter 19). In addition to anosognosia, he has left sensory neglect to visual and tactile stimuli, as well as left motor neglect. These features are most commonly seen in patients with nondominant (usually right) parietal lobe lesions, but can also occasionally be seen with lesions in the right frontal lobe, and in other locations. The right parietal gage preference further supports a right hemispheric frontal or parietal localization. However, decreased blink to threat is ordinarily caused by damage to primary visual pathways, and not by neglect. Therefore, the decreased blink to threat on the left suggests that the lesion is more posteriorly located, possibly involving the optic radiations as they travel beneath the right temporal and parietal lobes (Figure 10.1A). Mild corticobulbar and corticospinal findings can also be seen in parietal lesions, especially acutely (KCC 10.1).

The most likely clinical localization is right temporoparietal lobe, including the optic radiations.

3. Given the sudden onset of the deficits and the patient's age, the most likely diagnosis is TIA followed by ischemic infarct. The right temporoparietal lobe is supplied by the right MCA inferior division (see Table 10.1, Figures 10.7, 10.9). Another possibility is that the initial episode was a focal seizure, and that the patient had a tumor, hemorrhage, or infection with deficits that had previously been neglected by the patient, which became more severe on the day of admission.

Clinical Course and Neuroimaging

Head CT on the day of admission showed a mild hydrocephalus in the right temporoparietal area. Follow-up head CT 10 days later confirmed right MCA inferior division infarct that appeared very similar to Figure 10.19 (Case 10.6), except on the other side of the brain. Carotid Doppler studies and an MRA suggested occlusion versus critical stenoses of the right carotid artery (see KCC 10.5), so a conventional cerebral angiogram was done (see Chapter 4). Injection of the right carotid showed occlusion of the right common carotid artery (Figure 10.22A). Injection of the left carotid resulted in cross-filling to the right ACA and right MCA via the anterior communicating artery (Figure 10.22B). Therefore, the patient most likely had a right carotid occlusion, possibly on the day prior to admission, followed by thrombotic formation in the carotid, with embolization to the right MCA inferior division. This is similar to the cause of the infarct in Case 10.5, and should be contrasted with the case of carotid stenosis seen in Case 10.4.

The patient was treated with intravenous and, later, oral anticoagulation to try and reduce the risk of further emboli from his carotid. By 3 days after admission he was able to look voluntarily to the left, strength was normal on the left side when he was motivated, and reflexes were symmetrical. He still had decreased blink to threat on the left, and occasional (1/3 trials) left extension on double simultaneous tactile stimulation. Coma was eventually stopped, and in follow-up 1 year later the patient had a normal exam except for a left visual field cut (not precisely mapped out by the examiner).
2. Right uncal herniation would be caused by an expanding mass lesion in the right cranial cavity. Possible causes in this setting would include increased swelling and edema from the infarct, or hemorrhagic conversion.

CASE 10.10 LEFT HEMINEGLECT

Figure 10.22 Right Carotid Occlusion (A) Injection of right carotid showing occlusion of right common carotid artery. (B) Injection of left carotid showing cross-filling via the anterior communicating artery (ACOmM) to the right anterior cerebral artery (ACA) and the middle cerebral artery (MCA). A1 = initial segment of ACA, proximal to the first major branch at the AComM.

Occluded right common carotid artery

Left middle cerebral artery

Left carotid siphon

Left internal carotid artery

Clinical Course and Neuroimaging

An urgent head CT demonstrated increased swelling of the right hemisphere, with right-to-left midline shift and effacement of the interpeduncular cistern. The patient was intubated, hyperventilated, and given intravenous mannitol, which led to temporary improvement. Over the next 2 days an intracranial pressure (ICP) monitoring bolt was used, together with the neurologic exam, to gauge the response to escalating ICP-lowering measures (see KCC 5.3). On hospital day 4, however, the patient's right pupil became dilated, her ICP rose, and she developed bradycardia and hypertension (Cushing response, see KCC 5.3), which did not respond to mannitol. Therefore, after discussion with the family she was taken to the operating room for an investigational procedure called a hemispherectomy (see KCC 10.4), in which a large piece of skull is temporarily removed to decompress the underlying brain (Figure 10.23A). After a long, complicated hospital course and an inpatient rehabilitation stay, she was eventually discharged home with her family. On follow-up exam 2 months after presentation, she was soft-spoken and somewhat lethargic, and she had a persistent left hemiplegia and left hemianopia. However, she knew the correct month and year, and she was able to write her name and identify family members. Follow-up head CT after replacement of the bone flap showed resolution of the brain swelling (see Figure 10.23B).

CASE 10.12 UNILATERAL PROXIMAL ARM AND LEG WEAKNESS

CHIEF COMPLAINT
A 52-year-old right-handed woman went to her physician the morning after developing difficulty raising her left arm.

HISTORY
Past history was notable for hypertension and heavy cigarette smoking. After supper on the evening prior to admission, the patient tried to reach for a cup of coffee with her left hand but was unable to raise her left arm. As she started to walk away, this movement caused her left arm to flop up in the air slightly and knock over the coffee on the floor. She did not make much of this and went to sleep. The next morning, while shopping in the supermarket with her husband, she noticed that she could not raise her left arm to take items off the shelves. On the way home they stopped at her physician's office.

PHYSICAL EXAMINATION
Neck: Supple, with a right carotid bruit continuing into diastole.
Lungs: Clear.
Cardiac: Regular rate, with an S4 gallop.
Abdomen: Normal bowel sounds, soft.
Extremities: Normal.
Neurologic exam:
CRANIAL NERVES: Normal, except for decreased leftward fast phases of optokinetic nystagmus (see Chapter 13).
MOTOR: Normal fine finger movements. Power was 5/5 throughout on the right side. Left arm power was as follows: shrug 4+/5, deltoid 4/5, triceps 4/5, brachioradialis 4+/5, wrist extensors 4+/5, finger 5/5.
Left leg power was as follows: hip flexors 4/5, hip extensors 5/5, thigh adductors 5/5, thigh abductors 4/5, distal muscles 5/5.
REFLEXES:
Biceps 1+, Brachioradialis 1+, Triceps 2, Ankle 2+.
COORDINATION: Slowed finger-to-nose testing in the left arm because of weakness.
Gait: Tended to veer to the left. Fell to the left on attempted tandem (heel-toe) walking.
Sensory: Intact light touch, pinprick, joint position sense, and vibration sense. Normal graphesthesia, no extinction on double simultaneous stimulation.
LOCALIZATION AND DIFFERENTIAL DIAGNOSIS
1. On the basis of the symptoms and signs shown in bold above, where is the lesion?
2. What is the most likely diagnosis, and what are some other possibilities?
Discussion

1. The key symptoms and signs in this case are:
   - Weakness of the proximal left arm and leg, with left hyperreflexia and Babinski’s sign
   - Unsteadiness, veering to the left
   - Decreased leftward fast phases of optokinetic nystagmus
   - Right carotid bruit

This patient has unilateral proximal arm and leg weakness of the upper motor neuron type (see KCC 6.1), sparing the face. This pattern of weakness, sometimes called “main in the barrel” syndrome, is consistent with a lesion in the contralateral motor cortex proximal arm-trunk-proximal leg areas (see Figure 10.1). Damage to this region can be caused by ACA-MCA watershed infarcts (KCC 10.2). Gait unsteadiness with veering to the left can result from lesions in many locations (see KCC 6.5), including the right leg motor cortex. Leftward fast phases of optokinetic nystagmus can be impaired by right frontal lobe lesions.

2. The patient’s vascular risk factors include hypertension and cigarette smoking. Meanwhile, the presence of a right carotid bruit suggests right carotid stenosis. In this setting, decreased right carotid perfusion could occur if the systemic blood pressure suddenly decreased, or if the stenosis suddenly worsened—for example, from thrombus formation. The most likely diagnosis is therefore decreased right carotid perfusion, resulting in watershed infarct in the right ACA-MCA territory, including the right motor cortex proximal arm and leg areas and the right frontal lobe. Other possibilities include another type of cortical lesion in the same location, such as hemorrhage, tumor, or abscess.

Clinical Course

The patient’s physician sent her to the emergency room. A diffusion-weighted MRI scan (see Chapter 4) revealed an acute infarct in the right ACA-MCA watershed territory (see Figure 10.24A), which was confirmed 2 days later by conventional MRI (see Figure 10.24B; compare to Figure 10.14). The patient was admitted and started on intravenous heparin anticoagulation. MRA and carotid Doppler studies revealed a high-grade stenosis of the right internal carotid artery just above the carotid bifurcation. The patient therefore underwent a right carotid endarterectomy (see KCC 10.3). Pathologic examination of the endarterectomy specimen revealed severe atherosclerosis with superimposed mural thrombus, resulting in a 90% stenosis of the lumen. This finding suggests that thrombus could have temporarily occluded the artery at one time, causing the watershed infarct. After surgery the anesthetic therapy was changed from heparin to aspirin, and her strength gradually improved. When seen in follow-up 5 weeks after surgery, she had normal strength throughout, except for trace 4+/5 weakness of the left deltoid and iliotibial.

CASE 10.11 LEFT HEMINEGLIGENCE, HEMIPLEGIA, AND HEMIANOPIA

Figure 10.23 Right Middle Cerebral Artery (MCA) Stem Infarct, Treated with Hemispherectomy. Head CT axial images. (A) Scan performed four days after admission, shortly after hemispherectomy. A large swollen infarct is present in the right MCA territory with areas of increased density consistent with petechial hemorrhage. Removal of the overlying skull prevented fatal uncal herniation. A ventriculostomy was also temporarily placed in the left lateral ventricle to prevent hydrocephalus (see KCC 5.7). (B) Follow-up scan six weeks later. The infarct is no longer swollen, and the skull bone flap has been replaced.
CASE 10.12 UNILATERAL PROXIMAL ARM AND LEG WEAKNESS

Figure 10.24 Right ACA-MCA Watershed Infarct
(A) Coronal view from diffusion-weighted MRI on the day of admission showing acute right ACA-MCA watershed infarct.
(B) Axial view from conventional T2 weighted MRI 2 days later, confirming infarct in this distribution.

CASE 10.13 RIGHT FRONTAL HEADACHE AND LEFT ARM NUMBNESS IN A WOMAN WITH GASTRIC CARCINOMA

CHIEF COMPLAINT
A 75-year-old right-handed woman was admitted for gastric carcinoma and then developed a right frontal headache with left arm numbness and weakness.

HISTORY
Two weeks prior to admission, the patient noticed difficulty eating. She was admitted to the hospital on the general surgery service when a large mass was found in her abdomen, and an endoscopic biopsy revealed gastric carcinoma. On the evening after admission, the nurse found her lying on her left arm in an awkward position. The patient complained of a right frontal headache and left arm numbness. The surgical intern found that she had left-sided weakness, and a neurology consult was called.

PHYSICAL EXAMINATION
MENTAL STATUS: Alert and oriented × 3. Language normal. Able to recall 1/3 objects after 5 minutes, and 2/3 objects with prompting.
OKULAR NERVES: Pupils 3 mm, constricting to 1 mm bilaterally. Normal fundi. Visual field full, but with extinction on the left side to double simultaneous stimulation. Extraocular movements full, but with a right gaze preference. Facial sensation mildly decreased on the left side to light touch and pinprick. Mild left facial weakness, sparing the forehead. Normal hearing. Normal gag, palate elevation, and articulation. Tongue midline.
MOTOR: Left pronator drift. Power 5/5 throughout on the right side. Left arm strength 3/5 to 4/5. Left iliopeos and quadriceps 5/5, and left extensor hallucis longus 4/5.

REFLEXES:

COORDINATION: Normal rapid alternating movements on the right. Left side not tested.
GAIT: Not tested.
SENSORY: Mildly decreased light touch, pinprick, temperature, vibration, and joint position sense on the left side. Dramatic extinction on the left to double simultaneous stimulation. Decreased stereognosis and graphesthesia in the left hand.

LOCALIZATION AND DIFFERENTIAL DIAGNOSIS
1. On the basis of the symptoms and signs shown in bold above, where is the lesion?
2. What is the most likely diagnosis, and what are some other possibilities?

Discussion
1. The key symptoms and signs in this case are:
   • Right frontal headache
   • Weakness of the left face and arm more than the leg, with left Babinski's sign
   • Mildly decreased light touch, pinprick, temperature, vibration, and joint position sense on the left side, with decreased left stereognosis and graphesthesia
   • Left visual and tactile extinction

2. Weakness in the left face and arm that is greater than in the leg is usually caused by a lesion of the right face and arm motor cortex (see KCC 6.3; Figure 6.14D). The Babinski's sign supports the presence of an upper motor neuron lesion. Impaired primary and cortical sensation on the left side suggests a lesion in the right somatosensory cortex. The left neglect implies that the lesion may extend into parietal or, less likely, frontal association cortex. Right frontal headache has numerous possible causes (see KCC 5.1), including a lesion in the right hemisphere.
The most likely clinical localization is right primary motor cortex face and arm area, right somatosensory cortex, and right parietal association cortex.

2. Given the patient's age, the sudden onset of deficits, and the hypercoagulability associated with carcinoma (Table 10.5), the most likely diagnosis is ischemic stroke. Although the findings do not neatly fit a right MCA superior or inferior division infarct (see KCC 10.1), they might be explained by an infarct overlapping these territories. A hemorrhage in this area could also explain her deficits. Other possibilities include an abscess, or a tumor such as brain metastasis, especially given this patient's history. It should be noted that in about 10% of brain tumors, symptoms develop rapidly in a “stroke-like” manner.

**Initial Clinical Course**

A head CT (Figure 10.25A) showed hemorrhage with surrounding edema in the right parietal lobe extending to the face and arm regions of the precentral gyrus. The initial impression was hemorrhage into a brain metastasis, or cerebral infarct with hemorrhagic conversion. An MRI scan with gadolinium and an embolus workup were planned to investigate these possibilities. However, shortly after her head CT the patient suddenly became unresponsive and had left facial twitching, consistent with a seizure (see KCC 18.2). She was treated with intravenous anticonvulsants (diazepam and phenytoin) and she improved, although she had two more brief seizures over the next day and remained difficult to arouse. Repeat head CT showed no change in the blood, and head CT with intravenous contrast (Figure 10.25B) did not show any enhancing lesions consistent with metastases. On careful review of the contrast CT, an empty delta sign was noted in the superior sagittal sinus (see Figure 10.25B).

1. What is the significance of the empty delta sign?
2. What possible diagnosis should now be considered, and what tests should be done to investigate this possibility?

**Discussion**

1. The sagittal sinus normally fills uniformly with contrast, and a relatively dark region in the middle suggests a filling defect, possibly due to a blood clot (see Figure 10.25A). Note that in retrospect, there was a suggestion of dense material (high signal) in the sagittal sinus on the noncontrast scan as well (see Figure 10.25A).
2. Given this finding, superior sagittal sinus thrombosis should be strongly suspected (see KCC 10.7). Other features consistent with (but not specific to) superior sagittal sinus thrombosis include the headache, parasagittal hemorrhage, depressed level of consciousness, and seizures. The empty delta sign is suggestive but is not conclusive evidence for this diagnosis, so additional tests should be done, such as a magnetic resonance venogram or conventional angiography.

**Clinical Course and Neuroimaging**

A magnetic resonance venogram (Figure 10.26A) showed no appreciable flow in the superior sagittal sinus. This should be compared to the normal MR venogram from her initial patient (Figure 10.26B). Despite her hemorrhage, the patient was treated with low-dose anticoagulation using subcutaneous heparin, to prevent further thrombosis. She spent 3 weeks in inpatient rehabilitation, with improvement in her left arm strength and ambulation, and eventually underwent abdominal surgery for her gastric carcinoma.

**Brief Anatomical Study Guide**

1. The main functions of the cerebral hemispheres are summarized in Figure 10.1. The three main cerebrovascular territories are the anterior cerebral artery (ACA), middle cerebral artery (MCA), and posterior cerebral artery (PCA). The ACA and MCA arise from the anterior circulation, or carotid territory of the circle of Willis, while the PCA arises from the posterior circulation, or vertebrobasilar system (see Figures 10.2 and 10.3).

2. The ACA supplies the medial frontal and medial parietal lobes, including the sensorimotor cortex for the lower extremity (see Figure 10.4). The PCA supplies the medial and inferior occipital and temporal lobes, including the primary visual cortex. The MCA supplies the entire lateral surface of the cerebral hemispheres, including the face and arm sensorimotor cortex and many regions of association cortex (see Figure 10.5).

3. The MCA territory has the following three major subdivisions (see Table 10.1): the MCA superior division supplies most of the cortex above the Sylvian fissure, including the lateral frontal cortex and the face and arm peri Rolandic cortex. The MCA inferior division supplies the cortex of the lateral temporal and occipital lobes below the Sylvian fissure, as well as a variable portion of the lateral parietal cortex. The MCA deep territory includes the internal capsule and much of the basal ganglia (see Figures 10.7-10.9)

4. The ACA also has a deep territory, including portions of the anterior basal ganglia and internal capsule, while the deep territory of the PCA includes the thalamus, midbrain, and variable parts of the posterior internal capsule (Figure 10.8). The superficial and deep territories of all three major cerebral vessels are summarized in Figures 10.6 and 10.9. Deficits caused by occlusion of the middle cerebral arteries or their branches are summarized in Table 10.1.

5. Blockage of a cerebral artery or its branches often causes an infarct in a specific vascular territory. Infarcts can also occur through another mechanism when the systemic blood pressure drops, or when a parent vessel (such as the carotid artery) supplying more than one major cerebral vessel (e.g., the ACA and MCA) becomes blocked, resulting in infarction of the most distal territories of overlap of these vessels. These territories are called watershed zones (see Figure 10.10).

6. Venous drainage of the cerebral hemispheres occurs through the system of superficial and deep cerebral veins. The superficial veins drain mainly into the superior sagittal sinus and cavernous sinus, while the deep veins drain into the great vein of Galen (see Figure 10.11). Ultimately, all venous drainage for the brain reaches the internal jugular veins, mostly via the transverse and sigmoid sinuses.

**Additional Cases**

Related cases can be found for the following: cerebral infarct, or TIA (Cases 5.3, 5.6-1.3, 6.5, 7.1, 7.2, 11.1, 13.7, 14.1-14.8, 15.1, 18.3, 19.1-19.4, 19.6, 19.8, 19.9), aneurysm (Case 13.1), arteriovenous malformation (AVM) (Case 11.5), dissection (Case 13.6), and intracerebral hemorrhage (Cases 5.1, 5.3, 5.5, 5.6, 14.9, 19.3, 19.4). Other relevant cases can be found using the Case Index.
**CASE 10.13** RIGHT FRONTAL HEADACHE AND LEFT ARM NUMBNESS IN A WOMAN WITH GASTRIC CARCINOMA

Figure 10.25 Right Parietal Hemorrhage, and Empty Delta Sign

(A) Noncontrast scan showing right parietal hemorrhage with surrounding edema. (B) Repeat scan with intravenous contrast, showing empty delta sign.

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**CASE 10.13 (CONTINUED)**

Figure 10.26 Superior Sagittal Sinus Thrombosis

Magnetic resonance venogram (MRV). (A) MRV from patient in case 10.13, showing absence of flow in the superior sagittal sinus, likely due to thrombosis. (B) MRV in a normal patient, showing normal flow in the superior sagittal sinus, and cortical veins. Note that the transverse sinuses are not well seen in both A and B, because their initial portions near the torcular are being viewed end-on, and their more lateral portions are truncated by the imaging method. Compare to Figure 10.11.
CHAPTER 11

Visual System

Because of their structure, a single lesion in the visual pathways can affect both eyes, causing significant functional impairments. A 57-year-old man repeatedly visited the emergency room because of headaches. He experienced throbbing bilateral or right occipital pain and saw zigzagging lines in his visual field. He had also recently noticed a vision problem that caused him to frequently bump into objects on his left side. On examination, he was unable to see anything in the left lower quadrant of his visual fields in both eyes. In this chapter, we will learn about the normal anatomy and function of the neural pathways from the retina to the cortex, and we will use this knowledge to accurately diagnose and localize lesions in clinical cases.
Figure 11.4 The retina. (A) Spatial relationships between the retina and other structures of the eye. (B) Magnified view of the fovea, where light reaches photoreceptors (rods and cones) without passing through intervening layers. The main cell types of the retina are indicated.

(A) Inner plexiform layer
(B) Outer plexiform layer
(C) Photoreceptors in outer nuclear layer

(A) Axons traveling to optic nerve
(B) Amacrine cell
(C) Ganglion cell
(D) Bipolar cell
(E) Horizontal cell
(F) Retina

REVIEW EXERCISE

Name each of the five layers of the retina, proceeding from the outside toward the center of the eye. For each layer, describe the main cell types or synapses that occur (see Figure 11.4).

center ganglion cells, which send their axons into the optic nerve (see Figure 11.4). Unlike other neurons, photoreceptors and bipolar cells do not fire action potentials. Instead, information is conveyed along the length of these cells by passive electrical conduction, and they communicate through "non-traditional" synapses that release neurotransmitter in a graded fashion that depends on membrane potential. Ganglion cells, on the other hand, do fire action potentials as they convey information into the optic nerve.

In addition to this direct, or vertical, pathway through the retina, there are also interneurons called horizontal cells and amacrine cells (see Figure 11.4). These interneurons have lateral inhibitory or excitatory connections with nearby bipolar and ganglion cells. Therefore, a small spot of light on the retina causes excitation (or inhibition) of bipolar and ganglion cells directly in its path, or inhibition (or excitation) of the surrounding bipolar and ganglion cells. As a result of these lateral connections, bipolar and ganglion cells have receptive fields with a center-surround (concentric) configuration (Figure 11.5).

There are two classes of center-surround cells. On-center cells are excited by light in the center of their receptive field and inhibited by light in the surrounding area. Conversely, off-center cells are inhibited by light in the center and excited by light in the surrounding area. Beginning with the bipolar cells, many neurons in the visual pathway, including ganglion cells, lateral geniculate neurons, and input neurons of the primary visual cortex have center-surround receptive fields, which are either on-center or off-center. Beyond the input neurons of the visual cortex, neurons involved in vision have more sophisticated receptive field properties, which will be discussed later.

Retinal ganglion cells can be further classified as M cells (or P or A cells), which have large receptive fields, and respond best to gross stimulus features and movement, and P cells (or PF or B cells), which have smaller receptive fields, are more numerous, and are sensitive to fine visual detail and to colors. M cells have larger-diameter fibers and project to the magnocellular layers of the lateral geniculate nucleus of the thalamus (see Figure 11.7), while P cells have smaller-diameter fibers and project to the parvocellular layers of the lateral geniculate. There are also other retinal ganglion cells that fit neither class, some of which are sensitive to overall light intensity. M and P cells can be either on- or off-center cells.

Optic Nerves, Optic Chiasma, and Optic Tracts

The retinal ganglion cells send their axons into the optic nerve, which exits through the optic tract, while fibers from the right hemisphere of both eyes end up in the left optic tract, while fibers from the right hemisphere cross over in the optic chiasm. Lesions of the optic tract can result in blindness in the contralateral half of the visual field. Lesions of the optic nerve can result in blindness in the ipsilateral half of the visual field. Lesions of the optic chiasm can result in blindness in the ipsilateral half of the visual field, that is, blindness in both eyes.
Figure 11.6 Geniculate and Extrageniculate Visual Pathways. The geniculate (or geniculostriate) pathway relays in the lateral geniculate nucleus (LGN) and continues to the primary visual cortex via the optic radiations (see Figure 11.15). The extrageniculate pathways bypass the LGN via the brachium of the superior colliculus and relay in the pretectal area and superior colliculus. Projections from the pretectal area and superior colliculus then continue to the pulvinar en route to the lateral-geniculate nuclei (MGd) and inferior colliculus. These inputs are important relays in the auditory system that will be discussed in Chapter 12.

Lateral Geniculate Nucleus and Extrageniculate Pathways

The axons of retinal ganglion cells in the optic tracts form synapses on neurons in the lateral geniculate nucleus (LGN) of the thalamus, which in turn project to the primary visual cortex. A minority of fibers in the optic tract bypass the LGN to enter the brachium of the superior colliculus (see Figure 11.6). These retinal fibers form the extrageniculate visual pathways, which project mainly to the pretectal area and superior colliculus. As we will see in Chapter 13, the pretectal area is important in pupillary light reflexes and projects to the parasympathetic nuclei controlling the pupils (see Figure 13.8). The superior colliculus and pretectal area are important in directing visual attention and eye movements toward visual stimuli. The superior colliculus and pretectal area therefore project to numerous brainstem areas involved in these functions, as well as to association cortex (lateral parietal cortex and frontal eye fields of the prefrontal cortex) via relays in the pulvinar and lateral posterior nucleus of the thalamus (see Figure 11.6; see also Figures 7.7 and 7.8). Thus, the retino-tegmental-pulvinar-extratrigeminal cortex pathway functions in visual attention and orientation, while the retino-geniculo-occipital pathway functions in visual discrimination and perception.

The LGN has six layers, numbered 1 to 6 from ventral to dorsal (Figure 11.7). The first two magnocellular layers relay information from M cells of the retina, while layers 3 through 6, the parvocellular layers, relay information from P cells. The information from each eye remains segregated even after passing through the LGN. The segregation is preserved because axons from the ipsilateral and contralateral retinas synapse onto different layers of the LGN (see Figure 11.7). There are also intralaminar neurons that are important for relaying information regarding color vision. Most neurons of the LGN have on or off center-surround receptive fields, similar to retinal neurons (see Figure 11.5). However, some LGN neurons, particularly in the magnocellular layers, are on/off cells. These cells detect changes and fire transiently to both on and off stimuli.

Optic Radiations to Primary Visual Cortex

The axons leaving the LGN enter the white matter to sweep over and lateral to the atrium and temporal horn of the lateral ventricle (through the C shape of the lateral ventricle) and then back toward the primary visual cortex in the occipital lobe (Figure 11.8). As they do so, these axons fan out over a wide area, forming the optic radiations. Axons from the contralateral and ipsilateral retinal layers of the LGN (see Figure 11.7) are intermingled in the optic radiations, so lesions of the optic radiations usually cause homonymous defects affecting the contralateral visual field (see Figure 11.15E-G). The fibers of the inferior optic radiations are forward into the temporal lobe, forming Moyer's loop (see Figures 11.8, 11.15). The inferior optic radiations carry information from the inferior retina or the superior visual field (see Figure 11.1A). Temporal lobe lesions can therefore cause a contralateral homonymous superior quadrantanopia ("pie in the sky" visual field defect) (see Figure 11.15E). Conversely, the upper optic radiations pass under
Visual Processing in the Neocortex

Review the different cortical layers and their functions (see Figure 2.14). Most input to primary visual cortex arrives at cortical layer 4. Because of its functional importance in this region of the brain, layer 4 is relatively thick and is subdivided into sublayers 4A, 4B, 4Ca, and 4Cb (see Figure 11.10). Layer 4B contains numerous myelinated axon collaterals resulting in the pale-appearing striate of Gennari, which is visible in sections of the gray matter even with the naked eye. Because of this distinctive stria (see Figure 11.10), the primary visual cortex (area 17) is sometimes referred to as striate cortex.

Parallel Channels for Analyzing Motion, Form, and Color

Numerous channels of information undergo parallel processing in the visual system. The three best-characterized channels are for analyzing motion, form, and color. As already discussed, some of the information for these channels is...
Ocular Dominance Columns and Orientation Columns

The classic work of David Hubel and Torsten Wiesel in the 1960s demonstrated that the visual cortex has a columnar organization. As in the LGN, inputs to the primary visual cortex are segregated on the basis of whether they originated from the contralateral or ipsilateral eye. However, instead of terminating on different layers, inputs from each eye terminate in different alternating bands of cortex, each about 1 millimeter wide, called ocular dominance columns (Figure 11.12A; see also Figure 11.15A). As the original studies by Hubel, Wiesel, and collaborators demonstrated the ocular dominance columns using autoradiography and histological techniques on postmortem tissue from animals, today it is possible to image the ocular dominance columns and other patterns of cortical activity in living animals (including humans) using intrinsic optical signals related to neural activity, as shown in Figure 11.12A. In this experiment, optical signals were recorded from primary visual cortex with a camera looking down at the pial surface of the brain during presentation of visual stimuli. A visual stimulus presented to the right eye activated regions shown in white, while a stimulus presented to the left eye activated regions shown in black. This produced a typical pattern of ocular dominance columns consisting of alternating stripes of increased and decreased activation corresponding to inputs from the right and left eyes, respectively.

The receptive fields of neurons in the primary visual cortex input layers, such as layer 4, are mainly on and off center-surround cells (Figure 11.13A). However, these cells project to other neurons, above and below layer 4, which have more sophisticated receptive fields. **Simple cells** respond to segregated as early as the retinal ganglion cells and LGN. These three channels also project to different layers of the primary visual cortex (Figure 11.11A). The magnocellular layer of the LGN, conveying information about movement and gross spatial features, project mainly to layer 4C. The parvocellular layer of the LGN, conveying fine spatial information, terminate mainly in layer 4B. Information about color is also relayed by the parvocellular layers, as well as by the interlaminar zones, to specialized regions of cortical layers 2 and 3 called blobs (see Figure 11.14) because of their appearance on staining with the histochemical marker cytochrome oxidase.

From the primary visual cortex, or area 17, neurons project to **extrastriate** regions of visual association cortex, including areas 18, 19, and other regions of the parieto-occipital and occipitotemporal cortex (see Figure 11.11A). In the monkey, the three channels of information processing described here have been shown to project to distinct regions of area 18 named thin stripes, thick stripes, and interstripes, based on their staining patterns with cytochrome oxidase. From primary and secondary visual cortex (areas 17 and 18), two main streams of higher-order visual processing have been demonstrated in both animals and humans (see Figure 11.11B). The **dorsal pathways** project to parieto-occipital association cortex. These pathways answer the question “**Where?**” by analyzing motion and spatial relationships between objects, and between the body and visual stimuli. The **ventral pathways** project to occipitotemporal association cortex. These pathways answer the question “**What?**” by analyzing form, with specific regions identifying colors, faces, letters, and other visual stimuli. The effects of lesions in these two streams of higher-order visual processing will be discussed in Chapter 19.

**Figure 11.11 Visual Processing Pathways** (Top) Three parallel channels of visual information processing. (Bottom) Dorsal and ventral streams of higher-order visual processing.
The localization and diagnosis of visual disturbances involves two major steps. The first step is a detailed description of the nature of the visual disturbance, including its time course and whether positive phenomena such as brightly colored lights or negative phenomena such as regions of decreased vision are present. The second step is a description of the regions of the visual field for each eye that are involved. In this section, we will discuss the localization information that can be derived from the nature of the visual disturbance. In the next section, we will discuss the visual field defects seen with lesions in specific locations.

As with other disorders, the evaluation of visual disturbances involves taking a detailed history, followed by a complete exam, which includes examination of the eyes with an ophthalmoscope (see neuroex.com Video 25), as well as testing of visual acuity and of visual fields for each eye (see neuroex.com Video 27). Visual acuity is often reported using the Snellen notation of 20/XX. In this notation, the smallest line of the eye chart seen by the subject at 20 feet can be seen by a normal individual at the distance given in the denominator. Visual acuity can be impaired by a variety of ophthalmological disorders that are beyond the scope of this text (see References at the end of the chapter for details). Note that visual field defects do not typically affect visual acuity.

The distinction between a monocular or binocular visual disturbance is essential for localization. However, patients often describe visual changes as being in one eye, when in reality the left or right sides of the visual fields for both eyes are affected. While describing a transient visual disturbance, patients are sometimes able to recall improvement on covering one eye, suggesting a true monocular disorder. Often it is only by examination of the patient while the problem is still present that this distinction can be confirmed. Similarly, “blurred” vision is hard to interpret without further description; it can mean anything from corneal disease to a lesion in the visual cortex. “Blurred” vision can sometimes even be a sign of subtle diplopia, suggesting an ocular motility disorder (see Chapter 13).

Some important terms used to describe visual disturbances are listed in Table 11.1. Visual changes are often divided into positive and negative phenomena. Negative phenomena such as a scotoma or a homonymous visual field defect (see Table 11.1) can be caused by lesions at various locations in the visual pathways (see Figure 11.15; KCC 11.2). Patients may be aware of a dark brown, purplish, or white region of their vision where they cannot see. At other times they are unaware of the defect, and the region that cannot be seen is experienced in a manner similar to the physiological blind spot (see Figure 11.2), or to locations behind the head that are normally out of view. Regions of absent vision of this kind are nearly always a result of a lesion of the central visual pathways, while black, dark brown, or purplish scotomas are most often produced by retinal lesions.

Positive visual phenomena may be simple or formed. Simple visual phenomena such as lights, colors, or geometric shapes are caused by disturbances anywhere from the eye to the primary visual cortex. Important ophthalmological causes of positive phenomena include light flashes in retinal detachment and rainbow-colored halos around objects in acute glaucoma, although positive phenomena can be caused by numerous other ophthalmological diseases that are beyond the scope of this discussion. In migraine (see KCC 5.1), patients may experience visual blurring and scotomas that sometimes have a scintillating appearance or consist of jagged alternating light.

![Figure 11.14 Hypercolumn](image-url)
TABLE 11.1 Some Terms to Describe Visual Disturbances

<table>
<thead>
<tr>
<th>TERM</th>
<th>DEFINITION</th>
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<tbody>
<tr>
<td>Scotoma</td>
<td>A circumscribed region of visual loss</td>
</tr>
<tr>
<td>Homonymous defect</td>
<td>A visual field defect in the same region for both eyes</td>
</tr>
<tr>
<td>Refractive error</td>
<td>Indistinct vision improved by corrective lenses</td>
</tr>
<tr>
<td>Photopsias</td>
<td>Bright, unformed flashes, streaks, or balls of light</td>
</tr>
<tr>
<td>Phosphenes</td>
<td>Phosphenes produced by retinal shear or optic nerve disease</td>
</tr>
<tr>
<td>Eriotic phenomena</td>
<td>Seeing structures in one's own eye</td>
</tr>
<tr>
<td>Illusions</td>
<td>Distortion or misinterpretation of visual perception</td>
</tr>
<tr>
<td>Hallucination</td>
<td>Perception of something that is not present</td>
</tr>
</tbody>
</table>

and dark zigzag lines called a **fortification scotoma** (because of its resemblance to the water fortifications of medieval towns in Europe). These typically migrainous phenomena are thought to be related to transient dysfunction of the primary visual cortex (e.g., zigzagging lines may result from activation of alternating orientation columns). When patients instead experience pulsating colored lights or moving geometric shapes, ocipital seizures should be suspected, although occipital seizures may also produce migrainous visual phenomena at times.

**Formed visual hallucinations** (see Table 11.1), such as people, animals, or complex scenes, arise from the inferior temporal-occipital visual association cortex. Common causes of formed visual hallucinations include toxic or metabolic disturbances (especially hallucinogens, anticholinergics, and cyclosporin), withdrawal from alcohol or sedatives, focal seizures, complex migraines, neurodegenerative conditions such as Creutzfeldt-Jakob disease or Lewy body disease, narcolepsy, midbrain ischemia (peduncular hallucinosis; see KCC 14.3), or psychiatric disorders. Of note, in psychiatric disorders visual hallucinations are less common than auditory hallucinations, and they usually occur with accompanying sound. Formed visual hallucinations can also appear as a **release phenomenon**. Thus, patients with visual deprivation in part or all of their visual fields caused by either ocular or central nervous system lesions may occasionally see objects, people, or animals in the region of vision loss, especially during the early stages of the deficit. Visual hallucinations that occur in elderly patients as a result of impaired vision have been called Bollon syndrome.

Once the nature of a visual disturbance has been established (see KCC 11.4), including the time course and other clinical features, such as whether positive, negative, simple, or elaborate visual phenomena are present, the next step is to evaluate the visual pathways affected by the lesion. We will first describe the methods used for visual field testing and then discuss the interpretation and localizing value of specific visual field defects.

**Visual Field Testing**

Basic visual field testing can be done at the bedside, using **confrontation testing** (see neuroexam.com Video 27). The examiner should test each eye separately, by covering one eye at a time. The patient is instructed to look at the examiner's eye while the examiner holds visual stimuli such as fingers or a small cotton-tipped stick halfway between the patient and examiner. In this way, the examiner's visual field is being tested at the same time, which serves as a check on the patient's field. The examiner should test each quadrant while watching the patient carefully for central fixation. Moving or wiggling fingers are easier to see but are less sensitive for detecting regions of mildly decreased vision. Fingers should be held up simultaneously on the right and left sides at some point during the exam to test for extinction, a sign of visual neglect (see KCC 19.9). By convention, visual fields are recorded with the right eye on the right side of the page, as if viewing your own visual field (see Figure 11.1). Blink to threat can be a useful way of testing crude visual fields in the cooperative or lethargic patient (see neuroexam.com Video 28).

More formal visual field testing can be done, when appropriate, using **Goldmann perimetry**, with small lights of different sizes and intensities displayed on a screen in front of the patient (Figure 11.2). The normal visual field extends about 60° nasally and superiorly, and slightly further inferiorly and temporally. In addition to manually performed Goldmann perimetry, automated computerized perimetry is increasingly being used in some settings. However, automated perimetry usually only tests the central 30° of the visual field.

**Visual Field Defects**

The position and shape of the scotoma, and whether it affects one eye or both, are the most important pieces of information allowing localization of abnormalities in the visual pathways. Figure 11.15 summarizes the effects of lesions at various points in the pathways from retina to primary visual cortex that we have been discussing in this chapter, and review again here. A lesion of the retina causes a **monocular scotoma** (see Figure 11.15A), with the location, size, and shape depending on the location and extent of the lesion. Common causes include retinal infarcts (KCC 11.5), hemorrhage, degeneration, or infection. If the lesion is severe enough, the entire retinal may be involved, causing **monocular visual loss** (see Figure 11.15B). In addition to retinal disorders, monocular disturbances of vision can result from numerous other diseases of the eye (see ophthalmology texts for additional details).

Lesions of the optic nerve cause monocular visual loss or monocular scotomas (see Figure 11.15A,B), which may be partial or incomplete depending on the severity of the lesion. Common causes include glaucoma, optic neuritis, elevated intracranial pressure, anterior ischemic optic neuropathy, optic glioma, schwannoma, meningioma, and trauma.

The optic chiasm is located near the pituitary gland (see Figure 17.2B) and can be compressed by lesions arising in this area. Damage to the optic chiasm typically causes a **bitemporal hemianopia** (see Figure 11.15C), which is often more asymmetrical than shown in the figure. Common lesions in this area include pituitary adenoma, meningioma, craniopharyngioma, and hypothalamic glioma, although numerous other lesions can also occur in this location.

**Retrochiasmal lesions**, including the optic tracts, LGN, optic radiations, or visual cortex, generally cause **homonymous visual field defects**, meaning that the same regions of the fields for both eyes are involved. However, since the fibers from each eye are less fully mingled in the optic tract and LGN, visual field defects may not be perfectly congruous for more anterior retrochiasmal lesions, while they are usually perfectly congruous for lesions of the visual cortex.

Lesions of the optic tracts are relatively uncommon, and usually cause a **contralateral homonymous hemianopia** (see Figure 11.15D). Possible lesions include tumors, infarct, or demyelination.

Lesions of the lateral geniculate nucleus are also usually associated with a contralateral homonymous hemianopia (see Figure 11.15D), although sometimes more unusual visual field defects can occur, such as a keyhole-
Visual fields
(A) Monocular scotoma
Left

(B) Monocular visual loss

(C) Bitemporal hemianopia

(D, G, H) Contralateral homonymous hemianopia

(E, J) Contralateral superior quadrantanopia

(F, I) Contralateral inferior quadrantanopia

Lesions of primary visual cortex:
1. Upper bank lower bank
2. Upper bank
3. Lower bank

Optic nerve
Optic chiasm
Optic tract
Meyer's loop
Lateral geniculate nucleus
Optic radiation

Left

Right

Retina

Figure 11.15 Effects of Lesions in the Primary Visual Pathways: (Left) Visual field defects corresponding to various lesions (right, black bars) are identified by the letters A through J. Visual pathways are shown as seen from above.

Shape sector scotoma. Possible lesions include tumors, infarct, hemorrhage, toxoplasmosis, or other infections.

Lesions of the optic radiations include infarcts, tumors, demyelination, trauma, and hemorrhage. As discussed in the next section, lesions involving the temporal lobe, such as middle cerebral artery (MCA) inferior division infarcts, can interrupt the lower optic radiations as they loop through the temporal lobe (Meyer's loop; see Figure 11.8). Lesions of the temporal lobe therefore cause a contralateral superior quadrantanopia (see Figure 11.15I), or "pie in the sky" visual defect. Meanwhile, lesions involving the parietal lobe, such as MCA superior division infarcts, can interrupt the upper portions of the optic radiations as they pass through the parietal lobe (see Figure 11.8). Therefore, parietal lesions typically cause a contralateral inferior quadrantanopia (see Figure 11.15F), or "pie on the floor" visual defect. Lesions of the entire optic radiation cause a contralateral homonymous hemianopia (see Figure 11.15C).

The primary visual cortex may be damaged by posterior cerebral artery (PCA) infarcts, tumors, hemorrhage, infections, or trauma to the occipital pole. Lesions to the upper bank of the calcine fissure cause a contralateral inferior quadrantanopia (see Figure 11.15B), while lesions to the lower bank cause a contralateral superior quadrantanopia (see Figure 11.15D). Damage to the entire primary visual cortex causes a contralateral homonymous hemianopia (see Figure 11.15E). Smaller lesions cause homonymous scotomas in the appropriate portion of the contralateral visual field (see Figure 11.9).

Partial lesions of the visual pathways occasionally result in a phenomenon called macular sparing (Figure 11.16). This occurs because the fovea has a relatively large representation in its size, beginning in the optic nerve and continuing to the primary visual cortex (see, for example, Figure 11.9). Macular sparing can also occur in visual cortex because either the MCA or the PCA may provide collateral flow to the representation of the macula in the occipital pole (see Figure 10.5). Although the term "macular sparing" is usually used in the context of cortical lesions, other lesions may cause a relative sparing of the visual field as well. For example, external compression of the optic nerve, as seen in elevated intracranial pressure, may cause concentric visual loss (constricted visual field; see Figure 11.16A).

Disorders of higher-order visual processing caused by lesions of the visual association cortex are discussed in Chapter 19.

Figure 11.16 Examples of Macular Sparing: (A) Macular concentric visual loss caused, for example, by chronically elevated intracranial pressure or retinitis pigmentosa. (B) Left homonymous hemianopia with macular sparing caused, for example, by a right posterior cerebral artery infarct preserving the occipital pole. (C) Left superior quadrantanopia with macular sparing caused, for example, by a lesion of the inferior bank of the right calcine fissure preserving the occipital pole.

Review Exercise
First, cover all the visual fields in Figure 11.15, and for each lesion marked on the brain (A-J), draw the visual fields expected in a patient with that lesion. Next, cover the brain illustration, and for each visual field defect shown in the figure, state all possible locations where a lesion could be found to cause such a deficit.

Key Clinical Concept
BLOOD SUPPLY AND ISCHEMIA IN THE VISUAL PATHWAYS

The retina receives its blood supply primarily from branches of the ophthalmic artery, which originates just above the genu of the internal carotid artery (see Figure 10.2A). The retinal arteries and veins can be well visualized as they emerge from the optic disc by use of an ophthalmoscope (see neuroscope.com Vido 25; see also Figure 5.17). The three main causes of impaired blood flow in the ophthalmic artery and its branches are (1) embolii, often atheromatous material arising from the internal carotid artery; (2) stenosis, usually associated with diabetes, hypertension, or elevated intracranial pressure; and (3) vasculitis, as seen, for example, in temporal arteritis.
Central retinal artery occlusion and branch retinal artery occlusion can cause infarction of the entire retina or of the affected retinal sector, respectively. The retinal artery usually has two major branches—one covering the upper half, the other covering the lower half of the retina. An altitudinal scotoma in one eye can therefore result from occlusion of one of these branches (Figure 11.17). Smaller monocular scotomas can also occur from occlusion of smaller branches (see Figure 11.15A). Transient occlusion of the retinal artery caused by embolus results in a transient ischemic attack (TIA) of the retinal called amaurosis fugax, with brown out or loss of vision in one eye for about 10 minutes, sometimes described as being "like a window shade" moving down or up over the eye. This condition deserves to be worked up just like any other TIA (see KCC 10.3, 10.4), since it may be a warning sign for an impending retinal or cerebral infarct. A common cause of amaurosis fugax is ipsilateral internal carotid artery stenosis (see KCC 10.5), which causes artery-to-artery embolus.

The optic tracts, optic chiasm, and intracranial segment of the optic nerves receive their blood supply from numerous small branches arising from the proximal portions of the anterior cerebral artery (ACA), middle cerebral artery (MCA), and anterior and posterior communicating arteries. Clinically significant infarcts of these structures are therefore rarely seen.

The lateral geniculate nucleus has a variable blood supply arising from several vessels, including the anterior choroidal artery (branch of the internal carotid), thalamogeniculate artery, and posterior choroidal artery (branches of the posterior cerebral artery). Infarcts of the lateral geniculate generally produce a contralateral homonymous hemianopia (see Figure 11.15D), although more unusual field defects can also sometimes be seen, as mentioned earlier. In addition, there may be an associated contralateral hemiparesis or hemisensory loss due to involvement of the nearby posterior limb of the internal capsule and thalamic somatosensory radiations (see Figures 6.98, 10.8B).

The optic radiations pass through the parietal and temporal lobes, where they may be damaged by infarcts of the superior and inferior divisions of the middle cerebral artery, respectively (see Figure 11.8; see also Figure 10.6; Table 19.1). Damage to the upper portions of the optic radiations in the parietal lobe causes a contralateral homonymous hemianopia (see Figure 11.15F), while damage to Meyer's loop in the temporal lobe causes a contralateral superior quadrantanopia (see Figure 11.15E).

The primary visual cortex is supplied by the posterior cerebral artery (PCA; see Figure 10.5). Infarcts of the entire primary visual cortex cause a contralateral homonymous hemianopia (see Figure 11.15G). Smaller infarcts cause smaller contralateral homonymous defects (see Figure 11.15J; 11.16C). Sometimes disease of the basilar artery, which supplies both PCAs (see Figure 10.3), can cause bilateral PCA ischemia or infarcts. A bilateral altitudinal scotoma (see Figure 11.17B) is strongly suggestive of vertebrobasilar insufficiency causing bilateral infarcts or TIAs.

The inferior temporal visual association cortex ("what?" stream; see Figure 11.11B) is supplied by the PCA (see Figure 10.5). The lateral parieto-occipital visual association cortex ("where?" stream) lies in the MCA–PCA watershed territory (see Figures 10.5, 10.10). Infarcts of the inferotemporal or dorsolateral parieto-occipital visual association cortices cause characteristic disorders of higher-order visual processing that will be discussed in Chapter 19 (see KCC 19.13).

11.4 Optic neuritis is an inflammatory demyelinating disorder of the optic nerve that is epidemiologically and pathophysiologically related to multiple sclerosis (see KCC 6.6). Like multiple sclerosis, mean age of onset is in the 30s, onset after age 45 is rare, and there is about a 2:1 female-to-male ratio. In the careful follow-up, about 50% or more of patients with an isolated episode of optic neuritis will eventually develop multiple sclerosis.

The usual clinical features at onset include eye pain, especially with movement, and monocular visual problems. The visual impairment typically includes a monocular central scotoma (visual loss in the center of the visual field), decreased visual acuity, and impaired color vision. In severe cases, complete loss of vision in one eye may occur. Ophthalmoscopic exam may reveal a swollen optic disc if the inflammation extends to the fundus, causing papillitis, or the fundus may appear normal if the neuritis is entirely retrolubar (meaning behind the eye). Sometimes the disc will appear pale, termed optic disc pallor, suggesting prior episodes of optic neuritis.

A fairly sensitive way to detect impaired cone function in central vision is to test for red desaturation, by asking the patient to compare the appearance of a bright red object seen with each eye (see neuroexam.com Video 26). In patients with past or present optic neuritis, the object will often appear duller in the affected eye. Another very useful way to detect optic nerve dysfunction is to test for an afferent pupillary defect using the swinging flashlight test (see neuroexam.com Video 30; see also KCC 13.5). In addition, visual evoked potentials can provide evidence of impaired conduction in the visual pathways. In this test the patient is shown a shifting checkerboard pattern, which elicits a waveform that can be detected over the occipital cortex by electrodes placed on the scalp. The normal latency for visual evoked potentials is less than about 150 milliseconds. Prolonged latency with preserved amplitude suggests slowed conduction consistent with demyelination.

Onset of optic neuritis can be acute or slowly progressive over several days to weeks. Near complete recovery is commonly seen within 6 to 8 weeks, and sometimes over a few months. In some cases, especially after repeated bouts, there may be some permanent visual loss. A second episode occurs in about one-third of cases. Treatment for isolated optic neuritis is controversial at present. Another area of controversy is whether to perform further diagnostic tests to explore a possible diagnosis of multiple sclerosis. Most practitioners will have a frank discussion with the patient about the association between optic neuritis and multiple sclerosis and let the patient's preferences guide the extent of the workup. One practical issue is that unless recovery has already begun to occur, it is important to perform an MRI scan to rule out an infiltrative or compressive lesion of the optic nerve as the cause of symptoms.

If any atypical features are present, such as age over 45 years, lack of eye pain, bilateral symptoms, or lack of recovery, further investigations are warranted, including MRI with gadolinium, and blood tests including erythrocyte sedimentation rate, Lyme titer, syphilis serologies, Epstein-Barr virus, human immunodeficiency virus, B12, folate, serological tests for rheumatological disorders, and possibly lumbar puncture.
CASE 11.2 VISION LOSS IN ONE EYE

MINICASE
A 58-year-old man awoke one morning with blurred vision in the left eye, as if it were covered with a shaded piece of glass. This condition progressed over the next few days to nearly complete loss of vision in the left eye. He scheduled an appointment with an ophthalmologist, but by the time he was seen, about 2 weeks after the onset of symptoms, the patient felt his vision was 10% back to normal. There was no eye pain, but he did have a generalized headache. On exam, there was slight paller of the left optic disc when viewed with an ophthalmoscope. When a light was shone into the left pupil, the constriction of both pupils was less than when a light was shone into the right pupil. This result was best demonstrated with the swinging flashlight test (see KCC 11.4; 13.5). This patient's visual fields are shown in Figure 11.19. The remainder of the examination was normal.

LOCALIZATION AND DIFFERENTIAL DIAGNOSIS
1. On the basis of the symptoms and signs shown in bold above, where is the lesion?  
2. What is the most likely diagnosis, and what are some other possibilities?

Discussion
The key symptoms and signs in this case are:
- Monocular visual loss in the left eye, improving to a monocular central scotoma
- Left afferent pupillary defect
- Left optic disc pallor

Monocular visual loss or a monocular scotoma can be caused by a lesion in any location anterior to the optic chiasm, including the eye, retina, or optic nerve (see KCC 11.2; Figure 11.15A.B). The afferent pupillary defect (see KCC 11.4; KCC 13.5) in the left eye also supports a lesion in these locations. On ophthalmoscopic exam, the eye and retina were unremarkable, but the left optic disc, which is the entrance point of the optic nerve to the retina (see Figure 11.1), appeared pale, suggesting that there had been a previous lesion in the left optic nerve.

The most likely clinical localization is left optic nerve.

1. Given the patient's relatively young age, the improvement within a few weeks, and the characteristic central scotoma, the most likely diagnosis is optic neuritis of the left eye (KCC 11.4). Other possibilities include an ischemic lesion of the optic nerve caused by small-vessel disease (anterior ischemic optic neuropathy), but this is more common in older individuals with diabetes or hypertension. A neoplasm (metastasis, optic glioma, lymphoma, metastasis) or inflammatory process (sarcoid, Lyme disease) could be considered as well.
pressing or infiltrating the optic nerve is possible, but these conditions do not usually improve spontaneously.

**Clinical Course**

Visual evoked potentials (see KCC 11.4) showed a latency of 104 ms in the right eye and 148 ms in the left eye (normal is less than 115 ms). An MRI scan showed no infiltrative or compressive lesions of the optic nerve; however, there were several areas of increased T2 signal in the periventricular regions of the brain, suggesting possible demyelination (see KCC 6.6). On further discussion with the patient, it became apparent that there had been a similar episode of visual loss in the left eye that resolved spontaneously in a few weeks and likely represented a prior episode of optic neuritis. This previous episode may account for the optic palsy seen during the current episode, since this finding often takes time to develop. He admitted to occasionally having tingling in the fingers of both hands, and to experiencing times when he felt his gait was uncoordinated. A prolonged discussion was held with the patient and family about possible multiple sclerosis (see KCC 6.6). The diagnosis of multiple sclerosis was eventually confirmed 2 years later, when he unfortunately developed diplopia, decreased sensation in the left arm and leg, gait unsteadiness, and urinary frequency. A repeat MRI scan showed a new T2 bright area in the right medulla, and a lumbar puncture was normal except for the presence of two oligoclonal bands (see KCC 3.10). The patient improved spontaneously within 5 days and was then enrolled in a program using beta interferon to treat relapsing remitting multiple sclerosis.

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**CASE 11.3 MENSTRUAL IRREGULARITY AND BITEMPORAL HEMIANOPIA**

MINICASE

A 30-year-old woman went to an ophthalmologist because of several months of worsening vision that had begun to interfere with her driving. Past history was notable for long-standing menstrual irregularity and infertility. Exam was normal except for decreased vision primarily in the temporal portions of the visual fields bilaterally (Figure 11.20).

**LOCALIZATION AND DIFFERENTIAL DIAGNOSIS**

On the basis of the symptoms and signs shown in bold above, where is the lesion? What is the most likely diagnosis, and what are some other possibilities?

---

**CASE 11.4 HEMIANOPIA AFTER TREATMENT FOR A TEMPORAL LOBE TUMOR**

MINICASE

A 29-year-old man was referred to a neuro-opthalmologist because of worsening vision in his left visual fields. Past history was notable for complex partial seizures for 5 or 6 years, beginning with an optic-aural aura. One year ago an MRI revealed a left temporal lobe tumor. On resection, the tumor was found to be an oligoastrocytoma, and he was treated with chemotherapy and radiation therapy with an initially good response. Current exam was remarkable only for a left homonymous hemianopia (Figure 11.22).

**LOCALIZATION AND DIFFERENTIAL DIAGNOSIS**

On the basis of the symptoms and signs shown in bold above, where is the lesion? What is the most likely diagnosis, and what are some other possibilities?
Discussion
The key symptoms and signs in this case are:

- **Left homonymous hemianopia**

  A left homonymous hemianopia can be caused by a lesion anywhere in the right retrolenticular visual pathways, including the optic tract, lateral geniculate nucleus, optic radiations, or primary visual cortex (see KCC 11.2, Figure 11.13E, G, H). Given the previous history of a tumor, the most likely diagnosis is a recurrence of the tumor involving one or more of these structures on the right side of the brain. Note that the original tumor was in the left temporal lobe, so we would have to propose recurrence in a region somewhat removed from the original resection. Other, less likely possibilities include delayed radiation-induced necrosis, homonorphage, infarct, demyelination, or brain abscess.

Clinical Course and Neuroimaging

A brain MRI (Figure 11.23) revealed abnormal enhancement of the right optic tract, extending to the right lateral geniculate nucleus. The patient was admitted and treated with high-dose steroids with no significant improvement. His vision continued to deteriorate over the next 2 weeks, and he was readmitted for stereotactic biopsy of an enhancing area in the right temporal lobe, which showed malignant astrocytoma. Additional chemotherapy was tried, but he continued to worsen, developing progressive left hemiparesis, and he was ultimately transferred to a hospice for comfort care.

**CASE 11.3 MENSTRUAL IRREGULARITY AND BITEMPORAL HEMIANOPIA**

Figure 11.21 Brain MRI Showing a Meningioma of the Suprasellar Region Compressing the Optic Chiasm (A) Coronal T1-weighted image showing meningioma located just dorsal to the pituitary, and compressing the optic chiasm from below. (B) Sagittal T1-weighted image with intraventricular gadolinium contrast enhancement, showing characteristic features of a meningioma, including relatively uniform contrast enhancement, location adjacent to the meninges, and a tapering extension along the dural surface (*"dural tail"). As in (A), the tumor can be seen to compress the optic chiasm from below.

**CASE 11.5 VISUAL CHANGES CAUSED BY MIGRAINE HEADACHES?**

MINICASE

A 57-year-old right-handed man visited the emergency room several times because of headaches that had begun 4 months previously. He had throbbing bilateral or right occipital pain, and zigzagging lines in his field of vision. The headaches were often more severe in the afternoon, and they were relieved by nonsteroidal pain medication (naproxen). He had not previously had headaches of this kind, and he had no family history of migraines. Recently he noticed a vision problem causing him to frequently bump into objects on his left side. He was referred to a neurologist, and examination was normal except for a left inferior quadrantanopia (Figure 11.24). The examiner did not listen for a cranial bruit.

LOCALIZATION AND DIFFERENTIAL DIAGNOSIS

On the basis of the symptoms and signs shown in bold above, where is the lesion? What is the most likely diagnosis, and what are some other possibilities?
**CASE 11.4 HEMIANOPHIA AFTER TREATMENT FOR A TEMPORAL LOBE TUMOR**

**Figure 11.23** Brain MRI Showing a Tumor Involving the Right Optic Tract

(A) T1-weighted axial images with intravenous gadolinium contrast enhancement. (A) and (B) are adjacent sections progressing from inferior to superior.

- Gyrus rectus
- Optic nerve
- Optic chiasm
- Optic tract
- Prior tumor resection
- Midbrain
- Cerebellum
- Straight sinus
- Superior sagittal sinus
- Anterior choroidal artery
- Artery of lateral ventricle
- Region of LGN
- Region of optic radiation
- Primary visual cortex

**Discussion**

The key symptoms and signs in this case are:

- Left inferior homonymous hemianopia
- Right occipital headaches

A left inferior homonymous hemianopia can be caused by a lesion of the right superior optic radiation or the right superior bank of the calcarine fissure (see Figure 11.11B, I). The right occipital headache also suggests a lesion in the right occipital area. The throbbing quality of the headache and the photophobia symptoms with zigzagging lines are typical features of migraine headaches (see KCC 5.1). However, it would be unusual for a man in his late 50s, with no family history, suddenly to develop new-onset migraine. In addition, headache always occurring on the same side of the head is worrisome, and the fixed visual field defect suggests a more permanent deficit. Given his age, a brain tumor such as glioblastoma or brain metastasis should be considered first as the cause of his migraine-like headaches and visual field cut. Other possibilities include hemorrhage, infarct, or abscesses. Of note, arteriovenous malformations (AVMs) can cause migraine headaches that occur in the same location (see KCC 5.1, 5.6). They can also cause hemorrhage, ischemia, or infarcts, resulting in focal deficits.

**Clinical Course and Neuroimaging**

A brain MRI (Figure 11.25) showed multiple dark flow voids, consistent with a large AVM involving the superior portions of the right occipital lobe. Note that the AVM was located predominantly above the calcarine fissure and therefore affected the contralateral inferior quadrant of the visual field (see Figure 11.19). An angiogram was done to help guide therapy. On injection of the right carotid, the AVM was found to be fed by a large, tortuous, abnormal branch of the right MCA (Figure 11.26). Injection of the posterior circulation showed that it was also supplied by a similar abnormal branch of the right PCA (not shown). Numerous smaller branches supplied the AVM as well. It was decided that because of its large size and complicated vascular supply, the AVM was not amenable to treatment with surgery or embolization. The patient’s headaches resolved spontaneously, and he remained stable when seen in follow-up over the next 4 years. This case should be compared to the visual field defect seen with a larger cortical lesion in Case 10.3.

**Additional Cases**

Related cases in other chapters: localization of lesions in the visual pathways (Cases 5.1, 5.2, 5.8, 10.3, 10.4, 10.6, 10.8, 10.10, 10.11, 14.8, 17.2, 19.2); disorders of higher-order visual processing (Cases 19.5, 19.6, 19.8, 19.9); Other relevant cases can be found using the Case Index.

**Brief Anatomical Study Guide**

1. This chapter covers the visual pathways from retina to optic nerve, to optic tract, to lateral geniculate nucleus of the thalamus, to optic radiations, to visual cortex (see Figure 11.15).

2. Throughout these pathways there are three parallel channels for processing information related to motion/spatial analysis, form, and color (see Figure 11.11).
CASE 11.5 VISUAL CHANGES CAUSED BY MIGRAINE HEADACHES?

Figure 11.25 Brain MRI Showing an Arteriovenous Malformation (AVM) in the Superior Bank of the Right Calcarine Cortex. T1-weighted images. (A) Coronal section. (B) Sagittal section. Dark regions represent flow voids in the AVM.

CASE 11.5 (CONTINUED)

Figure 11.26 Arteriovenous Malformation (AVM) in the Right Superior Occipital Cortex. Cerebral angiogram, lateral view, following injection of the right internal carotid artery. The AVM can be seen to fill via abnormal branches of the right middle cerebral artery (MCA).

Brief Anatomical Study Guide (continued)

1. The retina (see Figure 11.4) has several different cell types, including photoreceptor rods, which are more sensitive to low levels of illumination; cones, which have higher spatial and temporal resolution and detect colors; and ganglion cells, which form the output layer of the retina.

2. Most retinal ganglion cells can be classified as M cells or P cells. M cells have large receptive fields, respond best to gross stimulus features and movement, and project to the magnocellular layers of the lateral geniculate nucleus. P cells are more numerous, have small receptive fields, are sensitive to fine visual detail and colors, and project to the parvocellular layers of the lateral geniculate nucleus.

3. The lateral geniculate nucleus (LGN) has six layers (see Figure 11.7), with inputs from each eye segregated in different layers. These segregated inputs are preserved in projections to layer 4 of the primary visual cortex (area 17), forming ocular dominance columns (see Figure 11.12A).
References

General References


Retinal Artery Occlusion


Optic Neuritis


Optic Nerve Injury Due to Orbital Trauma


Suprassellar Meningioma


Optic Tract Lesions


Lateral Geniculate Nucleus Lesions


Optic Radiation and Visual Cortex Lesions

Brainstem I: Surface Anatomy and Cranial Nerves

A 41-year-old woman noticed that she could not hear anything when the phone receiver was on her left ear. Also, over the previous year, she sometimes felt as though the room was spinning slightly when she moved her head. She developed some pain on the left side of her face and decreased taste on the left side of her tongue, as well as a decreased corneal reflex on the left side. This patient illustrates the complex variety of abnormalities that patients with cranial nerve disorders may experience. In this chapter, we will learn about the origins of cranial nerves in the brainstem, their courses to the periphery, and their various functions.
ANATOMICAL AND CLINICAL REVIEW

Located at the base of the cerebral hemispheres, the brainstem is a compact, stalk-like structure that carries nearly all information between the brain and the remainder of the body (Figure 12.1). This tight space is the corridor to all major sensory, motor, cerebellar, and cranial nerve pathways. However, the brainstem is not simply a conduit for information. It also contains numerous important nuclei of its own, which control the cranial nerves, level of consciousness, cerebellar circuits, muscle tone, posture, and cardiac, respiratory, and numerous other essential functions. If the brain were a city, then the brainstem would be both the Grand Central Station and Central Power Supply packed into one location. Thus, small lesions in the brainstem can result in substantial deficits, often involving multiple motor, sensory, and neuromuscular modalities.

An intimate knowledge of brainstem anatomy is a powerful clinical tool. Armed with an understanding of brainstem nuclei and pathways, the clinician can intelligently decide on appropriate diagnostic and therapeutic measures for patients with brainstem disorders. Brainstem anatomy is so complex yet so clinically relevant that we have devoted three full chapters (Chapters 12 through 14) to understanding it in detail. Thus, in this chapter, we will first review the surface features of the brainstem and then discuss the course and functions of each cranial nerve. Next, in Chapter 13 we will focus in greater detail on the cranial nerves and central pathways mediating eye movements and pupillary control. Finally, in Chapter 14 we will study the vascular supply and internal structures of the brainstem, including the major ascending and descending tracts, reticular formation, and other important brainstem nuclei.

Learning the cranial nerves initially requires some memorization. Over time, however, they become very familiar because of their important clinical relevance. The numbers, names, and main functions of the cranial nerves are listed in Table 12.1. Note that the cranial nerves have both sensory and motor functions. To learn the cranial nerves and their functions, two different review strategies are useful. In one, the cranial nerves are listed in numerical order and the sensory and motor functions of each nerve are discussed (see Table 12.4). In the second, the sensory and motor cranial nerve nuclei are listed, and the functions and cranial nerves served by each nucleus are discussed (see Table 12.3). Both approaches are clinically relevant, and we will use both strategies at various points in these brainstem chapters to integrate knowledge of the peripheral and central course of the cranial nerves.

Surface Features of the Brainstem

The brainstem consists of the midbrain,pons, and medulla (see Figure 12.1). It lies within the posterior fossa of the cranial cavity. The rostral limit of the brainstem is the midbrain-diencephalic junction (see Figure 12.1). Here the brainstem meets thalamus and hypothalamus at the level of the turrinum cerebelli. Midbrain joins pons at the pontomesencephalic junction, and pons meets medulla at the pontomedullary junction. The caudal limit of the brainstem is the cervicomedullary junction, at the level of the foramen magnum and pyramidal decussation (see Figures 12.1, 12.2A; see also Figure 6.8). The cerebellum is attached to the dorsal surface of the pons and upper medulla (see Figure 12.1). Although some authors have included the cerebellum or thalamus in the term “brainstem,” we adopt common clinical usage here and take brainstem to imply only midbrain, pons, and medulla. We discuss the thalamus and cerebellum at greater length elsewhere (see Chapters 7, 15).
On the dorsal surface of the midbrain are two pairs of bumps called the superior colliculi and inferior colliculi (see Figure 12.2B); together, these form the tectum (meaning "roof") of the midbrain. The ventral surface of the midbrain is formed by the cerebral peduncles, between which the interpeduncular fossa lies (see Figure 12.2A; see also Figure 5.6). The pons is limited dorsally by the fourth ventricle (see Figure 12.1). More dorsolaterally, the pons is attached to the cerebellum by large white matter tracts called the superior, middle, and inferior cerebellar peduncles (see Figure 12.2B). On the ventral surface of the medulla, the pyramids can be seen descending from the pontomedullary junction to the pyramidal decussation (see Figure 12.2A). It is often useful to divide the medulla into a rostral and a caudal portion. In the rostral medulla, the prominent bulges of the inferior olivary nuclei can be seen just lateral to the pyramids (see Figure 12.2A). In the caudal medulla, the inferior olivary nuclei are no longer seen, but the posterior columns and posterior column nuclei are visible on the dorsal surface (see Figure 12.2B).

The floor of the fourth ventricle extends from the pons to the rostral half of the medulla. Along the floor of the fourth ventricle, several bumps are visible. These include the facial colliculi, formed by the abducens nuclei and fibers of the facial nerve (see Figure 12.2B; see also Figure 14.1E). The hypoglossal trigone and vagal trigone (see Figure 12.2B) are formed by the hypoglossal nucleus (CN XII) and the dorsal motor nucleus of CN X, respectively. Recall that rostrally the fourth ventricle joins the cerebral aqueduct, which runs through the midbrain (see Figure 12.1). Caudally the fourth ventricle drains into the subarachnoid space via the foramina of Luschka (located laterally) and foramen of Magendie (located in the midline). The fourth ventricle ends caudally at the obex (see Figure 12.2B), marking the entry to the spinal cord central canal, which in adults is normally closed.
For those who are verbally inclined, several mnemonics exist for the cranial nerve names and numbers (see Table 12.1). However, the best visual mnemonic for the cranial nerves is the brainstem itself, since the cranial nerves emerge roughly in numerical sequence from rostral to caudal (see Figure 12.2). The first two cranial nerves do not emerge from the brainstem, but rather connect directly to the forebrain. The **olfactory bulbs** and **olfactory tracts (CN I)** run along the ventral surface of the frontal lobes in the **olfactory sulci** (see Figure 18.6). The **optic nerves** (CN II) meet at the optic chiasm, forming the optic tracts, which wrap laterally around the midbrain to enter the lateral geniculate nuclei of the thalamus (see Figures 11.6, 11.15).

Cranial nerves III through XII exit the brainstem either ventrally or ventrolaterally (see Figure 12.2A-C). The one exception is CN IV, which exits from the dorsal midbrain (see Figure 12.2B). We will see shortly that CN III, VI, and XII, which exit ventrally near the midline, together with CN IV, which exits dorsally, form a distinct functional group innervating somatic motor structures.

The **oculomotor nerves** (CN III) emerge ventrally from the interpeduncular fossa of the midbrain (see Figure 12.2A). Note that the oculomotor nerve usually passes between the posterior cerebral artery and the superior cerebellar artery (see Figure 14.17A). As we have just mentioned, the **trochlear nerve** (CN IV) is exceptional in exiting dorsally from the midbrain (see Figure 12.2B). The fibers of CN IV cross over as they emerge, an arrangement that is also unique to this cranial nerve. The **trigeminal nerve** (CN V) exits from the ventrolateral pars (see Figure 12.2A,C). The **abducens nerve** (CN VI) exits ventrally, at the pontomesencephalic junction (see Figure 12.2A,C). Then, proceeding in sequence, the **facial nerve** (CN VII), **vestibulocochlear nerve** (CN VIII), **glossopharyngeal nerve** (CN IX), and **vagus nerve** (CN X) exit ventrally to the midbrain and cerebellum laterally from the pontomesencephalic junction and medulla. The region where CN VII, VIII, and IX exit the brainstem is called the **cerebellopontine angle**. The **spinal accessory nerve** (also known as the **accessory spinal nerve**), CN XI, arises laterally from multiple roots along the innermost spinal cord. The **hypoglossal nerve** (CN XII) exits the medulla ventrally, between the pyramids and inferior olivary nuclei (see Figure 12.2A).

### Skull Foramina and Cranial Nerve Exit Points

**Skull Foramina and Cranial Nerve Exit Points**

When we discuss each cranial nerve in the sections that follow, we will describe its course in detail. For now, we will simply introduce the foramina through which the cranial nerves exit the skull (Figure 12.3, Table 12.2).

The oculomotor nerves exit via the **cribriform plate**, and the optic nerve via the **optic canal** (see Figure 12.3, Table 12.2). The **superior orbital fissure** transmits several nerves (CN III, IV, VI, and V2) into the orbit (see Figure 12.3A). O, CN III, IV, and VI mediate eye movements. The ophthalmic division of CN V (CN V1) conveys sensation for the eye and upper face. The **maxillary** (CN V2) and mandibular (CN V3) divisions of the trigeminal nerve exit via the **foramen rotundum** and **foramen ovale**, respectively, providing sensation to the remainder of the face (see Figure 12.7). CN VII and VIII both exit the cranial cavity via the **internal auditory meatus** to enter the auditory canal. CN VIII innervates the inner ear deep within the temporal bone. CN VII exits the skull to reach the muscles of facial expression via the **stylo mastoid foramen** (see Figure 12.3B). Finally, the **jugular foramen** transmits CN IX, X, and XI (see Figure 12.3A-B). Finally, the **hypoglossal nerve** (CN XII) controlling tongue movements, exits the skull via its own foramen, the **hypoglossal canal**, which lies just in front of the foramen magnum.
Figure 12.4 Development of Cranial Nerve Nuclei Sensory and Motor Longitudinal Columns


Sensory and Motor Organization of the Cranial Nerves

The cranial nerves are analogous in some ways to the spinal nerves, having both sensory and motor functions. Also like the spinal cord, motor cranial nerve nuclei are located more ventrally, while sensory cranial nerve nuclei are located more dorsally (Figure 12.4). However, cranial nerve sensory and motor functions are more specialized because of the unique anatomy of the head and neck. During embryological development, the cranial nerve nuclei are adjacent to the ventricular system (see Figure 12.4A). As the nervous system matures, three motor columns and three sensory columns of cranial nerve nuclei develop that run in an interrupted fashion through the length of the brainstem (see Figures 12.4, 12.5). Each column subserves a different motor or sensory cranial nerve function, which can be classified as shown in Table 12.2. The color codes for each column used in Figures 12.4 and 12.5 are in Table 12.3. Each column will be reviewed more in detail, moving from medial to lateral.

---

**Table 12.2 Cranial Nerve Exit Foramina**

<table>
<thead>
<tr>
<th>CN</th>
<th>Name</th>
<th>Exit Foramen</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Olfactory nerve</td>
<td>Cribriform plate</td>
</tr>
<tr>
<td>II</td>
<td>Optic nerve</td>
<td>Optic canal</td>
</tr>
<tr>
<td>III</td>
<td>Oculomotor nerve</td>
<td>Superior orbital fissure</td>
</tr>
<tr>
<td>IV</td>
<td>Trochlear nerve</td>
<td>Superior orbital fissure</td>
</tr>
<tr>
<td>V</td>
<td>Trigeminal nerve</td>
<td>V1: Superior orbital fissure</td>
</tr>
<tr>
<td>V1</td>
<td>Abducens nerve</td>
<td>Superior orbital fissure</td>
</tr>
<tr>
<td>V2</td>
<td>Facial nerve</td>
<td>Auditory canal (stylomastoid foramen)</td>
</tr>
<tr>
<td>V3</td>
<td>Vestibulocochlear nerve</td>
<td>Auditory canal</td>
</tr>
<tr>
<td>VI</td>
<td>Glossopharyngeal nerve</td>
<td>Jugular foramen</td>
</tr>
<tr>
<td>IX</td>
<td>Vagus nerve</td>
<td>Jugular foramen</td>
</tr>
<tr>
<td>X</td>
<td>Spinocervical nerve</td>
<td>Jugular foramen (jugular foramen)</td>
</tr>
<tr>
<td>XI</td>
<td>Hypoglossal nerve</td>
<td>Hypoglossal foramen (jugular foramen)</td>
</tr>
</tbody>
</table>

*The abducens nerve exits the dura through Talmus's canal (see Figure 12.2) and travels a long distance before exiting the skull at the superior orbital fissure.*

---

**Figure 12.5 Functional Columns of Brainstem Sensory and Motor Cranial Nerve Nuclei**

<table>
<thead>
<tr>
<th>Sensory nuclei</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trigeminal nuclei (SA: CN I)</td>
</tr>
<tr>
<td>Acoustic nuclei (GSE: CN III)</td>
</tr>
<tr>
<td>Facial nuclei (GSE: CN VII)</td>
</tr>
<tr>
<td>Abducens nuclei (SA: CN VI)</td>
</tr>
<tr>
<td>Hypoglossal nuclei (SA: CN XII)</td>
</tr>
<tr>
<td>Vocal nuclei (SA: CN IX)</td>
</tr>
<tr>
<td>Dorsal motor nucleus of CN X (GVE: CN X)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Motor nuclei</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visceral motor nuclei (SA: CN IX)</td>
</tr>
<tr>
<td>General somatic sensory nucleus (SA: CN X)</td>
</tr>
<tr>
<td>Special visceral sensory nucleus (SA: CN IX)</td>
</tr>
<tr>
<td>Special visceral autonomic nucleus (SA: CN IX)</td>
</tr>
<tr>
<td>Somatomotor nucleus (GVE: CN X)</td>
</tr>
<tr>
<td>Visceral sensory nucleus (SA: CN IX)</td>
</tr>
<tr>
<td>Motor cortex (SA: CN I)</td>
</tr>
<tr>
<td>Occipital cortex (SA: CN II)</td>
</tr>
<tr>
<td>Temporal cortex (SA: CN III)</td>
</tr>
<tr>
<td>Precentral gyrus (SA: CN IV)</td>
</tr>
<tr>
<td>Postcentral gyrus (SA: CN V)</td>
</tr>
</tbody>
</table>

---

**Key**

- **Motor nuclei**
- **Sensory nuclei**
The somatic motor nuclei are the oculomotor (CN III), trochlear (CN IV), abducens (CN VI), and hypoglossal (CN XII) nuclei, all of which remain adjacent to the midline (see Figures 12.4, 12.5, and Table 12.3). These nuclei send their efferent fibers to exit the brainstem close to the midline as well (see Figure 12.2). The somatic motor nuclei innervate the extraocular and intrinsic tongue muscles, which are derived embryologically from the occipital somites.

The visceral motor nuclei (see Figure 12.6A) are divided into two different columns of nuclei: branchial motor nuclei and parasympathetic nuclei (see Table 12.3). The branchial motor nuclei are the trigeminal motor nucleus (CN V), facial motor nucleus (CN VII), facial accessory nucleus (CN X), and the spinal accessory nucleus (CN XI). The branchial nuclei are located in the tegmentum (see Figures 12.4A, 12.5B). Both the somatic and branchial motor nuclei innervate striated muscles. However, unlike the somatic motor nuclei, the branchial motor nuclei innervate muscles derived from the branchial arches, including the muscles of mastication, facial expression, middle ear, pharynx, larynx, sternomastoid, and upper portion of the spinalis muscle.

The next column comprises the parasympathetic nuclei (see Figure 12.5). These are the Edinger-Westphal nucleus (CN III), superior (CN VII), and inferior (CN IX) salivatory nuclei, and the dorsal motor nucleus of the vagus (CN X). The parasympathetic nuclei supply innervation to all somatic and visceral muscles. The cranial autonomic nuclei innervate the cardiac, smooth muscle, and cardiac muscle of the heart, lungs, and digestive tract above the splenic flexure (see also Figure 6.13).


### Table 12.3

<table>
<thead>
<tr>
<th>Classification</th>
<th>Function(s)</th>
<th>Cranial Nerve(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Motor</strong></td>
<td>Extracranial muscles, extraocular muscles, and tongue muscles</td>
<td>CN III, IV, VI, XII</td>
</tr>
<tr>
<td>Somatic motor nuclei</td>
<td>Motor nuclei of CN V, CN VII, CN IX, CN X</td>
<td></td>
</tr>
<tr>
<td>Special visceral efferent</td>
<td>Edinger-Westphal nucleus, superior salivatory nucleus, and inferior salivatory nucleus</td>
<td>CN III, CN IX, CN X</td>
</tr>
</tbody>
</table>

### SENSORY

- **Vestibular sensory (special visceral efferent)**: Taste, CN IX, X
- **General visceral sensory (general visceral afferent)**: CN IX, X
- **General somatic sensory (special visceral afferent)**: CN VII, IX, X
- **Special visceral sensory (special somatic afferent)**: CN VIII

The visceral sensory nuclei are responsible for conveying information from the sense organs to the brainstem, allowing for integration of this information for further processing.

#### Functions and Course of the Cranial Nerves

In the sections that follow, we will review each of the cranial nerves and their functions in detail. Table 12.4 lists the motor and sensory functions of each cranial nerve. Note that some cranial nerves are purely motor (CN III, IV, VI, IX, XI, XII), some are purely sensory (CN I, II, VIII), and some have both motor and sensory functions (CN V, VII, IX, X). The information contained in Table 12.4 is of central importance to understanding the cranial nerves and should be very familiar to you by the time you complete this chapter. The relevant portions of Table 12.4 will be repeated as we introduce each cranial nerve in the sections that follow.

In addition to describing motor and sensory functions, we will review the course of each cranial nerve from brainstem nuclei to peripheral terminations, including the intracranial course of each cranial nerve, skull exit points (see Table 12.2), cranial nerve branches, and peripheral sensory or parasympathetic ganglia (Table 12.5). As we discuss each cranial nerve, we will also review common clinical disorders associated with it.

#### Review Exercise

Draw a sketch of the brainstem as in Figure 12.5. Fill in the three columns of motor nuclei and three columns of sensory nuclei. Draw each nerve as it supplies (see Figure 12.3, Table 12.3). You should be able to draw this sketch from memory.
### TABLE 12.4 Cranial Nerves: Sensory and Motor Functions

<table>
<thead>
<tr>
<th>NERVE</th>
<th>NAME</th>
<th>FUNCTIONAL CATEGORIES</th>
<th>FUNCTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>CN I</td>
<td>Olfactory nerve</td>
<td>Special somatic sensory</td>
<td>Olfaction</td>
</tr>
<tr>
<td>CN II</td>
<td>Optic nerve</td>
<td>Special somatic sensory</td>
<td>Vision</td>
</tr>
<tr>
<td>CN III</td>
<td>Oculomotor nerve</td>
<td>Special somatic sensory</td>
<td>Functions for eye movements</td>
</tr>
<tr>
<td>CN IV</td>
<td>Trochlear nerve</td>
<td>Parasympathetic</td>
<td>Functions for eye movements</td>
</tr>
<tr>
<td>CN V</td>
<td>Trigeminal nerve</td>
<td>Sensory input from skin</td>
<td>Sensations in skin and sensory input</td>
</tr>
<tr>
<td>CN VI</td>
<td>Abduces nerve</td>
<td>Special motor</td>
<td>Functions for eye movements</td>
</tr>
<tr>
<td>CN VII</td>
<td>Facial nerve</td>
<td>Special motor</td>
<td>Functions for eye movements</td>
</tr>
<tr>
<td>CN VIII</td>
<td>Vestibulocochlear nerve</td>
<td>Special sense of balance</td>
<td>Functions for balance of body</td>
</tr>
<tr>
<td>CN IX</td>
<td>Glossopharyngeal nerve</td>
<td>Special sense of taste</td>
<td>Functions for taste of food</td>
</tr>
<tr>
<td>CN X</td>
<td>Vagus nerve</td>
<td>Special sense of taste</td>
<td>Functions for taste of food</td>
</tr>
<tr>
<td>CN XI</td>
<td>Spinal accessory nerve</td>
<td>Special sense of balance</td>
<td>Functions for balance of body</td>
</tr>
<tr>
<td>CN XII</td>
<td>Hypoglossal nerve</td>
<td>Special sense of balance</td>
<td>Functions for balance of body</td>
</tr>
</tbody>
</table>

### TABLE 12.5 Cranial Nerves: Peripheral Sensory and Parasympathetic Ganglia

<table>
<thead>
<tr>
<th>NERVE</th>
<th>NAME</th>
<th>PERIPHERAL GANGLIA</th>
<th>FUNCTION(S) OF GANGLIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>CN I</td>
<td>Olfactory nerve</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>CN II</td>
<td>Optic nerve</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>CN III</td>
<td>Oculomotor nerve</td>
<td>Ciliary ganglion</td>
<td>Parasympathetic to iris and ciliary muscle</td>
</tr>
<tr>
<td>CN IV</td>
<td>Trochlear nerve</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>CN V</td>
<td>Trigeminal nerve</td>
<td>Trigeminal ganglion (semilunar or gasserian ganglion)</td>
<td>Primary sensory neuron cell bodies for sensation in facial, mouth, and visceral territories</td>
</tr>
<tr>
<td>CN VI</td>
<td>Abduces nerve</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>CN VII</td>
<td>Facial nerve</td>
<td>Sphenopalatine ganglion (petrosal part of pterygoid ganglion)</td>
<td>Parasympathetic to submandibular and sublingual salivary glands</td>
</tr>
<tr>
<td>CN VIII</td>
<td>Vestibulocochlear nerve</td>
<td>Spinal ganglion</td>
<td>Primary sensory neuron cell bodies for hearing of spinal cord</td>
</tr>
<tr>
<td>CN IX</td>
<td>Glossopharyngeal nerve</td>
<td>Otic ganglion</td>
<td>Primary sensory neuron cell bodies for sensation from middle ear, external auditory meatus, pharynx, and posterior one-third of tongue</td>
</tr>
<tr>
<td>CN X</td>
<td>Vagus nerve</td>
<td>Parasympathetic ganglia in 2nd and 3rd parts</td>
<td>Parasympathetic to heart, lungs, and digestive tract to level of splenic flexure</td>
</tr>
<tr>
<td>CN XI</td>
<td>Spinal accessory nerve</td>
<td>Inferior (nodose) vagal ganglion</td>
<td>Primary sensory neuron cell bodies for sensation from pharynx, external ear, and infratemporal nerves</td>
</tr>
<tr>
<td>CN XII</td>
<td>Hypoglossal nerve</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

**CN I: Olfactory Nerve**

**Functional category:** Special somatic sensory  
**Function:** Olfaction

Olfactory stimuli are detected by specialized chemosensory cells on bipolar primary sensory neurons in the olfactory neuroepithelium of the upper nasal cavities. Axons of these neurons travel via short olfactory nerves that traverse the cribriform plate of the ethmoid bone (see Figure 12.3A; Table 12.2) to synapse in the olfactory bulbs (see Figure 18.5; 18.6). From the olfactory bulbs, information travels via the olfactory tracts, which run in the olfactory sulcus between the gyrus rectus and orbital frontal gyri to reach olfactory processing areas, as discussed in Chapter 18. Note that although the ol-
factory bulbs and tracts are sometimes called CN I, these structures are actually not nerves, but are part of the central nervous system.

**KEY CLINICAL CONCEPT**

**ANOSMIA (CN I)**

Patients with unilateral anosmia, or olfactory loss, are rarely aware of the deficit because olfaction in the contralateral nostril can compensate. Therefore, when testing olfaction, the examiner must test each nostril separately (neurologists.com Video 24). Patients are often aware of bilateral anosmia and may complain of decreased taste because of the important contribution of olfaction to the perception of flavor.

Loss of the sense of smell can be caused by head trauma, which damages the olfactory nerves as they penetrate the cribriform plate of the ethmoid. In addition, viral infections can damage the olfactory neuroepithelium. Obstruction of the nasal passages can impair olfaction. Intracranial lesions that obstruct the base of the frontal lobes near the olfactory sulci can interfere with olfaction. Possible lesions in this location include meningiomas, metastatic breast tumors, vascular malformations, or sarcoidosis (a granulomatous inflammatory disorder that occasionally involves the nervous system, often causing cranial neuropathies). As we will discuss in RCC 19.11, frontal lobe deficits are often difficult to detect clinically, especially with small lesions. Therefore, lesions at the base of the frontal lobes can sometimes grow to a very large size, causing little obvious dysfunction other than anosmia. Large lesions of the olfactory sulcus region (typically meningiomas) can also sometimes produce a condition called Foster-Kennedy syndrome, in which there is anosmia together with optic atrophy in one eye (caused by ipsilateral tumor compression) and papillodema in the other eye (caused by elevated intracranial pressure).

**CN II: Optic Nerve**

**Functional category:** Special somatic sensory

**Function:** Vision

As we discussed in Chapter 11, the optic nerve carries visual information from the retina to the lateral geniculate nucleus of the thalamus and to the extrageniculocortical pathways (see Figures 11.6, 11.15; Figure 12.2A). The retinal ganglion cells are actually part of the central nervous system, so the optic nerves are, strictly speaking, tracts and not nerves. Nevertheless, with this accepted convention the portion of the visual pathway in front of the optic chiasm is called the optic nerve, and beyond this point it is referred to as the optic tract. The optic nerves travel from the orbit to the intracranial cavity via the optic canal (see Figure 12.3A, C; Table 12.2). The anatomy and disorders of visual pathways are discussed in greater detail in Chapter 11.

**CN III, IV, and VI: Oculomotor, Trochlear, and Abducens Nerves**

The cranial nerves that are responsible for controlling the extracranial muscles, are discussed in detail in Chapter 13. Briefly, CN VI abducteds the eye laterally in the horizontal direction; CN IV acts through a trochlea, or pulley-like structure in the orbit, to rotate the top of the eye medially and move it downward; and CN III achieves all other eye movements. The oculomotor (CN III) and trochlear (CN IV) nuclei are located in the midbrain, and the abducens (CN VI) nucleus is in the pons (Figures 12.5, 14.5, 14.4C). Recall that CN III exits the brainstem centrally in the interpeduncular fossa, CN IV exits dorsally from the inferior oblong, and CN VI exits ventrally at the pontomedullary junction (see Figure 12.2). CN III, IV, and VI then traverse the cavernous sinus (see Figure 13.11), and exit the skull via the superior orbital fissure (see Figure 12.3A,C, Table 12.2) to reach the muscles of the orbit. CN III also carries parasympathetics to the parasympathetic nucleus and to the ciliary muscle of the lens. The preganglionic parasympathetic neurones are located in the Edinger-Westphal nucleus in the midbrain (see Figure 12.3). They synapse in the ciliary ganglion located in the orbit (Figure 12.6). Postganglionic parasympathetic fibres then continue to the pupillary constrictor and ciliary muscles.
CN V: Trigeminal Nerve

The name "trigeminal" was given to this nerve because it has three major branches: the ophthalmic division (V1), maxillary division (V2), and mandibular division (V3) (Figure 12.7). The trigeminal nerve provides sensory innervation to the face and should be distinguished from the facial nerve, which controls the muscles of facial expression. The trigeminal nerve also has a small branchial motor root (see Figure 12.7), which travels with the mandibular division and is responsible for controlling the muscles of mastication and some other smaller muscles.

The trigeminal nerve exits the brainstem from the ventrolateral ports (see Figure 12.2A, C). It then enters a small fossa just posterior and inferoternal to the cavernous sinus called Meckel's cave. The trigeminal ganglion, also known as the semilunar or gasserian ganglion, lies in Meckel's cave and is the sensory ganglion of the trigeminal nerve (Figure 12.7; Table 12.5). The ophthalmic division (V1) travels through the inferior part of the cavernous sinus to exit the skull via the superior orbital fissure (Figures 12.3A, 12.7A; Table 12.5, see also Figure 13.11). The maxillary division (V2) exits via the foramen rotundum, and the mandibular division (V3) via the foramen ovale. A mnemonic for the exit points of these three branches is Single Room Occupancy, or SRO (for Superior, Rotundum, Oval). The sensory territories of V1, V2, and V3 are shown in Figure 12.7B. Recall that sensation to the occiput is conveyed by C2 (see Case 8.2). The trigeminal nerve also provides touch and pain sensation for the nasal sinuses, inside of the nose, mouth, and anterior two-thirds of the tongue. In addition, pain sensation for the supratentorial dura mater is supplied by the trigeminal nerve, while the dura of the posterior fossa is innervated by CN V and upper cervical nerve roots.

The trigeminal nuclei (Figures 12.8, 12.9) receive general somatic sensory inputs from CN V and other cranial nerves (see Table 12.5). The main inputs are carried by CN V and provide sensation for the face, mouth, ante- rior two-thirds of the tongue, nasal sinuses, and supratentorial dura. Smaller inputs from CN VII, IX, and X provide sensation for part of the external ear (Figure 12.7B; Table 12.4). In addition, CN IX provides sensation to the middle ear, posterior one-third of the tongue, and pharynx. CN X probably also contributes to pharyngeal sensation, and provides sensation for the infratentorial dura (see Table 12.4). As we will now see, the trigeminal sensory systems are analogous to the posterior column-medial lemniscal system and anteriorolateral systems of the spinal cord (Table 12.6).

The trigeminal nuclear complex runs from the midbrain to the upper cervical spinal cord (see Figure 12.8) and consists of three nuclei: the mesencephalic, chief sensory, and spinal trigeminal nuclei (see Table 12.6). The mesencephalic or principal trigeminal sensory nucleus and the spinal trigeminal nucleus provide sensory systems for the face and head that are analogous to the posterior columns and anteriorolateral systems, respectively (compare Figures 7.7, 7.2, and 12.8; see Table 12.6). The primary sensory neurons for these sensory systems are analogous to the neurons of the posterior columns and anteriorolateral systems.

### Table 12.6 Analogous Trigeminal and Spinal Somatosensory Systems

<table>
<thead>
<tr>
<th>NUCLEUS</th>
<th>SENSORY MODALITIES</th>
<th>MAIN PATHWAY TO THALAMUS</th>
<th>MAIN THALAMIC NUCLEUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trigeminal Sensory Systems</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mesencephalic trigeminal nucleus</td>
<td>Proprioception</td>
<td>Trigeminal thalamic</td>
<td>VPM</td>
</tr>
<tr>
<td>Chief trigeminal sensory nucleus</td>
<td>Fine touch, dental pressure</td>
<td>Trigeminal thalamic</td>
<td>VPM</td>
</tr>
<tr>
<td>Spinal trigeminal nucleus</td>
<td>Crude touch, pain, temperature</td>
<td>Trigeminal thalamic</td>
<td>VPM</td>
</tr>
<tr>
<td>Spinal Sensory Systems</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Posterior column nucleus</td>
<td>Fine touch, proprioception</td>
<td>Medial lemniscal</td>
<td>VPL</td>
</tr>
<tr>
<td>Dorsal horn</td>
<td>Crude touch, pain, temperature</td>
<td>Spinothalamic tract</td>
<td>VPL</td>
</tr>
</tbody>
</table>

VPL, ventral posterior lateral nucleus; VPM, ventral posterior medial nucleus.
Medium- and small-diameter primary sensory fibers conveying crude touch, pain, and temperature sensation enter the lateral pons with the trigeminal nerve and descend in the spinal trigeminal tract to synapse in the spinal trigeminal nucleus. Examine the spinal trigeminal nucleus and tract in the serial sections shown in Figures 14.4C and 14.5A-C. It should be clear from these sections that the spinal trigeminal nucleus is in the rostral extension of the dorsal horn. Similarly, the spinal trigeminal tract is analogous to the spinal tract (see Figures 6.4, 7.2). Secondary sensory neurons from the spinal trigeminal nucleus cross the brainstem to ascend as the trigeminothalamic tract (or ventral trigeminothalamic tract). The trigeminothalamic tract is analogous to the spinothalamic tract (see Figure 12.6) and the pathways travel together to the thalamus (see Figures 12.8, 14.3). Trigeminothalamic tract fibers synapse in the thalamic ventral posterior medial nucleus (VPM), and tertiary sensory neurons then travel in the internal capsule to the primary somatosensory cortex. Like the corticospinal pathways in the spinal cord, there are also pathways from the spinal trigeminal nucleus to intralaminar thalamic nuclei, the reticular formation, and other areas, to mediate the affective and arousal aspects of facial pain.

The spinal trigeminal tract and nucleus are somatotopically organized, with the mandibular division represented dorsally, the ophthalmic division ventrally, and the maxillary division in between (see Figure 12.9). In addition, concentric rings form an "onion skin"--like representation, with perioral areas represented more rostrally in the nucleus, and areas more removed from the mouth represented more caudally.

The mesencephalic trigeminal nucleus and tract run along the lateral edge of the periaqueductal gray matter of the midbrain (see Figure 14.3A,B) and mediate proprioception (see Table 12.6). The neurons of the mesencephalic trigeminal nucleus are the only case in which primary sensory neurons lie within the central nervous system instead of in peripheral ganglia (see Figure 12.8). The peripheral processes of these bipolar neurons convey proprioceptive input from the muscles of mastication and probably also from the tongue, and from the extrinsic muscles. In the monosynaptic jaw jerk reflex (see KCC 12.4; neuroexams.com Video 39), processes of mesencephalic trigeminal neurons descend to the pons and synapse in the motor trigeminal nucleus (see Figure 12.7A). Ascending and descending fibers form the mesencephalic trigeminal tract (see Figure 12.8; see also Figure 14.3A,B). Other central pathways of the mesencephalic trigeminal nucleus are still under investigation.

**REVIEW EXERCISE**

1. Cover the second column from the left in Table 12.6. For each nucleus in the left column, provide the sensory modalities served and the location of the nucleus (see Figure 12.8).

2. Which thalamic nucleus is most important for relaying somatosensory information from the face, and which is most important for relaying somatosensory information from the rest of the body to the cortex?
The branchial motor functions of the trigeminal nerve are mediated by the trigeminal motor nucleus (see Figure 12.7). This nucleus is located in the upper-pons region (see Figures 12.5 and 14.4b), near the level where the trigeminal nerve exits the brainstem. The branchial motor root of the trigeminal nerve runs inferomedial to the trigeminal ganglion along the floor of Meckel’s cave and then joins V2, to exit via the foramen ovale (see Figure 12.5A). It then supplies the muscles of mastication (see neuroexams.com Video 58), including the masseter, temporalis, and medial and lateral pterygoid muscles, as well as several smaller muscles, such as the tensor tympani, tensor veli palatini, mylohyoid, and anterior belly of the digastric. The upper motor neuron control reaching the trigeminal motor nucleus is predominantly bilateral, but unilateral lesions in the motor cortex or corticobulbar tract usually cause no deficit in jaw movement. Bilateral upper motor neuron lesions, however, can cause hyperreflexia manifested in a brisk jaw jerk reflex (see KCC 12.4).

Disorders of the trigeminal nerve are relatively uncommon, except for trigeminal neuralgia (tic douloureux). In this condition, patients experience severe paroxysmal pain lasting seconds to a few minutes, most often in the distribution of V1 or V2. Attacks usually begin after age 35. Painful episodes are often provoked by chewing, shaving, or touching a specific trigger point on the face. Neurologic exams, including facial sensation, is normal. The cause of trigeminal neuralgia in most cases is unknown. In some cases, compression of the trigeminal nerve by an aberrant vessel has been demonstrated, but the significance of this finding is uncertain. It is important to perform an MRI scan to exclude tumor or other lesions in the region of the trigeminal nerve as the cause. Trigeminal neuralgia can also occur in multiple sclerosis (see KCC 6.6), possibly caused by demyelination in the trigeminal nerve entry zone of the brainstem. Initial treatment of trigeminal neuralgia is with carbamazepine or baclofen. Refractory cases have been successfully treated with various procedures, including radiofrequency ablation, gamma knife (see KCC 16.4), and surgical decompression of the trigeminal nerve.

Sensory loss in the distribution of the trigeminal nerve or its branches (see neuroexams.com Video 36) can be caused by trauma, metastatic disease—especially in isolated jaw numbness, herpes zoster (see KCC 8.5), aneurysms of the petrous portion of the internal carotid artery (see Figures 4.16C, 12.3A), cavernous sinus or orbital apex disorders (see KCC 13.7), trigeminal or vestibular schwannoma (see KCC 12.5), or sphenoid wing meningioma (see KCC 5.8). Lesions of the trigeminal nucleus in the brainstem cause ipsilateral loss of facial sensation because the primary sensory fibers do not cross before entering the nucleus (see Figure 12.8). Common causes include infarcts (see Chapter 14), demyelination, or other brainstem lesions. Other lesions of the trigeminal nucleus in the pons or medulla also involve the nearby splanchnic tract (see Figures 7.2, 14.4C, 14.5A, B).

This combination of spinal trigeminal and splanchnic tract involvement in lateral brainstem lesions leads to a well-recognized pattern with sensory loss in the face ipsilateral to the lesion, but in the body contralateral to the lesion (see KCC 7.3, Figure 7.9B).

**CN VII: Facial Nerve**

<table>
<thead>
<tr>
<th>Functional category</th>
<th>Motor root</th>
<th>Function: Muscles of facial expression, stapedius muscle, and part of digastric muscle</th>
</tr>
</thead>
</table>

The main function of the facial nerve is to control the muscles of facial expression (see neuroexams.com Video 40); however, it has several other important functions as well. The main nerve trunk carries the branchial motor fibers controlling facial expression, while a smaller branch called the neurenter intermedius carries fibers for the parasympathetic (secretory) functions of the middle ear (including the eardrum and salivary glands), visceral sensory (taste), and general somatosensory functions (see Figure 12.10; see also Figure 12.6).

The facial nucleus is located in the branchial motor column, more caudally in the pons than the trigeminal motor nucleus (see Figure 12.5; see also Figure 14.4b). The fascicles of the facial nerve loop dorsally around the abducens nucleus, forming the facial colliculus on the floor of the fourth ventricle (Figures 12.28, 12.11). The nerve then exits the brainstem ventrolaterally at the pontomedullary junction (see Figure 12.2A,C). Upper motor neuron control of the facial nucleus is discussed in KCC 12.3 (see Figure 12.13). Briefly, lesions in the cortex or corticobulbar tracts cause contralateral face weakness that spares the forehead, while lesions of the facial nucleus, nerve fascicles in the brainstem, or peripheral nerve cause ipsilateral weakness of the entire face.

The facial nerve exits the brainstem ventrolaterally at the pontomedullary junction, lateral to CN VI in a region called the cerebellopontine angle (see Figure 12.2A,C). It then traverses the subarachnoid space and enters the internal auditory meatus (see Figure 12.3A; see also Figure 4.13C) to travel in the auditory canal of the petrous temporal bone together with the vestibulocochlear nerve (see Figure 12.14). At the genu of the facial nerve, the nerve takes a turn posteriorly and inferiorly in the temporal bone to run in the facial canal, just medial to the middle ear (see Figures 12.10, 12.16). The geniculate ganglion lies in the genu and contains primary sensory neurons for taste sensation in the anterior two-thirds of the tongue, and for general somatic sensation in a region near the external auditory meatus (Table 12.5; Figure 12.77). The main portion of the facial nerve runs ventrally to the skull at the stylomastoid foramen (Figures 12.3B, 12.16). It then passes through the parotid gland and divides into five major branchial motor branches to control the muscles of facial expression: the temporal, zygomatic, buccal, mandibular, and cervical branches (see Figure 12.10). Other smaller branchial motor branches innervate the stapedius (see Figures 12.10, 12.15), occipitalis, posterior belly of the digastric, and stylohyoid muscles. The cranial nerves controlling the middle ear muscles can be recalled by the mnemonic Trigeminal for Tensor Tympani and Seventh for Stapedius. Both the tensor tympani and the stapedius dampen movements of the middle ear muscles (see the section on CN VIII later in this chapter), providing feedback modulation of acoustic signal intensity.
Figure 12.10 Facial Nerve (CN VII) Summary of Facial nerve sensory and motor pathways.

The preganglionic parasympathetic fibers of the facial nerve originate in the superior salivatory nucleus (see Figure 12.10) and are carried by two small branches off the main trunk of the facial nerve. The greater petrosal nerve (CN VII) takes off at the genu of the facial nerve (see Figure 12.14) to reach the sphenopalatine (pterygopalatine) ganglion, where postganglionic parasympathetic cells project to the lacrimal glands and nasal mucosa (see Figure 12.10). The chorda tympani leaves the facial nerve just before the stylomastoid foramen and travels back upward to traverse the middle ear cavity before exiting the skull at the petrotypanic fissure (see Figures 12.38, 12.10). Just medial and posterior to the temporomandibular joint. The chorda tympani then joins the lingual nerve (a branch of CN V3) to reach the submandibular ganglion, where postganglionic parasympathetics arise to supply the submandibular and submaxillary salivary glands.

The lingual nerve and chorda tympani also carry special visceral sensory fibers mediating taste sensation (see neuroexam.com Video 41) for the an-
terior two-thirds of the tongue (see Figure 12.10). The primary sensory taste fibers have their cell bodies in the geniculate ganglion (Figure 12.12; see also Figure 12.14, Table 12.5). These cells synapse onto secondary sensory neurons in the rostral nucleus solitarius (see Figure 14.5A,B), also known as the gustatory nucleus. There are also taste inputs for the posterior tongue and pharynx that travel via CN IX and X to enter this nucleus. Ascending projections continue via the central tegmental tract (see Figure 12.12; see also Figures 14.3, 14.4) to reach tertiary sensory neurons in the ventral posterior medial nucleus (VPM) of the thalamus. Thalamic neurons from the VPM, in turn, project to the cortical taste area, which lies at the inferior margin of the postcentral gyrus adjacent to the tongue somatosensory area and extends into the parietal operculum and insula (see Figure 12.12). Taste pathways ascend mainly ipsilaterally in monkeys and cats.

Finally, a small branch of the facial nerve provides general somatic sensation for a region near the external auditory meatus that lies adjacent to similar regions supplied by CN IX and X (see Figure 12.7B). The somatosensory fibers for CN V, VII, IX, and X all synapse in the trigeminal nucleus (see Figure 12.5; Table 12.3).

12.6 As we discussed briefly in KCC 6.3, it is clinically important to distinguish between facial weakness caused by upper motor neuron lesions and facial weakness caused by lower motor neuron lesions. Upper motor neurons in the motor area of the primary motor cortex control lower motor neurons in the contralateral facial nucleus of the pons (Figure 12.13). In addition, the superior portions of the face, projections descend from the ipsilateral motor cortex as well as from the contralateral motor cortex. Thus, the lower motor neurons supplying the forehead and part of the orbicularis oculi receive upper motor neuron inputs from bilateral motor cortices. As a result, unilateral upper motor neuron lesions tend to spare the forehead and cause only mild contralateral orbicularis oculi weakness resulting in a slightly widened palpebral fissure, or inability to fully bury the eyelashes on forced eye closure. In upper motor neuron lesions the weakness affects mainly the inferior portions of the contralateral face (see Figure 12.13, lesion A). Lower motor neuron lesions, in contrast, affect the entire half of the face and do not spare the forehead (see Figure 12.13, lesion B). Additional clues that are sometimes present in upper motor neuron-type weakness include neighborhood effects such as hand or arm weakness, sensory loss, aphasia, or dysarthria, none of which are present in lower motor neuron lesions. The lesions shown in Figure 12.14 are somewhat oversimplified; in reality the upper motor neuron corticobulbar fibers controlling the facial nucleus project mainly to pontine interneurons that project, in turn, to lower motor neurons in the facial nucleus.

The most common facial nerve disorder by far is Bell’s palsy, in which all divisions of the facial nerve are impaired within a few hours or days and then gradually recover. The cause is unknown, although viral or inflammatory mechanisms have been suggested. The most striking feature is unilateral facial weakness of the lower motor neuron type, which can be mild but is often severe (see Figure 12.14, lesion B). Diagnosis is based on clinical history and exam (see neurolexan.com Videos 40, 41). Patients often initially complain of some retroauricular pain, likely caused by involvement of the general somatosensory component of CN VII (see Figure 12.7B). Hypoesthesia can occur because of stippling muscle weakness (see Figure 12.10). In addition, patients may suffer from "dry eye," resulting from decreased lacrimation with parasympathetic involvement (see Figure 12.10). Neurologic examination is notable for unilateral lower motor neuron-type facial weakness, sometimes associated with loss of taste on the ipsilateral tongue (last but mustard or sugar applied with a cotton swab). The remainder of the exam should be normal in Bell’s palsy. The presence of hand weakness, sensory loss, dysarthria, or aphasia suggests an upper motor neuron lesion. In clinically typical cases, imaging studies are not necessary. Treatment of Bell’s palsy is controversial, although some practitioners use steroids in certain cases. Incomplete eye closure and decreased tearing can cause corneal ulcerations. Therefore, patients should be given lubricating eye drops and instructions to tape the eye shut at night. About 80% of patients recover fully from Bell’s palsy within 3 weeks, although some are left with variable degrees of residual weakness. During recovery, regenerating facial nerve fibers sometimes reach the wrong target. For example, aberrant regeneration of parasympathetic fibers (see Figure 12.6) can result in the phenomenon of "crocodile tears," in which patients experience lacrimation instead of salivation when they see food. Aberrant regeneration of different motor branches of the facial nerve sometimes results in synkinesis, meaning abnormal move-
ment together. For example, if the patient is asked to close one eye, the ipsilateral pterygoid muscle may contract slightly, along with the orbicularis oculi.

In cases of bilateral lower motor neuron-type facial weakness, or if a patient experiences a second episode, a more thorough investigation is warranted. This should include an MRI scan with contrast looking for tumors or other infiltrative disorders, lumbar puncture (see KCC 5.10), and tests for Lyme disease, sarcoidosis, and HIV. In addition to the causes already mentioned, facial nerve injury may occur in head trauma, particularly in fractures of the petrous temporal bone. Facial weakness caused by upper motor neuron lesions is discussed in KCC 6.3. In addition, brainstem lesions can occasionally involve the facial nucleus or exiting nerve fascicles (see Figure 12.11); see also KCC 14.3.

The corneal reflex is elicited by gentle stroking of each cornea with a cotton swab; the response is eye closure (see neuroex.com Video 39). This reflex is mediated by both monosynaptic and polysynaptic pathways. The afferent limb is conveyed by the ophthalmic division of the trigeminal nerve to the chief sensory and spinal trigeminal nuclei. The efferent limb is then carried by the facial nerve to reach the orbicularis oculi muscles causing eye closure. A lesion of the trigeminal sensory pathways, the facial nerve, or their connections causes a decreased corneal reflex in the ipsilateral eye. The response of the contralateral eye in brainstem lesions is more variable. The corneal reflex is also modulated by inputs from higher centers. Therefore, lesions of sensorimotor cortex and its connections can cause a diminished corneal reflex in the eye contralateral to the lesion.

Since an eye blink response can also be elicited by an object moving toward the eye, when eliciting the corneal reflex the examiner must take care to ensure that the blink has been elicited by touch rather than a sudden movement toward the eye. In blink to threat (see neuroex.com Video 29) the afferent limb of the reflex is carried by the optic nerve (CN II), while in the corneal reflex, the afferent limb is carried by the trigeminal nerve (CN V).

The jaw jerk reflex is elicited by tapping on the chin with the mouth slightly open; the jaw jerks forward in response. The monosynaptic pathway for this reflex consists of primary sensory neurons in the mesencephalic trigeminal nucleus (see Figure 12.8), which send axons to the pontine nuclei in the motor trigeminal nucleus. In normal individuals the jaw jerk reflex is minimal or absent (see neuroex.com Video 39). In bilateral upper motor neuron lesions, such as amyotrophic lateral sclerosis (see KCC 6.7) or diffuse white matter disease, the jaw jerk reflex may be brisk.

CN VIII: Vestibulocochlear Nerve

| Functional category: | Special somatic sensory |
| Function: | Hearing and vestibular sensation |

This nerve carries the special somatic sensory functions of hearing and vestibular sense from the structures of the inner ear. The vestibulocochlear nerve exits the brainstem at the pontomedullary junction just lateral to the facial nerve, in a region called the cerebellopontine angle (see Figure 12.2A,C). It then traverses the subarachnoid space to enter the internal auditory meatus (see Figure 12.3A) together with the facial nerve and travels in the auditory canal of the petrous temporal bone to reach the cochlea and vestibular organs (Figure 12.14; see also Figure 4.13C). In the subsections that follow we will discuss the auditory and vestibular functions of CN VIII in turn.

Auditory Pathways

Sound waves are transmitted by the tympanic membrane and amplified by the middle ear ossicles—the malleus, incus, and stapes—to reach the oval window (Figure 12.15). The movements of the malleus are dampened by the tensor tympani muscle, and movements of the stapes are dampened by the stapedius in response to loud sounds. From the oval window, vibrations reach the inner ear structures. The inner ear, or labyrinth, consists of the cochlea, vestibule, and semicircular canals (see Figure 12.15). The labyrinth is composed of a bony labyrinth, which is lined with compact bone and contains the membranous labyrinth. The bony labyrinth is filled with fluid called perilymph, within which the structures of the membranous labyrinth are suspended. Interestingly, perilymph communicates with the subarachnoid space through a small perilymphatic duct (not shown). The membranous labyrinth, in turn, is filled with a fluid of slightly different ionic composition, called endolymph. The membranous labyrinth includes the cochlear duct, utricle, saccule, and semicircular canals (see Figure 12.15).

Acoustic vibrations from the oval window reach the scala vestibuli and are transmitted along the snail-shaped cochlea to the end, where it joins the scala tympani, and the pressure waves are ultimately relieved at the round window back in the wall of the middle ear. The vibrations also reach the cochlear duct (scala media) (see Figure 12.13, inset), where mechanoreceptor cilia on the hair cells are activated by movement of the basilar membrane relative to the stiffer tectorial membrane. The hair cells form excitatory synapses onto the terminals of primary sensory neurons. These bipolar sensory neurons have their cell bodies in the spiral ganglion, located along the central rim of the cochlea, and send their axons into the cochlear nerve (see Figures 12.14, 12.15). The hair cells of the cochlea, together with their supporting cells, are called the organ of Corti. There is a tonotopic representation along the length of the organ of Corti such that higher-frequency sounds activate hair cells near the oval window, while lower-frequency sounds activate hair cells near the apex of the cochlea (see Figure 12.15).
Let's follow the pathways for hearing centrally, from the cochlear nuclei to the primary auditory cortex (Figures 12.16, 12.17). Auditory information throughout these pathways is tonotopically organized. Primary sensory neurons in the spiral ganglion send their axons to the cochlear division of CN VIII to reach the dorsal and ventral cochlear nuclei, which are wrapped around the lateral aspect of the inferior cerebellar peduncle at the pontomesencephalic junction (see Figures 12.16, 12.17C). The hearing pathways then ascend through the brainstem bilaterally through a series of relays to reach the inferior colliculi, medial geniculate nuclei, and, ultimately, the auditory cortex. Because auditory information from each ear ascends bilaterally in the brainstem, with deconsecutions occurring at multiple levels, unilateral hearing loss is not seen in lesions in the central nervous system proximal to the cochlear nuclei.

Fibers from the dorsal cochlear nucleus pass dorsal to the inferior cerebellar peduncle, cross the pontine tegmentum, and ascend in the contralateral
Figure 12.17 Brainstem Sections of Auditory Pathways

Levels of sections are as indicated in Figure 12.16. (A) Mediobrain inferior colliculi. (B) Caudal nuclei at the level of the superior olivary nucleus and trapezoid body. (C) Rostral medulla showing entry of cochlear (auditory) nerve to cochlear nuclei. Myelinated cross sections of the human brainstem. (A and B models) from Martin J. H. 1996. Anatomical Text and Atlas, 2nd Ed. McGraw-Hill, New York. (C from The University of Washington Digital Anatomist Project.)

lateral lemniscus (see Figures 12.16, 12.17A,B). The lateral lemniscus is an important ascending auditory pathway in the pons and lower medulla that terminates in the inferior colliculus. Many fibers of the ventral cochlear nucleus pass ventral to the inferior cerebellar peduncle to synapse bilaterally in the superior olivary nuclear complex of the pons (see Figures 12.16, 12.17B). The superior olivary nuclei appear to function in localizing sounds horizontally in space. Crossing auditory fibers at this level form a white matter structure called the trapezoid body (see Figures 12.16, 12.17B). The trapezoid body is traversed at right angles by the medial lemniscus.

From the superior olivary nuclear complex, fibers ascend bilaterally in the lateral lemniscus to reach the inferior colliculi of the midbrain (see Figures 12.16, 12.17A). Descending fibers at the level of the inferior colliculus pass both dorsal and ventral to the cerebral aqueduct from the inferior colliculi; fibers ascend via the brachium of the inferior colliculus to the medial geniculate nuclei of the thalamus, which are located just lateral to the superior colliculi of the midbrain (see Figures 11.6, 12.16, 14.3A). From this thalamic relay, information continues in the auditory radiations to the primary auditory cortex. The primary auditory cortex (Brodmann’s area 41) lies on Heschl’s transverse gyri. We can see these straight, fingerlike gyri in brain specimens by opening the Sylvian fissure and looking at the superior surface of the temporal lobe. Just medial to the superior temporal gyrus (Figure 12.16; see also Figure 4.15D). The auditory association cortex, including Wernicke’s area, which will be discussed in Chapter 19. In addition to the nuclei already mentioned, there are several smaller nuclei in the hearing pathway, including the nuclei of the trapezoid body and the nuclei of the lateral lemniscus.

As noted already, lesions in the central nervous system proximal to the cochlear nuclei do not cause unilateral hearing loss because auditory information crosses bilaterally at multiple points in the brainstem. However, auditory information ascending through the brainstem and thalamus to the auditory cortex does contain relatively greater contribution from the contralateral ear. In auditory seizures, caused by abnormal electrical discharges in the auditory cortex, patients often perceive a tone or roaring sound like an airplane or a train coming from the side opposite the auditory cortex involved. Bilateral damage to the auditory cortex causes cortical deafness (see KCC 19.7).

Different feedback pathways from the brainstem to the cochleas in the vestibulocochlear nerve modulate the sensitivity of the hair cells to sounds of varying intensities. In addition, reflex pathways from the ventral cochlear nuclei reach the facial and trigeminal motor nuclei to contract the stapedius and tensor tympani muscles. These muscles dampen the response of the middle ear to loud sounds.

Vestibular Pathways

The vestibular nuclei are important for adjustment of posture, muscle tone, and eye position in response to movements of the head in space (Figure 12.18). Not surprisingly, therefore, the vestibular nuclei have intimate connections with the cerebellum, and with the brainstem motor and extracranial systems. In addition, an ascending pathway through the thalamus to the cortex provides awareness of head position that is integrated with visual and tactile spatial information in the parietal association cortex.

The semicircular canals (see Figures 12.14, 12.15) detect angular acceleration around three orthogonal axes by the movement of endolymph...
through the **ampullae** (see Figure 12.15, inset). This fluid movement deforms the gelatinous **cupula** within which the mechanoreceptor cilia of hair cells are embedded. The hair cells are located in a ridge within each ampulla, called the **cribra ampullaris**. The hair cells activate terminals of primary sensory neurons that have their cell bodies in the **vestibulocerebellum** of Scarpia and send axons into the vestibular nerve (see Figure 12.15). The utricle and saccule contain structures called **maculae** that resemble the crista amullaris, but rather than angular acceleration, they detect linear acceleration and head tilt (see Figure 12.15, inset). The maculae consists of calcified crystals called **otoliths** sitting on a gelatinous layer within which mechanoreceptor hair cells are embedded. Gravity or other causes of linear acceleration pull on the crystals and activate the hair cells. The **superior vestibular ganglion** receives input from the utricle, anterior saccule, and anterior and lateral semicircular canals. The **inferior vestibular ganglion** receives input from the posterior saccule and posterior semicircular canal.

Primary sensory neurons in the vestibular ganglia (see Figure 12.15) convey information about angular and linear acceleration from the semicircular canals and otolith organs, respectively, through the vestibulocerebellum of CN VIII to the vestibular nuclei. There are **four vestibular nuclei** on each side of the brainstem, lying on the lateral floor of the fourth ventricle, in the pons and medulla (see Figure 12.18). These nuclei can also be seen in the myelin sections in Figures 14.6C and 14.5A. The lateral vestibular nucleus gives rise to the lateral vestibulospinal tract, which, despite its name, is part of the medial descending motor systems (see Table 6-3). The lateral vestibulospinal tract extends throughout the length of the spinal cord, and is important in maintaining balance and posture (see Figure 6.11D). The **medial vestibulospinal tract** arises from the medial vestibular nucleus, with additional contributions primarily from the inferior vestibular nucleus. The medial vestibulospinal tract is also a medial descending motor system, but it extends only to the cervical spine and is important in controlling neck and head position. The medial vestibular nucleus is the largest of the vestibular nuclei. The inferior vestibular nucleus is responsible for identifying myelinated sections because fibers of the lateral vestibular nucleus (also called Deiters' nucleus) transverse the inferior vestibular nucleus as they descend toward the spinal cord (see Figure 12.18), giving the inferior vestibular nucleus a characteristic "checkerboard" appearance (see Figure 14.5A).

The **medial longitudinal fasciculus** (MLF) is an important pathway that connects the nuclei involved in eye movements to each other and to the vestibular nuclei (see Figure 12.18). The MLF can be identified in the sections in Figures 14.3-14.5 as a heavily myelinated tract running near the midline on each side, just under the olivocerebral and trochlear nuclei in the midbrain, and just under the floor of the fourth ventricle in the midline of the pontine nuclei. Fibers arising from the medial vestibular nucleus, with additional contributions mainly from the superior vestibular nucleus, ascend in the MLF to the olivocerebral, trochlear, and abducens nuclei. This pathway mediates the vestibulocular reflex, in which eye movements are adjusted for changes in head position (see neuroanatomy: Video 35). The function of the MLF in interconnecting the abducens and olivocerebral nuclei is discussed in Chapter 13. In another commonly used nomenclature, what we have called the MLF is referred to as the ascending MLF and the medial vestibulospinal tract is referred to as the descending MLF (see Figure 12.18).

The vestibular nuclei have numerous important reciprocal connections with the cerebellum. As we will discuss in Chapter 15, vestibular connections are mainly with the flocculonodular lobes and cerebellar vermis. These regions of the cerebellum are often called the vestibulocerebellum. A small number of primary vestibular sensory neurons bypass the vestibular nuclei and project directly to the vestibulocerebellum.

Ascending pathways from the vestibular nuclei relay in the ventral posteri or nucleus of the thalamus to reach the **cerebral cortex**. These pathways are still being investigated; however, one important cortical region for vestibular sensation appears to lie in the parietal association cortex, possibly in Brodmann's area 5.

**KEY CLINICAL CONCEPT**

**HEARING LOSS (CN VIII)**

Impaired hearing is usually divided into **conductive hearing loss**, caused by abnormalities of the external auditory canal or middle ear, and **sensorineural hearing loss**, usually caused by disorders of the cochlea or eighth nerve. When evaluating a patient for hearing loss, the practitioner should first examine the ears with an otoscope. Hearing can be tested with sounds of different frequencies, such as finger rubbing, whispering, or a ticking watch (see neuroanatomy: Video 42). Conductive and sensorineural hearing loss can often be distinguished with a simple 250- or 512-Hz tuning fork test. In the **Rinne test**, air conduction is compared to bone conduction for each ear. We measure **air conduction** by holding a vibrating tuning fork just outside each ear, and **bone conduction** by placing a tuning fork handle on each mastoid process (see neuroanatomy: Video 42). Normal individuals hear the tone better by air conduction. In conductive hearing loss, bone conduction is greater than air conduction because bone conduction bypasses problems in the external or middle ear. In sensorineural hearing loss, air conduction is greater than bone conduction in both ears (as in normal hearing); however, hearing is decreased in the affected ear. In the **Weber test** the tuning fork is placed on the vertex of the skull in the midline, and the patient is asked to report the side where the tone sounds louder (see neuroanatomy: Video 42). Normally, the tone sounds equal on both sides. In sensorineural hearing loss, the tone is louder on the normal side. In conductive hearing loss, the tone is louder on the affected side. You can verify this for yourself by producing temporary unilateral conductive hearing loss by closing each ear alternately. If you then hum, the tone should be louder on the occluded side.

Other tests that can help localize the cause of hearing loss include audiometry and brainstem auditory evoked potentials. An MRI scan with fine cuts through the auditory canal should be performed when disorders of the eighth nerve are suspected. Common causes of cochlear hearing loss include cermen in the external auditory canal, otitis, tympanic membrane perforation, and sclerosis of the middle ear ossicles. Common causes of sensorineural hearing loss include exposure to loud sounds, meningitis, ototoxic drugs, head trauma, viral infections, aging, Meniere's disease (see KCC 12.6), cerebellopontine angle tumors, and rarely, internal auditory artery aneurysm (see KCC 14.2).

Cerebellar tumors include acoustic neuroma (vestibular schwannoma), meningioma, cerebellar astrocytoma, epidermoid, gliomas, and metastases. The most common tumor by far in this location is...
acoustic neuroma, accounting for 5 to 10% of intracranial neoplasms in adults (see Table 5.6). Mean age of onset is 50 years, and the tumor is nearly always unilateral. The exception is in neurofibromatosis type 2, in which the tumors are bilateral and usually occur before age 21. This slow-growing tumor develops at the transitional zone between Schwann cells and oligodendrocytes, which occurs at the point where CN VIII enters the internal auditory meatus (see Figures 12.3A, 12.14). The term "acoustic neuroma" is a misnomer because the tumor is actually schwannoma, not a neuroma, and it nearly always arises from the vestibular, not acoustic, portion of this nerve with normal vestibular function. Initially, the tumor grows within the bony auditory canal, but then it expands into the cerebellopontine angle (see Figure 12.2A,C). Common early symptoms are unilateral hearing loss, tinnitus (ringing in the ear), and unsteadiness. The next cranial nerve to be affected is usually the nearby trigeminal nerve, with facial pain and sensory loss. Often the first sign of trigeminal involvement is a subtle decrease in the corneal reflex (see Figure 12.4). Interestingly, although the vestibular and facial nerves are compressed within the auditory canal, true vertigo is not usually a prominent symptom (although some unsteadiness is common), and the facial nerve does not usually become involved until the tumor is quite large. Eventually there is facial weakness, sometimes with decreased taste sensation on the side of the tumor.

With large tumors, cerebellar and corticospinal pathways are compressed, causing ipsilateral ataxia and contralateral hemiparesis. Impairment of swallowing and the gag reflex (CN IX and X) and unilateral impaired eye movements (CN III and VI) occur only in very large tumors. Ultimately, if left untreated, the tumor will compress the fourth ventricle, causing CSF outflow obstruction, hydrocephalus, herniation, and death. With adequate clinical evaluation and MRI scanning, acoustic nerve tumors can be detected at an early stage, when they still lie entirely within the auditory canal. Treatment has traditionally been by surgical excision. With small tumors, preservation of the facial nerve is often possible, and occasionally some hearing may even be spared in the affected ear. Recently, stereotactic radiosurgery (see KCC 16.4) has been used as an alternative to surgery for acoustic neuromas.

Schwannomas can occur on other cranial nerves, as well as on spinal nerve roots, causing radiculopathy or spinal cord compression. Trigeminal neuma is the second most common form of schwannoma affecting the cranial nerves. Schwannomas of the other cranial nerves are very rare.

2.6 "Dizziness" is a vague term used by patients to describe many different abnormal sensations. In taking the history, the examiner should clarify whether the patient is referring to true vertigo, meaning a spinning sensation of movement, or one of the other meanings of dizziness. Other uses of "dizziness" include light-headedness or faintness, nausea, and unsteadiness on one's feet. True vertigo is more suggestive of vestibular disorders than the other symptoms are. However, the situation is complicated by the fact that the other sensations listed here often accompany vertigo, and in some cases they may be the only presenting symptoms of vestibular disease.

Vertigo can be caused by lesions anywhere in the vestibular pathway, from labyrinth, to vestibular nerve, to vestibular nuclei and cerebellum, to parietal cortex. Most cases of vertigo are caused by peripheral disorders involving the inner ear, with central disorders of the brainstem or cerebellum being less common. It is essential to distinguish these possibilities because some central causes of vertigo, such as incipient brainstem stroke or posterior fossa hemorrhage, require emergency treatment to prevent serious sequelae. In taking the history of a patient with vertigo, it is therefore crucial to ask if any other symptoms suggestive of posterior fossa disease are present (see Table 14.6), such as diplopia, other visual changes, somatosensory changes, weakness, dysarthria, incoordination, or impaired consciousness. Patients with any of these abnormalities accompanying vertigo should be considered to have posterior fossa disease until proven otherwise and should be treated on an urgent basis. The general physical exam should also include orthostatic measurements of blood pressure and pulse in the supine and sitting or standing positions. Normally the systolic blood pressure drops by only about 10 to 20 mm Hg and the pulse increases by about 10 beats per minute when measured a few minutes after going from supine to a seated position with the legs dangling. Substantially greater changes suggest that the patient's symptoms may be caused by hypovolemia, antihypertensive medications, or cardiovascular or autonomic disorders, rather than by a vestibular lesion. In addition, during the general exam the tympanic membranes should be examined with an otoscope. A careful neurologic exam should be done to detect any abnormalities that may suggest a central cause for the vertigo.

Barany or Dix-Hallpike positional testing is a useful part of the exam that can help distinguish peripheral from central causes of vertigo (see neuromax.com Video 43). The patient sits on the bed or examining table. The examiner then supports the back of the patient as the patient lies back with the head turned so that one ear is down and the head extends over the edge of the table. This maneuver should be done rapidly but gently. The patient is asked to keep their eyes open and report any sensations of vertigo, while the examiner looks for nystagmus. This change of position causes maximal stimulation of the posterior semicircular canal of the ear that is down (the posterior semicircular canal of the ear that is up is probably also stimulated). The maneuver is then repeated with the other ear down.

With peripheral lesions affecting the inner ear (there is usually a delay of 2 to 5 seconds before onset of nystagmus and vertigo) (Table 12.7), nystagmus is horizontal or rotary and does not change directions while the patient remains in the same position. Nystagmus and vertigo then fade away within about 30 seconds. If the same maneuver is repeated, there is often adaptation (often called habituation or fatiguing), so that the nystagmus and vertigo are briefer and less intense each time. In contrast, with central lesions the nystagmus and vertigo may begin immediately, and there tends to be no adaptation (see Table 12.7). Horizontal or rotary nystagmus can also be seen with central lesions. However, vertical nystagmus, nystagmus that changes directions while remaining in the same position, or prominent nystagmus in the absence of vertigo is seen only in central, and not in peripheral, lesions.

### Table 12.7 Positional Testing to Distinguish Peripheral from Central Causes of Vertigo and Nystagmus

<table>
<thead>
<tr>
<th>Type of Lesion</th>
<th>Onset of Nystagmus</th>
<th>Adaptation (Habituation)</th>
<th>Characteristics of Nystagmus and Vertigo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral (inner ear)</td>
<td>Delayed</td>
<td>Yes</td>
<td>Horizontal or rotary, not vertical; does not change directions; prominent nystagmus only if vertigo is present as well.</td>
</tr>
<tr>
<td>Central (brainstem or cerebellum)</td>
<td>Immediate or Delayed</td>
<td>No</td>
<td>Horizontal, rotary, or vertical; may change directions; prominent nystagmus may occur in the absence of vertigo.</td>
</tr>
</tbody>
</table>
Let's briefly review a few specific peripheral and central causes of vertigo. Benign paroxysmal positional vertigo is possibly the most common cause of true vertigo. Patients experience brief episodes of vertigo lasting for a few seconds and occurring with change of position. When the symptom first occurs, the patient may be dizzy for several hours. However, after the first episode it is usually brief and occurs only with change of position, in some cases, the vertigo may be so intense that patients cannot walk. The presence of pieces of debris in the semicircular canals (especially the posterior canal) that push against the cupula (see Figure 12.15, inset) has been proposed as the mechanism for this disorder. Symptoms occur especially when the patient attempts to sleep and lies with the affected ear down, or if the patient turns to the affected side; however, if the patient remains still, the dizziness typically abates. Turning away from the affected ear or sitting up may also provoke symptoms. Adaptation exercises may be beneficial.

Viral infections or idiopathic inflammation of the vestibular ganglia or nerve may cause vestibular neuritis, a monophasic illness resulting in several days of intense vertigo and sometimes a feeling of unsteadiness that can last from weeks to months. In Meniere's disease, patients have recurrent episodes of vertigo, accompanied by fluctuating and sometimes stepwise, progressive hearing loss. Patients with Meniere's disease also often complain of tinnitus and a full feeling in the ear. The etiology is thought to be excess pressure in the endolymphatic system (see Figure 12.14, 12.15). Meniere's disease is most frequently treated with salt restriction and diuretics, although there have been no controlled studies of those therapies. There are multiple surgical procedures that have been effective in some patients, including vestibular nerve section, labyrinthectomy, endolymphatic sacotomy (decompression), and transantral gentamycin (to cause permanent loss of vestibular function on the affected side). Acoustic neuroma (vestibular schwannoma) can also be associated with vertigo and hearing loss (see KCC 12.5). However, patients with acoustic neuromas often complain of unsteadiness rather than true vertigo, and they do not usually have discrete episodes as in Meniere's disease.

Common central causes of vertigo include vertebrobasilar ischemia or infarct. Insults to the vestibular nuclei or cerebellum can cause vertigo often with other symptoms and signs of vertebrobasilar disease (see KCC 14.3; Table 14.6). It is essential to recognize this entity so that treatment is not delayed. Similarly, a small hemorrhage in the cerebellum or, rarely, in the brainstem may initially present mainly with vertigo and should be treated as soon as possible to prevent catastrophe. Cerebellar hemorrhage that presents initially with some nausea and dizziness, only to relent a few hours later, has been called "fetal gastrectomitis." Encephalitis, tumors, or demyelination in the posterior fossa can cause vertigo. In addition, numerous drugs and toxins, including alcohol and anticonvulsant medications, cause dysfunction of the vestibular nuclei and cerebellum, producing vertigo along with other toxic drugs such as Gentamicin cause one-third of the posterior area-three of the tongue, pharynx, middle ear, and a region near the external auditory meatus (see Figure 12.7B). The glossopharyngeal nerve has two sensory ganglia located within or just below the jugular foramen (see Table 12.5). General and special visceral sensation are conveyed by bipolar primary sensory neurons in the inferior (petrosal) glossopharyngeal ganglion. General sensory sensation is conveyed by bipolar primary sensory neurons in both the inferior and superior (jugular) glossopharyngeal ganglion.

The glossopharyngeal nerve was named for its role in sensation for the posterior tongue and pharynx; however, it has additional functions as well. It exits the brainstem as several rootlets along the upper ventrolateral medulla, just below the pontomedullary junction and just below CN VIII, between the inferior olive and the inferior cerebellar peduncle (see Figure 12.2A,C). The nerve traverses the subarachnoid space to exit the skull via the jugular foramen (see Figure 12.2A, B; Table 12.2).

The branchial motor portion of the nerve supplies one muscle, the stylopharyngeus (Figure 12.19), which elevates the pharynx during talking and swallowing and contributes (with CN X) to the gag reflex. There is evidence that the glossopharyngeal may provide some innervation to other pharyngeal muscles; however, most pharyngeal muscles are supplied primarily by the vagus (see the next section). The branchial motor component of CN IX arises from the nucleus ambiguus in the medulla (see Figure 12.19). "Ambiguous" is Latin for "ambigous," and this name can be remembered because the nucleus is difficult to discern on conventional stained sections (see Figure 14.5A,B). Parasympathetic preganglionic fibers in the glossopharyngeal nerve arise from the inferior salivatory nucleus in the pons (see Figure 12.19). These parasympathetic fibers leave the glossopharyngeal nerve via the lesser petrosal nerve and synapse in the otic ganglion to provide postganglionic parasympathetics to the parotid gland.

The general visceral sensory portion of the glossopharyngeal nerve conveys inputs from baroreceptors and chemoreceptors in the carotid body. These afferents travel to the caudal nucleus solitarius of the medulla, also known as the cardiorespiratory nucleus (see Figure 12.19). Glossopharyngeal special visceral sensation mediates taste for the posterior one-third of the tongue, which reaches the rostral nucleus solitarius, or gustatory nucleus (see Figures 12.5, 12.12, 12.19). General somatic sensory functions of CN IX are the sensation of touch, pain, and temperature from the posterior one-third of the tongue, pharynx, middle ear, and a region near the external auditory meatus (see Figure 12.7B). The glossopharyngeal nerve has two sensory ganglia located within or just below the jugular foramen (see Table 12.5). General and special visceral sensation are conveyed by bipolar primary sensory neurons in the inferior (petrosal) glossopharyngeal ganglion. General sensory sensation is conveyed by bipolar primary sensory neurons in both the inferior and superior (jugular) glossopharyngeal ganglion.
Figure 12.19 Glossopharyngeal Nerve (CN IX) Summary of glossopharyngeal nerve sensory and motor pathways.

The glossopharyngeal nerve derives its name from the wandering course it takes in providing parasympathetic innervation to organs throughout the body ("glossopharyngeal" means "wandering" in Latin). Other important functions are also served by the vagus nerve, as we will discuss here. The vagus nerve exits the ventrolateral medulla as several roots just below CN IX, between the inferior olive and the inferior cerebellar peduncle (see Figure 12.2A,C). It crosses the subarchnoid space and then leaves the cranial cavity via the jugular foramen (see Figures 12.3A,B, 12.20).

The largest part of the vagus nerve provides parasympathetic innervation to the heart, lungs, and digestive tract, extending nearly to the spleenic flexure (see Figures 6.13, 12.20). Parasympathetic preganglionic fibers arise from the dorsal motor nucleus of CN X, which runs from the rostral to the caudal medulla (see Figure 14.5A,B). The dorsal motor nucleus of CN X forms the vagal trigone on the floor of the fourth ventricle, just lateral to the hypoglossal trigone, near the obex (see Figure 12.2B). Postganglionic parasympathetic fibers innervated by the vagus are found in the terminal ganglia located within or near the effector organs. Recall that parasympathetic fibers to the gastrointestinal tract beyond the splenic flexure, and to the urogenital system, are provided by parasympathetic nuclei in the sacral spinal cord (see Figure 6.13).

The branchial motor component of the vagus (Figure 12.20) controls nearly all the pharyngeal muscles (swallowing and gag reflex) and the muscles of the larynx (voice box). The nucleus ambiguus supplies branchial motor fibers that travel in the vagus nerve to the muscles of the palate, pharynx, and larynx, and in the glossopharyngeal nerve (CN IX) to the stylopharyngeus (see Figure 12.19).

A branch of the vagus called the recurrent laryngeal nerve (see Figure 12.20) loops back upward from the thoracic cavity to control all intrinsic laryngeal muscles except for the cricothyroid, which is innervated by another branch of the vagus, the superior laryngeal nerve. The fibers in the recurrent laryngeal nerve arise from the caudal portion of the nucleus ambiguus. After they exit the brainstem, these fibers travel briefly with CN XI before joining CN X (see the next section). Some texts consider these caudal fibers of the nucleus ambiguous part of CN XI and refer to the caudal nucleus ambiguous as the caudal nucleus of CN XI. However, we include these fibers with CN X because they spend the majority of their course traveling with CN X, not CN XI. Upper motor neuron innervation to the nucleus ambiguous controlling the voice and voluntary swallowing is from bilateral motor cortex (see Figure 6.23).

General somatic sensory fibers of the vagus (see Figure 12.20) supply the pharynx, larynx, meninges of the posterior fossa, and a small region near the external auditory meatus (see Figure 12.2B). Note that below the larynx and pharynx, conscious (general somatic) sensation from the viscera is carried by spinal and not cranial nerves. However, unconscious, general visceral sensation from chemoreceptors and baroreceptors of the aortic arch, cardiorespiratory system, and digestive tract is carried to the brainstem by the vagus nerve. Many of these general visceral afferents reach the caudal nucleus solitarius (cardiorespiratory nucleus; see Figures 12.5, 14.5A). The vagus nerve also contains a small number of special visceral sensory fibers that carry taste sensation from the epiglottis and posterior pharynx to the rostral nucleus solitarius (gustatory nucleus; see Figures 12.5, 14.5A). The vagus nerve also contains a small number of special visceral sensory fibers that carry taste sensation from the epiglottis and posterior pharynx to the rostral nucleus solitarius (gustatory nucleus; see Figures 12.5, 14.5A).

The primary sensory neuron cell bodies for CN X general and special visceral sensation are located in the inferior (nucleus) vagal ganglion (Table 12.5), located just below the jugular foramen. Cell bodies for general somatic sensation are located in both the inferior vagal ganglion and the superior (jugular) vagal ganglion, which lies within or just below the jugular foramen.

**CN X: Vagus Nerve**

| Functional category: Branchial motor | Function: Pharyngeal muscles (swallowing) and laryngeal muscles (voice box). |
| Functional category: Parasympathetic | Function: Parasympathetics to heart, lungs, and digestive tract down to the splenic flexure. |
| Functional category: General somatic sensory | Function: Sensation from pharynx, meninges, and a small region near the external auditory meatus. |
| Functional category: Visceral sensory (special) | Function: Taste from epiglottis and posterior pharynx. |
| Functional category: Visceral sensory (general) | Function: Chemoreceptors and baroreceptors of the aortic arch. |
CN XI: Spinal Accessory Nerve

**Functional category:** Branchial motor  
**Function:** Sternomastoid and upper part of trapezius muscle

As its name implies, this nerve does not arise from the brainstem, but rather from the upper five or six segments of the cervical spinal cord (see Figure 12.2). The spinal accessory nucleus (also known as the accessory spinal nuclear) protrudes laterally between the dorsal and ventral horns of the spinal cord central gray matter (see Figure 14.5D) providing branchial motor fibers to this nerve. Nerve roots leave the spinal accessory nucleus and exit the lateral aspect of the spinal cord between the dorsal and ventral rootlets just dorsal to the dentate ligament and ascend through the foramen magnum to reach the intracranial cavity (see Figures 12.2A, 12.3A,B).

CN XI then exits the cranium again via the jugular foramen to supply the sternomastoid and upper portions of the trapezius muscle. The sternomastoid muscle turns the head toward the opposite side, and the trapezius is involved in elevating the shoulder (see neuroexam.com Video 46). The lower portions of the trapezius are usually supplied mainly by cervical nerve roots C3 and C4.

Note that the left sternomastoid turns the head to the right, and vice versa. Therefore, lower motor neuron lesions of CN XI may cause some ipsilateral weakness of shoulder shrug or arm elevation, and weakness of head turning away from the lesion. In turning the head, other neck muscles can sometimes compensate for the sternomastoid; therefore, in subtle cases, it is best to palpate the sternomastoid with one hand for contractions while the patient attempts turning their head against resistance offered by the examiner's other hand. Upper motor neuron lesions can also cause deficits of head turning, toward the side opposite the lesion. Therefore, it is thought that the central pathways for head turning project to the ipsilateral spinal accessory nucleus. However, the deficit in head turning to the side opposite the lesion in cortical lesions is often more of a gait preference than true weakness. With upper motor neuron lesions causing contralateral hemiparesis, the shoulder shrug is also often weak on the side of the hemiparesis.

Before it exits the cranium, the spinal accessory nerve is briefly joined by some fibers arising from the caudal nucleus ambiguus that exit from the lateral medulla adjacent to the vagus nerve. These fibers rejoin the vagus within a few centimeters and ultimately form the recurrent laryngeal nerve.

As noted in the previous section, because these fibers travel briefly with CN XI, some textbooks refer to them as the *cranial root* of CN XI. Despite this name, the recurrent laryngeal nerve fibers spend the majority of their course traveling with CN X and can functionally be considered part of the vagus.

CN XII: Hypoglossal Nerve

**Functional category:** Somatic motor  
**Function:** Intrinsic muscles of the tongue

The hypoglossal nerve exits the ventral medulla as multiple rootlets between the pyramid and inferior olivary nucleus (see Figure 12.2A,C). This nerve exits through its own foramen, the hypoglossal foramen (Figure 12.3A, B), and provides somatic motor innervation to all intrinsic and extrinsic tongue muscles except for the palatoglossus, which is supplied by CN X (see neuroexam.com Video 47). The hypoglossal nucleus is located near the midline on the floor of the fourth ventricle in the medulla (see Figure 12.3A, B).
KEY CLINICAL CONCEPT

14.2A\(3\)) forming the hypoglossal trigone, just medial to the dorsal nucleus of CN X (see Figures 12.10, 12.4B, 12.5).

Upper motor neurons for tongue movement arise from the tegmentum of the primary motor cortex (see Figure 6.2) and travel in corticobulbar pathways that decussate before reaching the hypoglossal nucleus. These lesions in the primary motor cortex or internal capsule will cause contralateral tongue weakness, while lesions of the hypoglossal nucleus, exiting fascicles, or nerve cause ipsilateral tongue weakness. Note that unilateral tongue weakness causes the side to which it is directed to weaken, while the weak side may be protruded. Thus, a lesion of the hypoglossal nerve will cause the tongue to deviate toward the side of the lesion.

Peripheral lesions of the lower cranial nerves are relatively uncommon. Most disorders of these cranial nerves are associated with central lesions (see Chapter 14). Like all other nerves, however, the lower cranial nerves are occasionally affected by diabetic neuropathy, demyelination, motor neuron disease, and toxic or infectious conditions. Let's briefly discuss a few disorders of the lower cranial nerves.

Glossopharyngeal neuralgia is clinically similar to trigeminal neuralgia but involves the sensory distribution of CN IX, causing episodes of severe throat and ear pain. Injury to the recurrent laryngeal nerve (a branch of CN X) can occur during surgery of the neck (such as carotid endarterectomy, cricovocal disc surgery, or thyroid surgery) and produces unilateral vocal cord paralysis and hoarseness (see KCC 12.8). The recurrent laryngeal nerve can also be infiltrated by apical lung tumors during its looping course through the upper thoracic cavity (see Figure 12.20), which produces hoarseness as part of Fanconi's syndrome (see KCC 9.1). Dorsum tumors are a rare cause that can affect the lower cranial nerves. Glomus bodies are normal small epitheliod structures that resemble the carotid bodies histologically, but whose function is unknown. Like the carotid bodies, they are richly innervated by CN IX but are located adjacent to the jugular foramen and along branches of CN IX leading to the middle ear cavity. Tumors arising from the glomus bodies are known by a variety of names, including glomus tumor and glomus jugulare. Patients with glomus jugulare often present with parietal area of CN IX, X, and XI, resulting from compression of these nerves in the jugular foramen. In addition, the tumor often extends to the nearby CN XII and can grow upward to affect CN VII and VIII in the temporal bone. When the tumor grows into the middle ear, it can sometimes be seen on otoscopic exam as a fleshly vascular mass. Treatment is by resection, although radiation therapy is also used in some cases.

Clinical examination of CN IX through XII and the functional effects of lesions of these nerves was discussed in the previous sections and is discussed in further detail in KCC 12.8.

Disorders of speech and swallowing can be very disabling, or even fatal, in some cases. Causes of these disorders can range from upper motor neuron lesions (corticobulbar pathways) to lower motor neuron lesions to disorders of the neuromuscular junction or muscles themselves, and can also result from cerebral or spinal dysfunction. Let's discuss some of the more common causes of each of these disorders.

Voice disorders occur when the larynx and vocal cords (more correctly called the vocal folds, or true vocal cords) are not functioning properly. Such malfunction can occur as the result of mechanical factors or as muscular disorders. Hoarseness of the voice usually results from disorders of the vocal cords causing asynchronous vibratory patterns. Hoarseness is often caused by mechanical factors such as swelling, nodules, polyps, or neuromas of the vocal cords. Breathlessness of the voice is caused by paralysis or paresis of the vocal cords, which results in incomplete adduction of one or both of the vocal cords and an air leak at the glottis. In common language, hoarseness is often called "hoarseness," although this is not strictly correct. Recall that the muscles of the larynx are innervated by the branchial motor portion of CN X. The recurrent laryngeal nerve can be injured during surgery in the neck or chest, or compressed by lung cancer as it loops through the upper thoracic cavity (see Figure 12.20). Voice disorders can also occur from lesions of CN X as it exits the brainstem, such as glomus jugulare (see KCC 12.7), or of the nucleus ambiguus in the medulla (see Figures 12.19, 12.20). The most common lesion of the medulla affecting the nucleus ambiguous is a lateral medullary infarct (see Figure 14.20D, Table 14.7). An abnormal, gravelly sounding voice can also occur in Parkinson's disease and other related movement disorders (see KCC 16.2). Spasmodic dysphonia is an uncommon form of dysphonia (see KCC 16.1) involving the larynx, presumably resulting from dysfunction of basal ganglia circuitry. Vocal cord lesions or abnormal vocal cord movements can best be evaluated by fiberoptic laryngoscopy, in which a flexible scope is used to directly visualize the vocal cords during speech.

Dysarthria is abnormal articulation of speech (see neuroex.com Video 45). Dysarthria should be distinguished from aphasia (see KCC 19.2). Whereas dysarthria is a motor articular disorder, aphasia is a disorder of higher cognitive functioning in which language formulation or comprehension is abnormal. Depending on the lesion, aphasia and dysarthria can occur together, or one can occur without the other. Dysarthria can range in severity from mild slurring to unintelligible speech. It can occur in lesions involving the muscles of articulation (jaw, lips, palate, pharynx, and tongue), the neuromuscular junction, or the peripheral or central portions of CN V, VII, IX, X, or XII. In addition, speech articulation can be abnormal because of dysfunction of the motor cortex face area (see Figure 6.2), cerebellum, basal ganglia, or descending corticobulbar pathways to the brainstem. Common causes of dysarthria include infarcts, multiple sclerosis, or other lesions affecting corticobulbar pathways (see KCC 6.3), brainstem lesions, or lesions of cerebellar pathways or basal ganglia; toxins (e.g., alcohol); other causes of diffuse encephalopathy; myasthenia gravis; and other disorders of neuromuscular junction, muscle, or peripheral nerves. A few other important but less common specific causes are to be aware of include amyotrophic lateral sclerosis (see KCC 6.7), botulism, and Wilson's disease.

Dysphagia is impaired swallowing. Dysphagia can be caused by esophageal strictures, neoplasms, or other local lesions, or it may have a neural or neuromuscular basis. When dysphagia is caused by neural or neuromuscular disorders, it often has the same causes as, and occurs together with, dysarthria (although dysarthria and dysphagia can occur independently as well). Swallowing is classically divided into four phases: the oral preparatory phase (preparation of the food bolus for swallowing by mastication); oral phase (movement of the bolus in an anterior-posterior direction by the oral tongue); pharyngeal phase (propulsion of the bolus through the pharynx by base-of-tongue driving force, aided by anterior-superior movement of the larynx); and the esophageal phase (opening of the upper esophageal sphincter, esophageal peristalsis, and emptying into the stomach). Thus, dysphagia can be caused by dysfunction of muscles of the tongue, palate, pharynx, epiglottis, larynx, or esophagus; by lesions of CN IX, X, XII, or their nuclei; or by dysfunction at the neuromuscular junction; or in the descending corticobulbar pathways.
Impaired oral and pharyngeal swallowing function and impaired reflux closure of the entrance to the trachea by the epiglottis and laryngeal muscles can lead to aspiration of food, and esophageal reflux can lead to aspiration of gastric secretions into the lungs. Aspiration pneumonia, caused by impaired swallowing function, is difficult to treat and is a common cause of death in disorders of the nervous system. Pharyngeal reflexes can be tested by the gag reflex. This reflex is elicited by stroking the posterior pharynx with a cotton-tipped swab. The gag reflex is mediated by sensory and motor fibres from both CN IX and X, although CN IX may be more important for the afferent limb, while CN X provides primarily the efferent limb. Although an impaired gag reflex may be indicative of impaired motor or sensory function of the pharynx, its absence or presence is not absolutely predictive of aspiration risk.

A simple way to assess soft palate function is to observe palate elevation with a penlight while asking the patient to say, “Adit” (see neuromuscle.com Video 44). In unilateral lesions of CN X or of the nucleus ambiguus, the uvula and soft palate will deviate toward the normal side, while the soft palate on the abnormal side hangs abnormally low, producing the stage curtain sign.

Brainstem nuclei involved in laughing and crying include CN VII, IX, X, and XII. Lesions of corticobulbar pathways in the subcortical white matter or brainstem can occasionally produce a bizarre syndrome called pseudobulbar affect. Patients with this syndrome exhibit uncontrollable bouts of laughter or crying without feeling the usual associated emotions of mirth or sadness. Pseudobulbar affect may be likened to an “upper motor neuron” disorder in which there is abnormal reflex activation of laughter and crying circuits in the brainstem, leading to emotional incontinence. The term pseudobulbar palsy is sometimes used to describe dysarthria and dysphagia caused by lesions not of the brainstem (bulb), but rather of the upper motor neurons fibers in the corticobulbar pathways (hence “pseudo”). Another neurologic cause of episodes of inappropriate laughter is a rare seizure disorder called gelastic epilepsy, which is usually associated with hypothalamic lesions (hypothalamic hamartomas) but can occasionally be seen in temporal lobe seizures (see ICC 18.2).

Review: Cranial Nerve Combinations

The preceding material is quite detailed, yet as we will see, it has numerous important clinical applications. Let’s review several functional combinations to help consolidate the details of cranial nerve anatomy and to clarify some regional aspects of sensory and motor function. Functional combinations involving the eye muscles will be discussed in Chapter 13.

1. Sensory and motor innervation of the face: Sensation is provided by the trigeminal nerve (CN V), while movement of the muscles of facial expression is provided by the facial nerve (CN VII).

2. Taste and other sensorimotor functions of the tongue and mouth: The anterior two-thirds and posterior one-third of the tongue are derived from different branchial arches and therefore have different innervation. For the anterior two-thirds of the tongue, taste is provided by the facial nerve (CN VII, chorda tympani), while general somatic sensation is provided by the trigeminal nerve (CN V, mandibular division). For the posterior one-third of the tongue, both taste and general somatic sensation are provided by the glossopharyngeal nerve (CN IX). Taste for the epiglottis and posterior pharynx is provided by the vagus nerve (CN X). General sensation for the teeth, nasal sinuses, and inside of the mouth, above the pharynx and above the posterior one-third of the tongue, is provided by the trigeminal nerve (CN V).

3. Sensory and motor innervation of the pharynx and larynx: For the pharyngeal gag reflex, general somatic sensation is provided by both the glossopharyngeal and the vagus nerves (CN IX and X), but branchial motor innervation is provided mainly by the vagus (CN X). For the larynx, the vagus provides both sensory and motor innervation. General somatic sensation for organs below the level of the larynx is provided by the spinal nerves.

4. Sensory and motor innervation of the ear: General somatic sensation for the middle ear and inner tympanic membrane is provided by the glossopharyngeal nerve (CN IX), while sensation for the external ear and outer surface of the tympanic membrane is provided by the trigeminal nerve (CN V, mandibular branch), facial (CN VII), glossopharyngeal (CN IX), and vagus (CN X) nerves (see Figure 12.7B). Hearing and vestibular sense travel in the vestibulocochlear nerve (CN VIII). Branchial motor innervation for the tensor tympani comes from the trigeminal nerve (CN V), while innervation for the stapediaus comes from the facial nerve (CN VII). An aid to remembering this information is the fact that “tensor tympani” and “trigeminal” start with the letter “T,” while “stapedius” and cranial nerve “seven” start with “S.” Similarly, the tensor veli palatini is supplied by the trigeminal nerve, while all other muscles of the soft palate are supplied by the vagus.

5. Sensation from the meninges: Sensation from the supratentorial dura mater is carried by the trigeminal nerve (CN V), while the dura of the posterior cranial fossa is supplied by the vagus (CN X) and by the upper cervical nerve roots.

6. General visceral sensation: Unconscious, general visceral sensation from baroreceptors and chemoreceptors is carried by the glossopharyngeal nerve (CN IX) for the carotid body and sinus, and by the vagus nerve (CN X) for the aortic arch and other thoracoabdominal viscera.

Additional understanding of cranial nerve combinations will be gained through clinical practice.
**CASE 12.1 ANOSMIA AND VISUAL IMPAIRMENT**

MINICASE

A 51-year-old man began having difficulty reading over the course of 5 to 6 weeks. He saw his doctor, and on review of systems it was noted that he had lost his sense of smell about 3 years earlier. On exam, he had a visual acuity of 20/20 in the right eye and 20/40 in the left eye. He was unable to smell coffee or soap with either nostril.

**LOCALIZATION AND DIFFERENTIAL DIAGNOSIS**

1. On the basis of the symptoms and signs shown in bold above, where is the lesion?
2. What is the most likely diagnosis, and what are some other possibilities?

**Discussion**

1. The key symptoms and signs in this case are:
   - Bilateral anosmia
   - Difficulty reading and left decreased visual acuity

   The anosmia could be caused by bilateral lesions of the olfactory mucosa or the olfactory nerves, bulbs, or tracts (see KCC 12.1). Decreased acuity in the left eye is consistent with a disorder in the left eye or the left optic nerve (see KCC 11.2). Deficits of CN I and CN II together suggest a lesion at the base of the frontal lobes, where these two cranial nerves cross the midline. (See Figure 18.6) Before CN II exits the cranial via the optic canal (Figure 12.3A), it is also possible that the anosmia is an unrelated incidental finding.

   The most likely clinical localization is bilateral orbital frontal areas.

2. Given the prolonged course, a slow-growing tumor at the base of the frontal lobes such as a meningioma should be suspected. Other tumors or chronic inflammatory disorders in this region are also possible, but less likely.

**Clinical Course and Neuroimaging**

The patient underwent a brain MRI (Figure 12.21B,C). Figure 12.21A shows a normal MRI demonstrating the anatomical structures at the base of the frontal lobes. With the labels covered, identify the olfactory bulbs, olfactory sulcus, gyrus rectus, and cribriform plate. The images of our patient in this case, taken with gadolinium enhancement, are shown in Figure 12.21B and C. An enhancing mass at the base of the frontal lobes extends along the dural surface in the region of the olfactory bulbs and extends over the cribriform plate into the upper nasal passages (Figure 12.21B). The mass also extends back to encase the left optic nerve (Figure 12.21C). On the basis of its appearance and the patient's history, it was felt that this was most likely a meningioma, although the irregular borders of the lesion that appeared to infiltrate adjacent structures were somewhat unusual for a meningioma.

A biopsy of the mass was performed through the nose, via a transethmoidal approach. Interestingly, pathology revealed nonscarring granulomas consistent with sarcoidosis (KCC 12.1). Additional workup supported the diagnosis of sarcoidosis confined to the nervous system. The patient was treated with steroids, and his vision improved in the left eye, but he remained unable to smell.

*This patient was described previously as a case report in the New England Journal of Medicine, Volume 335, pp. 1668-1674, 1996.*

**CASE 12.2 CHEEK NUMBNESS AND A BULGING EYE**

MINICASE

A 51-year-old woman saw an ophthalmologist because she noticed that her left eye seemed to be bulging out increasingly for the past 3 to 4 years, and she had recently developed left-sided headaches. Exam was normal except for an outward bulging of her left eye (proptosis) and decreased sensation to touch and pinprick over her left cheek.

**LOCALIZATION AND DIFFERENTIAL DIAGNOSIS**

1. Which division of cranial nerve provides sensation to the cheek? Where does this nerve exit the skull?
2. What diagnosis is suggested by the slowly developing left proptosis over the course of several years, together with the cheek sensory deficit and left-sided headache?

**Discussion**

1. The key symptoms and signs in this case are:
   - Left-sided headaches
   - Left proptosis

   Decreased sensation to touch and pinprick over the left cheek. The maxillary division of the trigeminal nerve (CN V2) provides sensation to the cheek (see Figure 12.7). This branch of the trigeminal nerve exits the skull through the foramen rotundum (see Figures 12.3, 12.7, Table 12.2).

2. The history and exam findings suggest a slow-growing mass lesion such as a meningioma (see KCC 5.8) involving the left foramen rotundum area causing V2 sensory loss and extending into the left orbit, causing proptosis.

**Clinical Course and Neuroimaging**

The patient underwent an MRI scan with gadolinium enhancement (Figure 12.22) that revealed an enhancing mass lying outside the brain in the region of the left foramen rotundum (compare Figure 12.3A) and extending into the left orbit. This appearance was felt to be consistent with a meningioma (see KCC 5.8). Because of concern that the mass would soon lead to impaired vision in the left eye, the patient was referred to a neurosurgeon. A left frontotemporal craniotomy was performed (see KCC 5.11), and a firm grayish reddish mass was carefully dissected off the sphenoid wing and removed from the orbit. Pathologic examination confirmed the diagnosis of meningioma. Postoperatively the patient did well, and she had no further problems.
CASE 12.1 ANOSMIA AND VISUAL IMPAIRMENT

Figure 12.21 Mass in Orbital Frontal Region T1-weighted MRI images with intravenous gadolinium enhancement. (A) Coronal image from a normal patient showing relationship of olfactory bulbs to the frontal lobes, and cribriform plate. (B, C) Coronal images from patient in Case 12.1, with B and C progressing from anterior to posterior.

CASE 12.1 (CONTINUED)

(C)

CASE 12.2 CHEEK NUMBNESS AND A BULGING EYE

Figure 12.22 Menigioma in Region of Left Foramen Rotundum Axial T1-weighted MRI with intravenous gadolinium contrast enhancement.
CASE 12.3 JAW NUMBNESS AND EPISODES OF LOSS OF CONSCIOUSNESS

MINICASE
A 24-year-old woman was admitted to the cardiology service after an episode of syncope. Upon further probing, it was found that the patient had had three prior episodes of loss of consciousness over recent years, during which she was unresponsive for a few minutes, had some poorly described shaking movements, and was then confused for up to a half an hour. On review of systems, the patient described a patch of numbness over her left jaw that had been present for approximately 2 years. Exam was normal except for decreased light touch, pinprick, and temperature sensation in the left jaw and lower face (Figure 12.23).

LOCALIZATION AND DIFFERENTIAL DIAGNOSIS
1. On the basis of the symptoms and signs shown in bold above, where is the lesion?
2. What is the most likely diagnosis, and what are some other possibilities?

Discussion
1. The key symptoms and signs in this case are:
   - Decreased light touch, pinprick, and temperature sensation in the left jaw and lower face
   - Episodes of unresponsiveness lasting for a few minutes, with shaking movements, followed by confusion for up to a half an hour

   The patient’s sensory loss was in the distribution of the mandibular division of the trigeminal nerve (CN V₃, see Figure 12.78). A lesion near the foramen ovale or of the mandibular division of CN V could therefore, explain the deficit (see Figures 12.3A, 12.7A). Brief episodes of unresponsiveness can have numerous causes (see KCC 10.3; Table 10.2). Over 90% of cases are non-neurologic in origin and are caused by transient hypoxemia (vasovagal syncope), cardiac arrhythmias, or other medical conditions. However, patients with cardiogenic syncope typically recover immediately after the episode ends. Persistent deficits, such as the confusion seen in our patient, suggest a neurologic cause such as seizures (see KCC 18.2), vertebrobasilar transient ischemic attack (see KCC 10.3, 14.3), or vertebrobasilar migraine (see KCC 5.1). The shaking reported in this patient is suggestive of seizures, although a better description would have been helpful. One way to unify this patient’s findings into a single diagnosis would be to postulate a mass lesion near the left foramen ovale that extends to the adjacent left medial temporal lobe, causing seizures. We will see in Chapter 18 that the fimbria structures of the temporal lobes are especially prone to epileptic seizures.

2. Possible causes of a lesion in the vicinity of the foramen ovale and medial temporal lobe include metastasis, meningioma, trigeminal neuroma, aneurysm of the petrous segment of the internal carotid artery, or sarcoidosis (see KCC 12.2).

Clinical Course and Neuroimaging
The patient underwent both an MRI and a CT scan of the head (Figure 12.24). Figure 12.24A is an axial proton density-weighted MRI image showing a roundish mass compressing the left medial temporal lobe, lying in the path of CN V in Meckel’s cave. Figure 12.24B is a coronal T1-weighted MRI image with gadolinium showing enhancement of the mass and extension downward through the foramen ovale. The “dumbbell” shape of this mass, extending through a bony foramen is typical of a schwannoma (see KCC 12.5).

Figure 12.24C is an axial CT scan image, using bone windows to demonstrate erosion of the mass through the temporal bone in the region of the left foramen ovale. The mass appeared to lie outside the substance of the brain and was felt to represent a schwannoma (trigeminal neuroma), meningioma, or giant aneurysm. The patient was started on anticonvulsant medications, and an angiogram was done, but no aneurysm was visualized. Therefore, she underwent a left frontal transtemporal craniotomy, and a tanish white mass was identified under the left temporal lobe. The tumor was carefully removed in a 10-hour operation, with care taken not to damage adjacent cranial nerves or blood vessels. Pathologic examination was consistent with a schwannoma.

Postoperatively the patient made an excellent recovery, with further seizures, but she had persistent numbness of the left jaw.

CASE 12.4 ISOLATED FACIAL WEAKNESS

MINICASE
A 26-year-old woman developed pain behind her left ear one evening. When she looked in the mirror the next morning, she noticed that her left face was drooping. In addition, her left ear was sensitive to loud sounds. She saw her physician, who gave her some medication for the pain, but over the next 2 days her left eye developed a "scratchy" painful sensation, so she came to the emergency room. Exam was notable for marked left facial weakness, including the forehead. Taste was not tested. The remainder of the exam was normal.

LOCALIZATION AND DIFFERENTIAL DIAGNOSIS
1. On the basis of the symptoms and signs shown in bold above, where is the lesion?
2. What is the most likely diagnosis, and what are some other possibilities?

Discussion
1. The key symptoms and signs in this case are:
   - Left retroauricular pain, hyperacusis, and facial weakness including the forehead
   - Painful, scratchy sensation in left eye

   This patient had lower motor neuron-type facial weakness (see Figure 12.10), together with hyperacusis and retroauricular pain on the left side. These findings are compatible with a lesion of the left facial nerve affecting the branchial motor and general somatic sensory function (see Table 12.6; Figures 12.7B, 12.10).

   The painful, scratchy eye is a bit of a puzzle. However, patients with a facial nerve lesion may have parasympathetic involvement (see Figure 12.10) causing decreased lacrimation; also they are often not able to completely close the affected eye, especially while they are sleeping, which can lead to corneal desiccation and corneal ulcers.

2. The time course, retroauricular pain, and lack of other medical problems or other findings on exam make Bell’s palsy the most likely diagnosis. For some other, less likely possibilities, see KCC 12.3.

Clinical Course
The patient was examined by an ophthalmologist but did not have corneal damage. She was given lubricating eyedrops and instructed to tape her left eyelid shut at night. In addition, she was treated with a brief course of oral steroids, Lyme titer, antinuclear antibody (ANA), and venereal disease research laboratory (VDRL) tests were undertaken and were negative. When
the patient was seen in follow-up 1 month later, her facial weakness had completely resolved. She also no longer had ear pain or hyperacusis.

Related Case. A CT scan from another patient with left facial weakness, including the forehead, is shown in Figure 12.25 (page 594). This patient was a 39-year-old woman who fell off the back of a pickup truck, striking her occiput on the pavement without loss of consciousness. In addition to left lower motor neuron-type facial weakness, her exam was notable for left hemotympanum (see Table 3.9) and decreased taste on the left side of the tongue (tested by use of a cotton swab and mustard; see neuroexam.com Video 41). Figure 12.25 shows CT scans sagittal reconstructions, which allow the course of CN VII to be followed through the temporal bone from medial to lateral. Note the presence of blood in the middle ear and several fractures of the temporal bone. At the time of discharge, this patient's facial weakness was unchanged, and she did not return for follow-up.

**CASE 12.3 JAW NUMBNESS AND EPISODES OF LOSS OF CONSCIOUSNESS**

Figure 12.24 Trigeminal Schwannoma Eroding through Left Foramen Ovale (A) Axial proton density-weighted MRI image. (B) Coronal T1-weighted image with intravenous gadolinium. (C) Axial CT scan image using bone windows.
CASE 12.5 HEARING LOSS AND DIZZINESS

CHIEF COMPLAINT
A 41-year-old woman was referred to an otolaryngologist for dizziness and progressive hearing loss in the left ear.

HISTORY
One year ago, the patient began having episodes of mild dizziness, which felt like the room was spinning when she moved her head. Two months ago, she noticed greatly reduced hearing in her left ear, making it impossible to use the telephone receiver unless it was on her right ear. In addition, she had some left facial pain and decreased taste on the left side of her tongue. Past medical history was notable for a melanoma resected from the right hip region 8 months previously, with one positive lymph node.

PHYSICAL EXAMINATION
Ears: Normal otoscopic exam of the external auditory canals and tympanic membranes.
Neck: Supple.
Lungs: Clear.
Heart: Regular rate with no murrums or gallops.
Abdomen: Benign.
Extremities: No edema.
Dermatologic: No skin lesions.
Neurologic exam: MENTAL STATUS: Alert and oriented x 3. Mildly anxious, but otherwise normal.

COGNITION: Normal on finger-to-nose and heel-to-shin testing.
Gait: Normal.
Sensory: Intact pinprick, vibration, and joint position sense.

LOCALIZATION AND DIFFERENTIAL DIAGNOSIS
1. On the basis of the symptoms and signs shown in bold above, where is the lesion?
2. What is the most likely diagnosis, and what are some other possibilities?

Discussion
1. The key symptoms and signs in this case are:
   - Decreased hearing in the left ear, with air conduction greater than bone conduction
   - Episodes of mild dizziness
   - Left facial pain and decreased left corneal reflex
   - Decreased taste on the left side of the tongue
2. The patient had hearing loss with sensorineural pattern that localized to the left cochlea or the left vestibulocochlear nerve (see KCC 12.5). Episodic dizziness can be caused by dysfunction anywhere in the pathways of vestibular sensation, including the labyrinth, vestibular ganglia, CN VIII, vestibular nuclei, or parietal cortex (see KCC 12.6). Given the sensorineural hearing loss, however, the dizziness is probably also caused by a problem in the left inner ear or CN VIII. Similarly, left facial pain (CN V), decreased corneal reflex (CN VII), or CN VII; see KCC 12.4) and decreased taste (CN VII) could each result from lesions in the left facial area or from lesions in the left brainstem. Since unilateral hearing loss must be caused by a lesion outside of the brainstem (see KCC 12.5), the most parsimonious explanation is a lesion in the left cerebellopontine angle, where CN V, VII, and VIII all lie in close proximity (see Figure 12.24,A).
3. The most likely clinical localization is CN V, VII, and VIII in the left cerebellopontine angle.
4. The most common lesion of the cerebellopontine angle is a schwannoma (see KCC 12.5). Our patient in this case recently had a melanoma, so metastasis should also be considered, especially since melanoma often metastasizes to the brain. Other less likely possibilities include meningioma, epidermoid, and glioma. Meningeal disease (see KCC 12.6) could account for hearing loss and dizziness, but not for this patient's abnormalities of CN V and VII.

Clinical Course and Neuroimaging
The otolaryngologist ordered a brain MRI with gadolinium and special thin cuts through the region of the internal auditory canal (Figure 12.26). In these T1-weighted images, an enhancing mass can be seen in the left cerebellopontine angle. The mass appears to lie entirely outside of the brainstem and has a lateral knot extending into the left internal auditory meatus in the petrous portion of the temporal bone. These findings are highly suggestive of an acoustic neuroma (vestibular schwannoma; see KCC 12.5).

The patient was referred to a neurosurgeon and admitted for removal of the tumor. As is often the case with this kind of surgery, the procedure was a collaboration between neurosurgery and otolaryngology. The left occipital bone was opened behind the transverse sinus, the dura was opened, and the left cerebellar hemisphere was gently retracted to reveal the tumor. The tumor was carefully dissected away from the adjacent cerebellum; pons; CN V, VII, IX, and X; and branches of the posterior inferior cerebellar artery (see Figure 15.2). The functioning of the facial nerve was monitored continuously during the resection by use of a stimulating electrode placed on CN VII and by EMG (electromyography); see KCC 9.2) leads placed in the orbicularis occuli and labial muscles. Thus, although the facial nerve was severely distorted by the tumor, its function was preserved. CN VII, however, was sacrificed because it was completely encapsulated by tumor, resulting in unilateral deafness. The pathology report confirmed schwannoma. Postoperatively the patient suffered from vertigo (see KCC 12.6) and had nystagmus at rest for 1 to 2 days, which then resolved. She also had complete left facial paralysis that resolved over the course of several months, and she subsequently did well.
**CASE 12.4 RELATED CASE**

Figure 12.235 Left Temporal Bone Fracture in Region of Facial Canal. Reconstructed sagittal CT scan images through the left temporal bone, with (A) through (D) progressing from medial to lateral.

- (A) Cochlea, Auditory canal (CN VII, VIII)
- (B) Region of genu of CN VII, Semicircular canals
- (C) Styloid process, Fracture, Blood in tympanic cavity (middle ear), Facial canal (CN VII)
- (D) External auditory meatus, Facial canal (CN VII), Temporomandibular joint, Stylomastoid fascia

**CASE 12.5 HEARING LOSS AND DIZZINESS**

Figure 12.236 Left Acoustic Neuroma (Vestibular schwannoma). Axial T1-weighted MRI images with intravenous gadolinium contrast. (A) and (B) are adjacent sections progressing from inferior to superior.

- (A) Temporal lobe, Cavernous sinus, Enhancing tumor, Vestibulocochlear nerve (CN VIII)
- (B) Medulla, Fourth ventricle, Pons, Petrous temporal bone, Region of internal auditory meatus
CASE 12.6 HOARSE VOICE FOLLOWING CERVICAL DISC SURGERY

MINICASE
A 38-year-old salesperson developed left neck and shoulder pain and evaluation revealed a cervical disc herniation, for which she underwent a discotomy and fusion via an anterior approach through the neck (see KCC 8.5). Her symptoms of cervical radiculopathy resolved. However, in the recovery room following surgery she noticed a marked change in her voice, which now had a breathy, "hoarse" quality. She was reassured that this was a temporary effect of the intubation. Nevertheless, over the next 2 months she continued to have severe breathlessness of her voice, making it difficult for her to do her work as a personal shopper. She was referred to an otolaryngologist for evaluation. Exam was normal, aside from the breathiness. Her voice had a soft breathy quality suggesting that an air leak was present in her larynx.

LOCALIZATION AND DIFFERENTIAL DIAGNOSIS
On the basis of the symptoms and signs shown in bold above, where is the lesion, and what is the most likely cause?

Discussion
The key symptoms and signs in this case are:

- Breathy "hoarse" voice

Breathlessness of the voice (often called hoarseness, although this is not strictly accurate) can be caused by any disorder that prevents complete closure of the vocal folds (true vocal cords) during phonation (see KCC 12.8). Incomplete vocal cord closure can be caused by lesions anywhere in the pathway from the medulla oblongata to the vagus nerve (CN X). To the recurrent laryngeal nerve, to the muscles of the larynx (see Figure 12.30). Given this patient's history of surgery on the left side of her neck, the most likely diagnosis is stretch injury or laceration of the left recurrent laryngeal nerve. Note that injury to the superior laryngeal nerve does not usually cause noticeable deficits, since it only supplies the cricothyroid muscle (a subtle deficit in reaching high notes is occasionally noted by professional singers), and injury of the vagus itself is uncommon during neck surgery because of its deep location.

Clinical Course and Videostroboscopic Imaging

To confirm the diagnosis, the otolaryngologist performed fiberoptic video imaging of the larynx using a laryngoscope inserted through the mouth (Figure 12.27). The process of stroboscopy matches the pharyngeal frequency to a strobe light and by offsetting the phase slightly, it gives the illusion of slow-motion vibratory cycles of the true vocal cords. This process demonstrated normal movement of the right cord during phonation and during breathing. However, the left cord was paralyzed, and remained in an abducted position. Thus, her left cord paralysis resulted in incomplete closure of the glottis during phonation and caused this patient's breathiness.

Although recurrent laryngeal nerve injuries sometimes recover over time, this patient was eager to have the problem fixed immediately because of the severity of her deficit, its duration, and the importance of her voice for her work. Therefore, she underwent a procedure in which a precisely curved silastic insert was placed into the left paraglottic space. The insertion was performed while visualizing the cords and testing voice quality until the left cord was restored to a sufficiently medial position to allow normal approximation of the cords during phonation. Follow-up over time showed that her left recurrent laryngeal nerve injury was indeed permanent. However, the procedure enabled an immediate and complete recovery of her normal voice.

CASE 12.7 HOARSENESS, WITH UNILATERAL WASTING OF THE NECK AND TONGUE MUSCLES

CHIEF COMPLAINT
A 34-year-old man was referred to an otolaryngologist for progressive hoarseness, dysphagia, and weakness of the left sternocleidomastoid and tongue.

HISTORY
Four months prior to presentation, the patient developed a persistent cough and respiratory infection that did not resolve. Soon afterward he noticed difficulty swallowing thick foods, and his voice gradually became hoarse. Three weeks prior to presentation, he began to have decreased hearing in the left ear, some ataxia in his tongue, and mild left-sided headache. He lost 40 pounds in the 4 months since developing symptoms.

PHYSICAL EXAMINATION
Heart: Regular rate with no gallops or murmurs.
Abdomen: Soft, nontender.
Extremities: Normal.
Neurologic examination:
cranial nerves: Pupils 4 mm. Contrasting 2 mm bilaterally. Visual fields full. Normal optic discs. Extracranial movements intact. Facial sensation intact to light touch and pinprick. Intact corneal reflexes. Mildly decreased left nasolabial fold. Decreased hearing to finger rub on the left. Gag intact. UVULA deviated to the right with palate elevation. Voice hoarse and breathy in quality. Left trapezius and sternomastoid muscles had fasciculations and strength of 4/5. Tongue had marked asymmetrical atrophy and fasciculations of the left side, with tongue deviating to the left on protrusion. On laryngoscopic examination, the left vocal cord was paralyzed (see Case 12.6). Motor: No pronator drift. SS5 power throughout.

Discussion
1. The key symptoms and signs in this case are:

- Difficulty swallowing, decreased left palatal movement, hoarseness, and left vocal cord paralysis
- Left trapezius and sternomastoid weakness and fasciculations
- Left tongue deviation, atrophy, and fasciculations
- Decreased hearing in the left ear
- Mildly decreased left nasolabial fold
- Alteration in taste
- Left-sided headache

This patient has multiple abnormalities of the cranial nerves on the left side of the head. Although each individual abnormality could be explained by a small brainstem lesion, all of the relevant nuclei could not be involved together without also involving other nearby structures, such as the anterolateral system, inferior cerebellar peduncle, and descending sympathetic pathway (see Figure 12.31). In addition, as in Case 12.5, the unilateral hearing loss suggests that the lesion lies outside of the brainstem (see KCC 12.3).

Taking each of the above deficits in turn, the swallowing muscles of the pharynx and the left palate are innervated by the left CN IX, although CN IX may contribute to the gag reflex as well. A lesion of the left CN X could also
explain hoarseness (breathiness) and left vocal cord paralysis, since the larynx is innervated by the vagus as well. Left trapezius and sternomastoid weakness and fasciculations suggest a lower motor neuron lesion (see KCC 6.3.) of the left spinal accessory nerve (CN XI). Similarly, deviation of the head to the left, with atrophy and fasciculations, suggests a lower motor neuron lesion of the left hypoglossal nerve (CN XII). Decreased hearing in the left ear can be caused by a lesion in the left external auditory canal, middle ear, cochlea, or vestibulocochlear nerve (CN VIII). Although a decreased left nasolabial fold could be caused by upper motor neuron- or mild lower motor neuron-type weakness, given the other findings a peripheral lesion of the left facial nerve (CN VII) is more likely. A facial nerve lesion could also explain the alteration in taste. Unilateral headaches can have many causes (see KCC 5.3), but in this setting they support the presence of an intracranial lesion on the left side of the head.

To summarize, this lesion involves CN VII, VIII, IX, X, XI, and XII on the left side. These cranial nerves exit the left lower brainstem and leave the cranium via the internal auditory meatus, jugular foramen, and hypoglossal canal (see Figures 12.2A-C, 12.3A-B; Table 12.2). Note that large lesions of cerebellar pontine angle usually involve CN V (see KCC 12.3 and Case 12.5). Since CN V was spared in this case, it suggests that the lesion lies farther down.

The most likely clinical localization is a large lesion lying just outside of the left ventrolateral medulla, or in the vicinity of the left internal auditory meatus, jugular foramen, and hypoglossal canal.

2. Possible lesions in this location include meningioma, schwannoma, metastases, granulomatous disease, and glomus tumors (see KCC 12.7).
CASE 12.7 HOARSENESS, WITH UNILATERAL WASTING OF THE NECK AND TONGUE MUSCLES

Figure 12.28 Left Glossus Jugularis Tumor (A) Axial T1-weighted MRI image with gadolinium. (B) Coronal T2-weighted MRI image.

CASE 12.8 UNCONTROLLABLE LAUGHTER, DYSPHORIA, DYSPHAGIA, AND LEFT-SIDED WEAKNESS

CHIEF COMPLAINT
A 27-year-old male saxophone player came to the emergency room because of worsening dysphoria, dysphagia, left-sided weakness, and episodes of uncontrollable laughter.

HISTORY
Two and a half years prior to presentation, the patient developed episodes of left face and mouth pain precipitated by chewing. One year prior to presentation, he started having episodes of uncontrollable laughter, not accompanied by appropriate affect. When he persisted in laughing repeatedly at his girlfriend's father's wake, he was referred to a psychiatrist, who tried behavior modification therapy without benefit. Two to 3 months prior to presentation, he developed increasing difficulty playing the saxophone, and he noticed slurred speech and occasional choking on his food. He found he also had an unstable gait, bumping into objects on his left side, difficulty buttoning his shirt with his left hand, and urinary urgency and difficulty initiating urination.

PHYSICAL EXAMINATION
Vital signs: T = 98°F, P = 72, BP = 130/70, R = 12.
Neck: Supple with no bruits.
Lungs: Clear.
Heart: Regular rate with no gallops or murmurs (but difficult exam because of frequent laughter).
Abdomen: Soft, nontender.
Extremities: Normal.
Neurologic exam:
Cranial Nerves: Pupils 4 mm, constricting to 2 mm bilaterally. Visual fields full. Normal optic discs.
Motor: Mild left pronator drift. Slowed finger tapping in the left hand. Tone slightly increased in left lower extremity. Power 4/5 in left deltoid, biceps, wrist extensors, finger extensors, iliotibial, hamstrings, tibialis anterior, and extensor hallucis longus, but otherwise 5/5 throughout.

COORDINATION: Finger-to-nose and heel-to-shin testing slowed, but without ataxia.
Gait: Slightly unsteady, with stiff left lower extremity.
Sensory: Intact light touch, pinprick, temperature, vibration, and joint position senses and graphesthesia.

LOCALIZATION AND DIFFERENTIAL DIAGNOSIS
1. On the basis of the symptoms and signs shown in bold above, which nerves (see Table 12.4) and which long tracts (see Chapters 6 and 7) are affected by the lesion?
2. In what general region of the nervous system can a single lesion produce all of these findings?
3. What are some possible lesions in this location?

Discussion
1. The key symptoms and signs in this case are:
   - Episodes of left face and mouth pain
   - Episodes of uncontrollable laughter not accompanied by appropriate affect
   - Dysarthria, dysphagia, absent gag reflex
   - Mild weakness of head turning to the left

*This patient was described previously as a case report by Shafqat et al. in Neurorogic Volume 90, pp. 1918-1919, 1998.
• Left face arm and leg weakness, with increased tone, hyperreflexia, and gait unsteadiness

• Urinary urgency and difficulty with initiation

The episodes of left face and mouth pain precipitated by chewing were initially suggestive of a trigeminal nerve (CN V) disorder, such as trigeminal neuralgia (see KCC 12.2). However, later findings suggest a lesion affecting central nervous system pathways. These include the development of pseudobulbar affect, suggesting a lesion of the corticobulbar pathways (see KCC 12.8), left hemiparesis with upper motor neuron signs compatible with corticobulbar and corticospinal dysfunction (see KCC 6.3), and urinary dysfunction, also compatible with impairment of descending pathways controlling micturition (see KCC 7.9). Dysesthesias, dysphagia, and absent gag reflexes (CN IX, X) in this patient, along with impaired CN XI function, further support a combination of cranial nerve dysfunction along with involvement of long tracts. These findings suggest a lesion affecting CN V, IX, X, and XI, as well as corticobulbar, corticospinal, and descending spinocerebellar pathways.

2. A lesion of the brainstem in the region of the pontine nuclei could affect these multiple cranial nerves and long tracts. A lesion affecting this many brainstem structures while preserving other brainstem nuclei and pathways would be fairly extensive, yet cause patchy involvement.

3. Given the gradual onset of symptoms over several years involving multiple brainstem structures, one possibility would be multiple sclerosis (see KCC 6.6) affecting primarily the brainstem. Other possibilities include a brainstem vascular malformation (see KCC 6.6), a granulomatous disorder such as sarcoidosis (see KCC 12.1), or a slow-growing tumor such as a brainstem glioma or meningioma (see KCC 5.8).

Clinical Course and Neuroimaging

The patient underwent a head CT scan in the emergency room revealing a mass lesion, which was better visualized by MRI scan (Figure 12.29). Note the presence of a large mass lying outside of the brain adjacent to the dura and enhancing uniformly with gadolinium, consistent with a meningioma (see KCC 5.8). The mass could be seen to cause severe compression and distortion of the pons and left middle cerebellar peduncle (see Figure 12.2A). The patient's relatively mild deficits given this degree of distortion attest to the chronic nature of this lesion. The mass could also be seen to extend into the region of Meckel's cave adjacent to the left cavernous sinus (see Figure 12.2A), possibly explaining the patient's early symptoms of left facial pain. The patient underwent a multistage resection, involving preoperative embolization by interventional radiology, and two collaborative operations involving teams of neurosurgeons and otolaryngologists. He made an excellent recovery with minimal deficits. On follow-up examination 1 year later, he still had new episodes of inappropriate laughter, and he had some mild diplopia that he had developed following surgery, but he was otherwise without deficits. Repeat MRI scan showed near complete removal of the tumor (see Figure 12.6C), with only a small portion left where it was adherent to CN IV.

Additional Cases

Related cases can be found in other chapters for: upper or lower motor neuron cranial nerve disorders (Cases 5.3, 5.5, 5.7, 5.8, 6.3, 6.5, 10.4, 10.5, 10.6, 11.1, 11.3, 13.1, 13.3, 13.5, 14.1, 14.4, 14.7, 15.4, 17.2, 18.2). Other relevant cases can be found using the Case Index.
**CASE 12.8 UNCONTROLLABLE LAUGHTER, DYSARTHRIA, DYSPHAGIA, AND LEFT-SIDED WEAKNESS**

Figure 12.29 Meningioma Compressing the Pons: T1-weighted MRI images with intravenous gadolinium enhancement. (A) Sagittal view. (B) Axial view. (C) Follow-up MRI axial view 1 year after surgery.

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**CASE 12.8 (CONTINUED)**

(B)

**Brief Anatomical Study Guide (continued)**

9. The facial nerve (CN VII) controls the muscles of facial expression to be distinguished from the trigeminal nerve that mediates facial sensation via fibers that arise from the facial nucleus in the pons (see Figure 12.11). The facial nerve travels along with CN VIII in the auditory canal and then exits the skull via the stylomastoid foramen (see Figures 12.30, 12.10). Upper motor neuron control of the facial nucleus is bilateral for the upper parts of the face, so in unilateral upper motor lesions the contralateral side can compensate, resulting in sparing of the upper face muscles (see Figure 12.13). The facial nerve also has sensory fibers that provide taste sensation for the anterior two-thirds of the tongue reaching the nucleus solitarius (see Figure 12.12), and somatic sensation fibers for a region around the outer ear traveling to the trigeminal nucleus (see Figure 12.78).

Sensory cell bodies lie in the geniculate ganglion. Parasympathetic arising from the superior salivatory nucleus travel in CN VII via the sphenopalatine ganglion and submandibular ganglion, respectively, to the lacrimal glands and salivary glands (see Figure 12.6).

10. The vestibulocochlear nerve (CN VIII) carries auditory information from the cochlea to the dorsal and ventral cochlear nuclei (see Figures 12.15-12.17). The primary sensory cell bodies lie in the spiral ganglion. Central auditory pathways cross multiple times, so unilateral lesions in the central nervous system do not cause clinically significant unilateral hearing loss (see Figure 12.16). Information about head position and acceleration is carried by the vestibular portions of CN VIII arising from the semicircular canals and otolith
Brief Anatomical Study Guide (continued)

organisms (see Figure 12.15). Primary cell bodies are in the vestibular ganglia, and this information travels to the vestibular nuclei in the brainstem to influence unconscious posture and balance, eye movements, and conscious perception of movement through multiple pathways (see, e.g., Figure 12.18).

11. The glossopharyngeal nerve (CN IX) exits the skull via the jugular foramen (see Figures 12.3A, B, 12.19, Table 12.2)). Motor fibers arising from the nucleus ambiguus provide innervation of the stylopharyngeal muscle, important for pharynx elevation during speech and swallowing. Sensory fibers from chemoreceptors and baroreceptors in the carotid body reach the caudal nucleus solitarius (cardiorespiratory nucleus). Taste sensory fibers from the posterior one-third of the tongue travel to the rostral nucleus solitarius (gustatory nucleus). Somatic sensation from the posterior tongue, pharynx, middle ear, and external ear travels via CN IX to the trigeminal nuclei. Finally, parasympathetic arising from the inferior salivatory nucleus activates the parotid salivary gland via the otic ganglion.

12. The vagus nerve (CN X) also has multiple functions, providing parasympathetic innervation for the viscera arising from the dorsal motor nucleus of CN X (see Figures 12.5, 12.20, see also Figure 14.5A, B). In addition, motor fibers of the vagus arising from the nucleus ambiguus supply the pharynx (swallowing) and larynx (voice). Sensory fibers from the aortic arch travel to the caudal nucleus solitarius. Sensory fibers for the pharynx, larynx, outer ear, and meninges of the posterior fossa travel to the trigeminal nuclei.

13. The spinal accessory nerve (CN XI) (see Figure 12.2A, C) arises from the spinal accessory nucleus (see Figure 12.5) and innervates the sternomastoid and upper portions of the trapezius muscles. Because of the mechanical attachments of the sternomastoid muscle, lesions of CN XI cause weakness of head turning to the side opposite the lesion.

14. The hypoglossal nerve (CN XII) (see Figure 12.2A, C) arises from the hypoglossal nucleus (see Figures 12.4, 12.5) and supplies intrinsic tongue muscles. Hypoglossal nerve lesions cause the tongue to deviate toward the side of the lesion when the tongue is protruded.

References

General References


Cribiform and Suprasellar Meningiomas


Central Nervous System Sarcomatosis


Trigeminal Nerve Lesions


Facial Nerve Lesions


Acoustic Neurona


Globus Jugulare

Brainstem II: 
Eye Movements and Pupillary Control

Damage to the eye movement pathways can interfere with normal vision and can also affect pupil and eyelid control. A 48-year-old woman developed gradually worsening left eye pain and double vision over the course of 18 months. Her left pupil appeared dilated and did not constrict in response to light. Her left eye had limited upgaze, downgaze, and medial gaze, but normal lateral gaze. In addition, her left upper eyelid drooped about 3 mm lower than the right one. In this chapter we will learn about the brainstem circuits, nerves, and muscles involved in movement of the eyes, eyelids, and pupils, and about the effects of lesions or illness on these functions.
ANATOMICAL AND CLINICAL REVIEW

Movement of the eyes and pupils occurs continuously, mostly imperceptible to us, and enables us to maximize the information derived from the relatively small visual area represented in the fovea. Abnormalities of the pupils and eye movements are often warning signs of pathology in the brainstem or cranial nerves and should therefore be evaluated carefully. In this chapter we will discuss the anatomy of both the extracocular muscles that cause the eye to move within the orbits and the internal ocular muscles that control pupillary size and lens accommodation. We will also discuss common disorders affecting these systems. Eye movement disorders and pathways are often separated into two levels:

1. **Nuclear and infranuclear pathways** involve the brainstem nuclei of CN III, IV, and VI; the peripheral nerves arising from these nuclei; and the eye movement muscles.

2. **Supranuclear pathways** involve brainstem and forebrain circuits that control eye movements through connections with the nuclei of CN III, IV, and VI.

We will follow this bipartite organization in this chapter. First we will discuss the peripheral course of CN III, IV, and VI, the muscles innervated by them; and the locations of their brainstem nuclei. Next we will discuss the central and peripheral pathways involved in pupillary control. Then we will discuss CNS supranuclear pathways that control extracocular movements through connections with the nuclei of CN III, IV, and VI. By understanding the anatomy of eye movements and pupillary control, we can often use the neurologic exam to localize a lesion in the central nervous system or the periphery, providing essential guidance to further diagnostic tests and therapeutic interventions.

Extraocular Muscles, Nerves, and Nuclei

The mechanical systems and information processing involved in eye movement control constitute a remarkable design in natural engineering. The muscles, nerves, and nuclei described in this section enable precise, smooth, and rapid eye movements to occur in a synchronized and coordinated fashion.

**Extracocular Muscles**

There are six extracocular muscles for each eye (Figure 13.1). The lateral rectus, medial rectus, superior rectus, and inferior rectus muscles move the eye laterally, medially, superiorly, and inferiorly, respectively (see Figure 13.1A). These muscles originate in a common tendinous ring at the orbital apex and insert onto the sclera. In addition to the simple horizontal and vertical eye movements performed by the rectus muscles, there are also **torsional** movements, in which the eye is rotated slightly about its axis. To provide balanced torsional movements, there are two more extracocular muscles: the superior and inferior obliques (see Figure 13.1B). The **superior oblique** muscle originates on the sphenoid bone in the posterior medial orbit and passes anteriorly through the *trochlea*, a pulley-like fibrous loop on the medial superior orbital rim (see Figure 13.1D). It then inserts on the superior surface of the eye to produce internal or movement of the upper pole of the eye inward (see Figure 13.1D). Meanwhile, the **inferior oblique** has no trochlea, but it originates along the anterior medial orbital wall and inserts on the inferior surface of the eye to produce external, or movement of the upper pole of the eye outward.

The movement produced by an extracocular muscle depends on the direction in which the muscle pulls relative to the main axis of the eye (see Figure 13.1C,D). Therefore, as the eyes move by rotating in the orbit, the extracocular muscles can have different actions (Table 13.1). Thus, depending on eye position, the rectus muscles can also produce torsional eye movements, and the oblique muscles can make important contributions to vertical eye movements. For example, when the eyes are facing forward, the superior rectus attaches to the eye at an angle of 23° to the eye's main axis (see Figure 13.1C). Therefore, contraction of the superior rectus causes both elevation and internation of the eye. Conversely, contraction of the inferior rectus causes depression and eversion. If an eye is abduced (moving horizontally toward the temple) by 25° so that its axis lines up with the superior rectus muscle, this muscle will now cause a pure elevation movement of the eye. If the eye is adducted (moving horizontally toward the nose), the superior rectus has more of an intorsion action. Similarly, as shown in Figure 13.1D, the superior and inferior oblique muscles contribute to vertical movements of the eye. For example, when the eye is adducted (left eye in Figure 13.1D), the superior oblique comes more in line with the axis of the eye and therefore causes depression. Likewise, the inferior oblique causes elevation, especially when the eye is adducted. However, as the eye is adducted (right eye in Figure 13.1D)
TABLE 13.1 Actions and Innervation of the Extraocular Muscles

<table>
<thead>
<tr>
<th>MUSCLE</th>
<th>MAIN ACTIONS ON THE EYE</th>
<th>COMMENTS</th>
<th>INNERRATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lateral rectus</td>
<td>Abduction</td>
<td>Abduction = temporal (lateral) movement of eye</td>
<td>Abducens nerve (CN VI)</td>
</tr>
<tr>
<td>Medial rectus</td>
<td>Adduction</td>
<td>Adduction = nasal (medial) movement of eye</td>
<td>Oculomotor nerve (CN III)</td>
</tr>
<tr>
<td>Superior rectus</td>
<td>Elevation and intorsion</td>
<td>Elevation increases with abduction; intorsion increases with abduction</td>
<td>Oculomotor nerve (CN III)</td>
</tr>
<tr>
<td>Inferior rectus</td>
<td>Depression and exintorsion</td>
<td>Depression increases with abduction; exintorsion increases with abduction</td>
<td>Oculomotor nerve (CN III)</td>
</tr>
<tr>
<td>Inferior oblique</td>
<td>Elevation and exintorsion</td>
<td>Elevation increases with abduction; exintorsion increases with abduction</td>
<td>Oculomotor nerve (CN III)</td>
</tr>
<tr>
<td>Superior oblique</td>
<td>Depression and intorsion</td>
<td>Depression increases with abduction; intorsion increases with abduction</td>
<td>Trochlear nerve (CN IV)</td>
</tr>
</tbody>
</table>

...the superior oblique becomes more perpendicular to the eye's axis and therefore causes mainly intorsion. Similarly, the inferior oblique causes mainly ex torsion when the eye is abducted. The main actions of the extraocular muscles are summarized in Table 13.1.

Other eye muscles will be discussed in this chapter that are not extraocular muscles. These include the levator palpebrae superior, which elevates the eyelid; the pupillary constrictor and dilator muscles, which cause the pupil to become smaller and larger; and the ciliary muscle, which adjusts the thickness of the lens in response to viewing distance.

Extraocular Nerves and Nuclei

The oculomotor (CN III), trochlear (CN IV), and abducens (CN VI) nerves pass through the cavernous sinus and then enter the orbit through the superior orbital fissure (see Figure 12.3A,C). The **oculomotor nerve** (CN III) supplies all extraocular muscles except the lateral rectus and superior oblique. Shortly after entering the orbit, the oculomotor nerve splits into two major branches. The **superior division** supplies the superior rectus and also innervates the levator palpebrae superioris, a muscle important for eyelid elevation. The **inferior division** of the oculomotor nerve supplies the medial rectus, inferior rectus, and inferior oblique muscles. The oculomotor nerve also carries preganglionic parasympathetic fibers to the pupillary constrictor muscles and to the ciliary muscles of the lens (see Figure 12.6). The **trochlear nerve** innervates the superior oblique muscle, and the **abducens nerve** innervates the lateral rectus (see Table 13.1).

Recall that the oculomotor (CN III), trochlear (CN IV), and abducens (CN VI) nuclei, together with the hypoglossal (CN XII) nucleus, constitute the somatic motor column of cranial nerve nuclei (see Figure 12.5; Table 12.3). These nuclei all lie near the midline, adjacent to the ventricular system, and their fibers exit the brainstem ventrally near the midline, with the exception of CN IV, which exits dorsally (see Figure 12.2). Let's discuss each of these nuclei and the intracranial segments of these nerves in more detail.

The **oculomotor nuclei** are located in the upper midbrain at the level of the superior colliculus and red nuclei, just ventral to the periaqueductal gray matter.
TABLE 13.2 Subnuclei of the Oculomotor Nucleus (CN III) and Their Functions

<table>
<thead>
<tr>
<th>Subnuclei</th>
<th>Muscles Innervated</th>
<th>Side Innervated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edinger-Westphal</td>
<td>Superior oblique</td>
<td>Right</td>
</tr>
<tr>
<td>Dorsal nucleus</td>
<td>Inferior rectus</td>
<td>Left</td>
</tr>
<tr>
<td>Intermediate nucleus</td>
<td>(superior rectus)</td>
<td>Superior oblique</td>
</tr>
</tbody>
</table>
On examination, eye movements are usually reported in degrees or millimeters from the primary position. When an extracocular muscle is not working properly, a **dysconjugate gaze** results, causing diplopia. A helpful rule of thumb is that the image further toward the direction of gaze is brought closer to the normal eye by the abnormal eye. For example, when looking at an object to the right, if one eye does not move to the right then it will form a second image that appears displaced to the right.

The **red glass test** can also be helpful in examining patients with diplopia. A transparent piece of red glass or plastic is held over one eye, usually the right, and a small white light is held directly in front of the patient. The image seen by the right eye is therefore red, and the image seen by the left eye is white. The patient is then asked to follow the light as it is moved to different positions of gaze, and to report the locations of the white and red images. Normally the white and red images are fused in all positions of gaze. Examples of the red glass test in different kinds of diplopia are shown in Figures 13.5-13.7. More quantitative methods for measuring diplopia—usually employed by eye movement specialists—are also available.

Abnormal lateral deviation of one eye is called **exotropia**, and abnormal medial deviation is called **esotropia**. Vertical deviation is usually described only with respect to the eye that is higher, and it is called **hypertropia**. A useful test for subtle dysconjugate gaze is to shine a flashlight directly in front of the patient on both eyes simultaneously, and then to examine the position of the reflection of the light on each cornea. Normally the reflection is symmetrical on the two corneas. Another helpful test for subtle eye muscle weakness is the **cover-uncover test**. Visual input normally helps maintain the eyes yoked in the same direction. Therefore, when an eye is covered while looking in the direction of a fixed mark, it may drift slightly back toward the neutral position. This mild weakness present only with an eye covered is called a **phoria** (as in exophoria, esophoria, etc.) in contrast to a tropia.

In young children, because the visual pathways are still developing, concomitant eye muscle weakness can produce **strabismus** (dysconjugate gaze) that over time causes suppression of one of the images, resulting in **amblyopia** (decreased vision in one eye). For this reason, early intervention is essential.

Complete disruption of oculomotor nerve function causes paralysis of all extracocular muscles except for the lateral rectus and superior oblique. Therefore, the only remaining movements of the eye are some abduction and some depression and intorsion (see Figure 13.1, Table 13.1). Because of decreased tone in all muscles except the lateral rectus and superior oblique, the eye may come to lie in a “down and out” position at rest (Figure 13.5A). In addition, paralysis of the levator palpebrae superior causes the eye to hang open (complete ptosis) unless the upper lid is raised with a finger. The pupil is dilated and unresponsive to light because of involvement of the parasympathetic fibers that run with the oculomotor nerve.

Partial impairment of oculomotor nerve function can cause different combinations of these findings to appear in milder form. For example, the eye movements may be impaired, with minimal pupil abnormalities, or the pupil may be involved, with only mild eye movement abnormalities.

When the examiner takes the history of someone with oculomotor palsy, the patient may report that the diplopia is worse when looking at near objects and better when looking at distant objects, since convergence is impaired. Red glass testing in third-nerve palsy generally reveals better diplopia that is most severe when looking up and medially with the affected eye (see Figure 13.5B).

Common causes of oculomotor nerve palsy include diabetic neuropathy and head trauma in which shearing forces damage the nerve. Another important cause of oculomotor palsy is compression of the nerve by intracranial aneurysms, most often arising from the junction of the posterior communicating artery (Pcom) with the internal carotid artery (see Figures 13.2, 5.6; KCC 5.6). Less commonly, third-nerve palsy can be caused by aneurysms arising from the Pcom—posterior cerebral artery (PCA) junction, from the basilar artery— PCA junction, or from the basilar artery—superior cerebellar artery (SCA) junction (see Figure 5.20). The oculomotor nerve can also be damaged by other abnormalities in the subarachnoid space, cavernous sinus, or orbit, such as infection, tumor, or venous thrombosis. Herniation of the medial temporal lobe over the edge of the tentorial cerebellum can compress the oculomotor nerve (see Figure 13.2; see also Figure 5.6). Recall that in addition to an ipsilateral oculomotor nerve palsy, transsellar uncinate herniation also often causes coma and hemiplegia (see KCC 5.6). Ophthalmoplegic migraine is a condition usually seen in children that causes reversible oculomotor nerve palsy. Lesions in the midbrain such as lacunar infarcts (see KCC 10.4), or other infarcts involving the oculomotor nucleus or the exiting nerve fascicles, can also cause an oculomotor palsy (see Figure 14.20A, Table 14.9; see also Table 13.2). In addition, muscle disorders or disorders of the neuromuscular junction such as myasthenia gravis (see KCC 8.1), can sometimes mimic the eye movement abnormalities and ptosis seen in oculomotor palsy.

Since aneurysms can cause life-threatening intracranial hemorrhage (see KCC 5.6), there should be a high index of suspicion for aneurysms in patients presenting with third-nerve palsy. Aneurysms classically cause a painful **oculomotor palsy that involves the pupil**. The oculomotor palsy may be subtle or complete. These patients should be considered to have a Pcom aneurysm until proven otherwise. A good-quality CT or MRI/MRA scan should be done without delay, followed immediately by a conventional four vessel angiogram, to establish the diagnosis and guide treatment. Complete oculomotor palsy that spares the pupil is not caused by aneurysms (with rare exceptions); it is usually caused by diabetes. The reason is thought to be that the parasympathetic fibers are located near the surface of the nerve, and if the nerve compression is severe enough to cause complete paralysis of the muscles innervated by CN III, then the pupillary fibers should be involved as well.

In partial oculomotor palsy that spares the pupil, the findings could be caused by partial compression of CN III by an aneurysm, so an angiogram is usually necessary.
Lesions of the oculomotor nerve within the orbit can sometimes affect the superior division or inferior division in isolation. A lesion of the superior division causes weakness of the superior rectus and levator palpebrae superioris, producing so-called double elevator palsy.

**KEY CLINICAL CONCEPT**
**TROCHLEAR PALSY (CN IV)**

The trochlear nerve produces depression and intorsion of the eye. Therefore, in trochlear nerve palsy there is **vertical diplopia**. If the weakness is severe, the affected eye may show **hypovertroopia** (Figure 13.6A). There may also be exotropia of the eye, which is not usually visible to the examiner. Patients with trochlear nerve palsy often report that they can improve the diplopia by looking up (chin tuck) and by **tilting the head away from the affected eye** because these maneuvers compensate for the hypertropia and exotropia, respectively (see Figure 13.6A). In addition, recall that the depressing action of the superior oblique is most pronounced when the eye is adducted (see Figure 13.1D; Table 13.1). Therefore, the vertical diplopia is most severe when the affected eye is looking downward and toward the nose, which can be confirmed with red glass testing (see Figure 13.6B). To summarize, diagnosing a fourth-nerve palsy usually involves demonstrating typical findings through the following four steps (Fick's three-step test, plus the "missing step"):

1. The affected eye has hypertropia.
2. Vertical diplopia worsens when the affected eye looks nasally.
3. Vertical diplopia improves with head tilt away from the affected eye.
4. Vertical diplopia worsens with downgaze.

Another test that is sometimes useful is to have the patient look at a horizontal line. In a trochlear-nerve palsy, the patient will see two lines, with the lower line tilted (see Figure 13.6C). These two lines form an arrowhead, with the "point" directed toward the affected side.

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**REVIEW EXERCISE**

How would the eyes appear and what head position would be seen in a patient with a complete left trochlear nerve palsy? Draw the expected results of red glass testing for this patient. (Compare to Figure 13.6.)

---

Lesions of the abducens nerve produce **horizontal diplopia**. In some cases esovertroopia (see KCC 13.1 of the affected eye may be present as well. In contrast to a third-nerve palsy, patients report that the diplopia is better when they are viewing near objects and worse when they are viewing far objects. On examination, the affected eye does not abduct normally (Figure 13.7A). In milder abducens palsy there may simply be incomplete "burial of the sclera," on lateral gaze. Diplopia worsens when the patient tries to abduct the affected eye, which can be confirmed by red glass testing (Figure 13.7B). Some patients may tend to turn the head toward the affected eye in an effort to compensate for the diplopia. A stable sixth-nerve palsy can sometimes be detected.

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**KEY CLINICAL CONCEPT**
**ABDUCENS PALSY (CN VI)**

The relationship between compensatory head positions and eye movement abnormalities can easily be remembered because the head movement is always in the direction of action normally served by the affected muscle. For example, in a right abducens palsy the head is held down and tilted to the left; the normal action of the right abducens nerve is depression and intorsion of the eye. The trochlear nerve is the most commonly injured cranial nerve in head trauma, probably because of its long course and thin caliber, making it susceptible to shearing injury. Other causes of trochlear nerve pathology are the subarachnoid space, cavernous sinus, or orbit include neoplasm, infection, and aneurysms. In many cases the cause remains unknown, and these cases may be caused by microvascular damage to the nerve, especially in patients with diabetes. Vascular or neoplastic disorders within the midbrain or near the pons (e.g., pineal gland or anterior cerebellum) can also affect the trochlear nuclei or nerve fascicles.

Other causes of **vertical diplopia** include disorders of extraocular muscles, myasthenia gravis, lesions of the superior division of the oculomotor nerve affecting the superior rectus, and skew deviation. **Skew deviation** is defined as a vertical disparity in the position of the eyes of supranuclear origin. Unlike trochlear palsy, skew deviation the vertical disparity is typically (but not always) relatively constant in all positions of gaze. Skew deviation can be caused by lesions of the cerebellum, brainstem, or even the inner ear.

Other causes of head tilt include cerebellar lesions, meningiomas, incipient anterior herniation, and torticollis. It is often helpful to look at old photographs to establish if the head tilt is old or new.

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**Figure 13.6** Trochlear Nerve (CN IV) Palsy (A) Appearance of eyes in the presence of a right trochlear nerve palsy. Hypertroopia can be compensated for by tucking the chin and looking up slightly. Exotropia can be compensated for by tilting the head away from the affected eye. (B) Results of red glass testing with right trochlear nerve palsy. Red glass was placed over the right eye. (C) Appearance of a horizontal white line to the patient with a red glass over the right eye.

**Figure 13.7** Abducens Nerve (CN VI) Palsy (A) Appearance of eyes in three different positions of gaze, in the presence of a right abducens nerve palsy. Red glass testing in the same three positions of gaze, with right abducens nerve palsy. Red glass was placed over the right eye.
The Pupils and Other Ocular Autonomic Pathways

The pupils are controlled by both parasympathetic and sympathetic pathways. The parasympathetic pathways involved in pupillary constriction are shown in Figure 13.8 (see also Figure 12.6). Light entering one eye activates retinal ganglion cells, which project to both optic tracts because of fibers crossing over in the optic chiasm. Fibers in the extraganglionate pathway continue in the brachium of the superior colliculus past the lateral geniculate nucleus to reach the pretectal area (Figure 13.6) as seen also Figure 11.6) just medial to the midbrain. After synapsing, axons then travel bilaterally to the Edinger-Westphal nuclei, which contain preganglionic parasympathetic neurons. Some of the crossing fibers travel in the posterior commissure (see Figure 13.8; see also Figure 12.1). The Edinger-Westphal nuclei lie just dorsal and anterior to the oculomotor (CN III) nuclei near the midline (see Figures 13.3, 14.3A). Preganglionic parasympathetic fibers travel bilaterally from the Edinger-Westphal nuclei via the oculomotor nerves to reach the ciliary ganglia in the orbit (see Figure 13.8). From there, postganglionic parasympathetic fibers continue to the pupillary constrictor muscles to cause the pupils to become smaller. Note that a light shine in one eye causes a direct response in the same eye and a consensual response in the other eye (see neuroex.com Video 29) because information crosses bilaterally at multiple levels.

Bilateral pupillary constriction also occurs through a slightly different circuit during the accommodation response (see neuroex.com Video 31). This response occurs when a visual object moves from far to near, and it has the following three components:

- Pupillary constriction
- Accommodation of the lens ciliary muscle
- Convergence of the eyes

The accommodation response is activated by visual signals relayed to the visual cortex (see Figure 13.8). From there, through pathways still under investigation, the pretectal nuclei are again activated, causing bilateral pupillary constriction mediated by the parasympathetic pathways shown in Figure 13.8. Contraction of the ciliary muscle of the lens is parasympathetically mediated by the same pathway. The lens is normally under tension from the suspensory ligament (Figure 13.9A). The ciliary muscle acts as a sphincter (like the pupillary constrictor), so when it contracts it causes the suspensory ligament to relax, producing a rounder, more convex lens shape (Figure 13.9B). Convergence is mediated by mechanisms described later in this chapter.
Figure 13.9 Actions of the Ciliary Muscle and the Pupilary Muscles
(A) When viewing a distant object, the ciliary muscle and the pupilary constrictor muscle are relaxed. (B) When viewing a near object, the ciliary muscle and the pupilary constrictor muscle contract.

Figure 13.10 Sympathetic Pathways Causing Pupillary Dilation

The sympathetic pathway responsible for pupillary dilation is shown in Figure 13.10. A descending sympathetic pathway from the hypothalamus travels in the lateral brainstem and cervical spinal cord to reach thoracic spinal cord levels T1 and T2. This pathway is thought to be in approximately the same location in the brainstem as the spinothalamic tract (see Figure 13.10; see also Figure 7.2) because lesions of the spinothalamic tract tend to be associated with Horner's syndrome (see KCC 13.5, 13.6). This descending sympathetic pathway activates preganglionic sympathetic neurons in the intermediolateral cell column of the upper thoracic cord (see Figure 13.10, inset; see also Figures 6.12B, 6.13A). Axons of the preganglionic sympathetic neurons exit the spinal cord via ventral roots T1 and T2, and skirt the apex of the lung before joining the paravertebral sympathetic chain via white rami communicantes. The axons ascend to synapse in the superior cervical ganglion. From there, postganglionic sympathetic fibers ascend through the carotid plexus along the walls of the internal carotid artery, ultimately reaching the pupilary dilator muscle (see Figures 13.9A, 13.10).

This sympathetic pathway is also important in controlling the smooth muscle of the superior tarsal muscle (Müller's), which elevates the upper lid, causing a wide-eyed stare in conditions of increased sympathetic outflow. Recall that the levator palpebrae superioris is composed of skeletal muscle and also functions in eyelid opening under the control of CN III. Sympathetics from the pathway shown in Figure 13.10 also innervate the smooth muscle of the superior palpebral (Müller's), which prevents the eye from sinking back in the orbit, as well as the cutaneous arteries and sweat glands of the face and neck. These various sympathetic functions are impaired in Horner's syndrome (see KCC 13.5, 13.6).

Abnormalities of the pupil can be caused by peripheral or central lesions, by sympathetic or parasympathetic lesions, or by disorders of the iris or visual pathways. Pupillary abnormalities can be bilateral or can affect one side only, in which case anisocoria, or pupillary asynergy, is present. In the subsections that follow, we will review the anatomical basis of several important pupillary abnormalities.

Oculomotor Nerve Lesion
As discussed earlier under oculomotor palsy (see KCC 13.2), lesions of the efferent parasympathetic pathway from the Edinger-Westphal nucleus to the pupilary constrictor muscle (see Figure 13.8) can cause impaired pupillary constriction, resulting in a dilated pupil. When the lesion is complete, the pupil is of large size and is sometimes called a "blown pupil." The anisocoria is more obvious in ambient light than in a darkened room (Table 13.3A). There is a decreased or absent direct response when light is shone in the affected eye, as well as a decreased or absent consensual response when light is shone in the opposite eye.

Horner's Syndrome
This important constellation of findings is caused by disruption of sympathetic pathways to the eye and face (see Figure 13.10). The classic syndrome consists of ptosis, miosis, and anhidrosis, as well as several other minor abnormalities. Ptosis, or upper eyelid drooping, is caused by loss of innervation to Müller's smooth muscle in the upper lid. Miosis, or decreased pupil size, is caused by loss of sympathetic innervation to the pupil dilator muscle, resulting in impaired dilation of the pupil. Unlike oculomotor nerve lesions, anisocoria is more obvious in the dark than in ambient light (Table 13.3B). Careful observation can reveal that the pupil still has a direct and consensual constractive response to light. However, there is a dilation lag relative to the normal pupil when the light is removed. Testing the ciliospinal reflex is some-

**REVIEW EXERCISE**
Fill in the blanks: Preganglionic parasympathetic fibers travel from the ______ nucleus in the midbrain via the ______ nerve to reach neurons in the ______ ganglion. The postganglionic parasympathetic fibers, in turn, project to the pupilary ______ muscle of the iris. (See Figure 13.8.)

**KEY CLINICAL CONCEPT PUPILARY ABNORMALITIES**

**REVIEW EXERCISE**
Fill in the blanks: Fibers controlling sympathetic outflow descend from the hypothalamus through the ______ (medial or lateral) brainstem and spinal cord to reach preganglionic sympathetic neurons in the ______ cell column. These exit via the ______ and ______ roots and ascend in the sympathetic chain to synapse on neurons in the ______ ganglion. The postganglionic sympathetic fibers then ascend along the carotid plexus to ultimately reach the pupilary ______ muscle of the iris. (See Figure 13.10.)
Table 13.3: Common Pupil Abnormalities

<table>
<thead>
<tr>
<th>LESION OR CONDITION</th>
<th>DARK ROOM AMBIENT LIGHT DIRECT RESPONSE: LIGHT IN AFFECTED EYE</th>
<th>CONSENSUAL RESPONSE: LIGHT IN UNAFFECTED EYE</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Left oculomotor nerve lesion</td>
<td><img src="image1" alt="Image" /> <img src="image2" alt="Image" /></td>
<td><img src="image3" alt="Image" /> <img src="image4" alt="Image" /></td>
<td>There may be associated ptosis and eye movement abnormalities.</td>
</tr>
<tr>
<td>B. Left Horner's syndrome</td>
<td><img src="image5" alt="Image" /> <img src="image6" alt="Image" /></td>
<td><img src="image7" alt="Image" /> <img src="image8" alt="Image" /></td>
<td>There is a dilation lag in going from light to dark. Other features of Horner's syndrome (ptosis, anhidrosis) may be present.</td>
</tr>
<tr>
<td>C. Left afferent pupillary defect</td>
<td><img src="image9" alt="Image" /> <img src="image10" alt="Image" /></td>
<td><img src="image11" alt="Image" /> <img src="image12" alt="Image" /></td>
<td>The swinging flashlight test is useful in subtle cases.</td>
</tr>
<tr>
<td>D. Benign essential anisocoria</td>
<td><img src="image13" alt="Image" /> <img src="image14" alt="Image" /></td>
<td><img src="image15" alt="Image" /> <img src="image16" alt="Image" /></td>
<td>The same relative anisocoria is present in all lighting conditions. No dilation lag.</td>
</tr>
</tbody>
</table>

Afferent Pupillary Defect (Marcus Gunn Pupil)

In this condition, the direct response to light in the affected eye is decreased or absent, while the consensual response of the affected eye to light in the opposite eye is normal (see Table 13.3C). The afferent pupillary defect is caused by decreased sensitivity of the affected eye to light, resulting from lesions of the optic nerve, retina, or eye. Recall that lesions at or behind the optic chiasm would affect inputs from both eyes (see Figure 13.8) and therefore do not generally produce a Marcus Gunn pupil. A useful way to detect an afferent pupillary defect is with the swinging flashlight test [neurocom.com Video 30]. The flashlight is moved back and forth between the eyes every 2 to 3 seconds. The afferent pupillary defect becomes obvious when the flashlight is moved from the normal to the affected eye, and the affected pupil dilates in response to light (see Table 13.3C). This abnormal dilation should be distinguished from nistagmus, which is a normal brief oscillation of the pupil size that sometimes occurs in response to light.

Essential Physiological Anisocoria

A slight pupillary asymmetry of less than 0.6 millimeters is seen in 20% of the general population. This asymmetry can vary from one examination to the next, sometimes within a few hours. There are no other associated abnormal findings, such as dilation lag, changes in the asymmetry with lighting conditions, or eye movement abnormalities (see Table 13.3D).

Pharmacological Miosis and Mydriasis

Numerous pharmacological agents can affect pupillary size and can cause confusion in diagnosis, particularly in the comatose patient. Opiates cause bilateral pinpoint pupils, and barbiturate overdose can also cause bilateral small pupils, mimicking pontine lesions. Anticholinergic agents affecting muscarinic receptors, such as scopolamine or atropine, can cause dilated pupils. Pupillary dilation may be unilateral if topical exposure occurs in one eye only; mimicking central herniation. When exposure to anticholinergic agents is suspected, 1% pilocarpine eye drops can be useful because they cause pupillary constriction in parasympathetic lesions but cannot overcome pharmacological muscarinic blockade. In general, diagnosis and treatment of suspected acute brainstem lesions should not be delayed, but the history should include possible drug exposure, and laboratory testing must include a toxicology screen. Pharmacological testing using eye drops containing cocaine, hydromorphone, or different strengths of pilocarpine can be useful for establishing the diagnosis in cases of anisocoria with equivocal or subtle findings (see the references for additional details).

Light-Near Dissociation

In light-near dissociation, the pupils constrict much less in response to light than to accommodation (see Figure 13.8). The mechanism for this disparity is not known for certain, and the mechanism may not be the same in different disorders. The classic example of light-near dissociation is the Argyll Robertson pupil associated with neurosyphilis, in which, in addition to light-near dissociation, the pupils are also small and irregular. Light-near dissociation can also be seen in diabetes and Adie's myotic pupil (see the next subsection), and as

*Optic tract lesions (an uncommon disorder) can reportedly be associated with a consensual afferent pupillary defect. In addition, with specialized testing (in which a light is shone onto one-half of the retina at a time), an afferent pupillary defect can be demonstrated in the ipsilateral heminoma of both eyes for lesions behind the optic chiasm.
part of Parinaud’s syndrome (see KCC 13.9), which is associated with compression of the dorsal midbrain.

**Adie’s Myotonic Pupil**

This disorder is characterized by degeneration of the ciliary ganglion or postganglionic parasympathetic neurons (see Figure 13.8) resulting in a mid-dilated pupil that reacts poorly to light. Some pupillary constriction can be elicited with the accommodation response, but the pupil then remains constricted and dilates very slowly. The cause is not known.

**Midbrain Corectopia**

In this relatively rare condition, lesions of the midbrain can sometimes cause an unusual pupillary abnormality in which the pupil assumes an irregular, off-center shape.

**Eye opening** is performed by striated skeletal muscle of the levator palpebrae superior (CN III) together with Müller’s smooth muscle in the upper lid (sympathetics). The frontal muscle of the forehead (CN VI) performs an accessory role. **Eye closure** is performed by the orbicularis oculi muscle (CN VII).

**Ptosis**, or drooping of the upper eyelid, can be seen in Horner’s syndrome, as discussed in KCC 13.5. Other causes of unilateral or bilateral ptosis include oculomotor nerve palsy affecting the levator palpebrae superior, myasthenia gravis, and redundant skin folds associated with aging (pseudoptosis). Causes of bilateral ptosis or closed eyes without loss of consciousness include non-dominant partial lid lesions, dorsal lesions of the oculomotor nuclei affecting the central cranial nuclei (see Figure 13.3; Table 13.2), and voluntary closure associated with photophobia in migraine or meningial irritation.

Weakness of the orbicularis oculi caused by facial nerve or upper motor neuron lesions (see Figure 12.13) can cause a widened palpebral fissure that may be mistaken for ptosis of the opposite eye. Careful examination of the pupil using the irises as a reference point can usually resolve this dilemma. In ptosis the upper lid comes down farther over the iris in the affected eye (see Figure 13.05A), while in facial weakness the palpebral fissure is widened because of sagging of the lower lid in the affected eye (see Figure 12.13).

**Cavernous Sinus and Orbital Apex**

We will now briefly discuss the cavernous sinus and orbital apex because CN III, IV, and VI all pass through this region and lesions here produce characteristic syndromes that often affect eye movements (see KCC 13.7). The cavernous sinus consists of a collection of venous sinuses sandwiched on either side of the pituitary that receives venous blood from the eye and superficial cortex and ultimately drains via several pathways into the internal jugular veins (see Figure 10.10). The other venous sinuses, the cavernous sinus lies between the periorbita and dural layers of the dura mater. The cavernous sinus surrounds the carotid siphon and several important nerves (Figure 13.11); see also Figures 12.3A, 13.2, and 13.4). The abducens nerve (CN VI), which lies closest to the carotid; and the oculomotor (CN III), trochlear (CN IV), and ophthalmic (CN V1) nerves, which run in sequence within the lateral wall of the cavernous sinus (see Figure 13.11). These nerves pass forward to enter the orbital apex via the superior orbital fissure (see Figure 12.3A,C). The maxillary nerve (CN V2) skirts the lower portion of the cavernous sinus and often runs through it for a short distance before exiting via the foramen rotundum (see Figure 12.3A). Sympathetic fibers traveling in the carotid plexus (see Figure 13.10) en route to the pupillary dilator muscle traverse the cavernous sinus as well.

The optic nerve lies just above the cavernous sinus and enters the orbital apex via the optic canal (see Figures 12.3A, 13.2). The orbital apex is the region where nearly all nerves, arteries, and veins of the orbit converge before communicating with the intracranial cavity via the optic canal and superior orbital fissure (see Figure 12.3C). It is important to be familiar with the structures of the cavernous sinus and orbital apex to understand how lesions in these regions can affect multiple cranial nerves (see KCC 13.7).

Lesions of the cavernous sinus or orbital apex can affect isolated nerves, or they can affect all the nerves traversing these structures. A complete lesion of the cavernous sinus disrupts CN III, IV, and VI, causing ophthalmoplegia, usually accompanied by a dilated pupil. Isolated palsy of CN V1, and variable involvement of V3 causes sensory loss in this division of the trigeminal nerve. Horner’s syndrome can also occur because of disruption of ocular sympathetic, but this condition may be difficult to appreciate in the setting of a third nerve lesion (sometimes the Horner’s syndrome is apparent in the affected eye in the dark; see Table 13.3). Orbital apex lesions produce the same deficits as cavernous sinus syndrome, but they are more likely to involve CN II also, causing visual loss, and often are associated with proptosis, or bulging of the eye, due to mass effect in the orbit. In both cavernous sinus and orbital apex lesions, partial deficits of the nerves mentioned here often occur when the lesion is less severe. Since the cavernous sinus and orbital apex are contiguous, both structures can be affected by a single lesion. Impaired venous drainage in both disorders can cause vascular engorgement of the orbital structures.

Causes of cavernous sinus syndrome include metastatic tumors, direct extension of nasopharyngeal tumors, meningioma, pituitary tumors or pituitary apoplexy, aneurysm of the intracavernous carotid, cavernous carotid arteriovenous fistula, bacterial infection causing cavernous sinus thrombosis, septic thrombosis, idiopathic granulomatous disease (Tolosa-Hunt syndrome), and fungal infections such as aspergillosis or mucormycosis. In cavernous carotid aneurysms or fistulas, the abducens nerve is often involved first because it lies closest to the carotid artery (see Figure 13.11). In pituitary apoplexy, there is hemorrhage within the pituitary gland, often in the setting of a pituitary tumor, which can sometimes extend into the adjacent cavernous sinus. Orbital apex syndrome can be caused by metastatic tumors, orbital cellulitis (bacterial infection), idiopathic granulomatous disease (orbital myositis or pseudotumor), and fungal infections such as aspergillosis. Cavernous sinus and orbital apex syndromes are medical emergencies requiring prompt recog-
Supranuclear Control of Eye Movements

Circuits for the supranuclear control of eye movements extend from the brainstem and cerebellum to the forebrain and exert their influence on the final common output nuclei of CN III, IV, and VI. There appear to be at least three dedicated circuits in the brainstem that feed much of the information from supranuclear control systems to the output nuclei, generating the following:

- Horizontal eye movements
- Vertical eye movements
- Vergence eye movements

We will first discuss the brainstem pathways generating movements in these three directions. Next, for each of these movement directions we will discuss how larger-scale networks, including the cortex, basal ganglia, cerebellum, and vestibular nuclei, generate different types of eye movements for different purposes. These different types of eye movements include the following:

- **Saccades** are rapid eye movements reaching velocities of up to 700° per second (see neuroexam.com Video 33). They function to bring targets of interest into the field of view. Vision is transiently suppressed during saccadic eye movements. Saccades are the only type of eye movements that can easily be performed voluntarily, although they can be elicited by reflexes as well.

- **Smooth pursuit** eye movements are not under voluntary control, and they reach velocities of only 100° per second (see neuroexam.com Video 20). They allow stable viewing of moving objects.

- **Vergence** eye movements maintain binocular fixation by both eyes as targets move toward or away from the viewer (see neuroexam.com Video 32). The velocity is about 20° per second.

- **Reflex** eye movements include optokinetic nystagmus (see neuroexam.com Video 34) and the vestibulo-ocular reflex (see neuroexam.com Video 35). **Nystagmus** is a rhythmic form of reflex eye movements composed of slow eye movements in one direction interrupted repeatedly by fast saccadlike eye movements in the opposite direction.

### Brainstem Circuits for Horizontal Eye Movements

Horizontal eye movements are generated by the lateral rectus and medial rectus muscles, controlled by the abducens and oculomotor nuclei, respectively (Figure 13.12). As we discussed in Chapter 12, the **medial longitudinal fasciculus (MLF)** interconnects the oculomotor, trochlear, abducens, and vestibular nuclei (see Figure 12.18). Through connections in the MLF, eye movements are normally locked together, resulting in conjugate gaze in all directions. For example, during horizontal eye movements the actions of the abducens and oculomotor nuclei are coordinated through connections in the MLF, as shown in Figure 13.12. Through this circuit, the abducens nucleus does more than just control abduction of the ipsilateral eye. In reality, the abducens nucleus is a **horizontal gaze center**, controlling horizontal movement of both eyes in the direction ipsilateral to the side of the nucleus (see Figure 13.12). Thus, some neurons in the abducens nucleus project to the ipsilateral lateral rectus muscle, while others project via the MLF to the contralateral oculomotor nucleus, which in turn, activates the contralateral medial rectus muscle.

In the pontine tegmentum near the abducens nucleus is an additional important horizontal gaze center called the **paramedian pontine reticular formation (PPRF)** that provides inputs from the cortex and other pathways to the abducens nucleus, resulting in lateral horizontal gaze (see Figure 13.12). As we will discuss later in this chapter, the vestibular nuclei also connect to the extraocular nuclei via the MLF, resulting in vestibulo-ocular reflexes.

### Examination of Figure 13.13 should make clear how different lesions in the brainstem affect horizontal gaze. Lesions of the abducens nerve cause impaired abduction of the ipsilateral eye (see Figure 13.13, Figure 13.1, and also KCC 13.4). Lesions of the abducens nerve should be distinguished from lesions of the abducens nucleus, which produce an ipsilateral lateral gaze palsy involving both eyes because of the connections through the MLF (see Figure 13.13).
1. Cover Figure 13.13B. For each lesion in Figure 13.13A, describe the expected eye positions on leftward and rightward gazes.

2. Cover the labels in Figure 13.13B. State the possible lesion locations and the side involved that would produce the eye movement abnormalities shown.

13.13, Lesson 2). Similarly, lesions of the PPRF cause an ipsilateral lateral gaze palsy (see Figure 13.13, Lesson 3).

Lesions of the MLF interrupt the input to the mediodorsal nucleus. Therefore, the eye ipsilaterally to the lesion does not adduct fully on attempted horizontal gaze (see Figure 13.13, Lesson 4). In addition, for uncertain reasons there is also paraplegia of the opposite eye, possibly because of mechanisms trying to bring the eyes back into alignment. This classic neurologic syndrome produced by an MLF lesion is called an internuclear ophthalmoplegia (INO). By definition, the side of the INO is the side of the lesion in the MLF. In an INO, eye adduction on the affected side is impaired with horizontal gaze but is often spared during convergence because the inputs to the oculomotor nucleus mediating convergence (see the next section) arise from the pretectal region and hence do not travel in the caudal MLF. Common causes of INO include multiple sclerosis plaques, pontine infarcts, or neoplasms involving the MLF. A subtle INO can sometimes be detected only by testing of horizontal saccades in both directions (see neurocom.com videos 33), and observation of a slight lag in the adduction of the eye on the affected side.

Finally, if a lesion involves both the MLF and the adjacent abducens nucleus or PPRF, there is a combination of an ipsilateral INO and an ipsilateral lateral gaze palsy (see Figure 13.13, Lesson 5). Thus, the ipsilateral eye cannot move at all horizontally, and the contralateral eye loses half of its movements, preserving only its ability to abduct, resulting in the quintessential one-and-a-half syndrome for this disorder.

Brainstem Circuits for Vertical and Vergence Eye Movements

Vertical eye movements are mediated by the superior and inferior recti, and superior and inferior oblique muscles (see Figure 13.1, Table 13.1). Brainstem centers controlling vertical eye movements are located in the rostral midbrain reticular formation and pretectal area. The ventral portion of this region is thought to mediate downgaze, while the more dorsal region (in the vicinity of the posterior commissure) mediates upgaze. One important nucleus that is thought to mediate downgaze is the rostral interstitial nucleus of the MLF. Other lesser nuclei in this area that may also play a role include the nucleus of the Darkscheivitch and the interstitial nucleus of Cajal. Lesions such as infarcts or tumors (discussed in the next section) of the dorsal part of the vertical eye movement center cause impaired upgaze, while lesions in the ventral part cause impaired downgaze. In addition, in locked-in syndrome (see KCC 13.1) large pontine lesions can disrupt the bilateral corticospinal tracts and abducens nuclei, eliminating body movements and horizontal eye movements. However, sometimes the vertical eye movement centers in the midbrain are spared, allowing the patient to communicate entirely through vertical eye movements.

Convergence of the eyes is produced by the medial recti, divergence by the lateral recti. The exact anatomical locations for centers in the brainstem controlling vergence have not been defined, but there appear to be separate pools of neurons in the midbrain reticular formation mediating either convergence or divergence movements. Vergence movements are under the control of descending inputs from the visual pathways in the occipital and parietal cortex and constitute part of the accommodation response discussed previously.

**KEY CLINICAL CONCEPT**

**PARKINSON'S SYNDROME**

Some clinical aspects of the brainstem circuits that control vertical eye movements were discussed in the preceding section and in KCC 13.3. In this section we will discuss an additional syndrome that includes vertical eye movement abnormalities: Parkinson's syndrome is a constellation of eye abnormalities usually seen with lesions comprising the dorsal midbrain and prefrontal cortex. The four components of Parkinson's syndrome are:

1. Impairment of vertical gaze, especially upgaze. This may be due to compression of the dorsal part of the vertical gaze center (see the preceding section).
2. Large, irregular pupils that do not react to light but sometimes may react to near-far accommodation. This light-near dissociation (KCC 13.5) may occur as a result of disruption of optic tract fibers traveling to the Edinger-Westphal nucleus via dorsal pathways including the posterior commissure (see Figure 13.8), while fibers descending from the visual cortex take a different route and are relatively spared.
3. Eyelid abnormalities ranging from bilateral lid retraction or "hitching" to bilateral ptosis.
4. Impaired convergence, and sometimes convergence-retraction nystagmus, especially on attempted upgaze (the eyes rhythmically converge and retract in the orbit).

The most common causes of Parkinson's syndrome are pheochromocytomas (see KCC 5.4) and hydrocephalus (see KCC 5.7). Hydrocephalus can cause dilatation of the suprapineal recess of the third ventricle (see Figure 5.11), which pushes downward onto the collicular plate (tectum) of the midbrain. Thus, hydrocephalus, especially in children, can produce the bilateral setting-sun sign, in which the eyes are deviated inward because of bilateral sixth-nerve palsies (see KCC 13.4) and downward because of a Parkinson's syndrome.

Control of Eye Movements by the Forebrain

Multiple parallel pathways descend from the cerebral cortex to control eye movement circuits in the brainstem; we will mention only a few of the better-known pathways here. Descending cortical pathways either directly to the brainstem centers for horizontal, vertical, or convergence eye movements (discussed earlier) or via relays in the midbrain superior colliculi.
The best-known cortical area that controls eye movements consists of the frontal eye fields (Figure 13.14). Based mainly on animal studies, this former corticofugal area in humans was assumed to correspond to Brodmann's area 8 (see Figure 2.15). However, recent functional imaging studies have suggested that the frontal eye fields in humans may be more posteriorly placed, at the junction between the superior temporal sulcus and the precentral sulcus, in Brodmann's area 6. Some authors consider the frontal eye fields to overlap the premotor and prefrontal cortices (see Figure 19.11A), reflecting their roles in eye movements and selective attention, respectively. The frontal eye fields generate saccades in the contralateral direction via connections to the contralateral PPRF (Figure 13.12). More posterior corticofugal regions of the parieto-occipito-temporal cortex (see Figure 13.14) primarily influence the smooth pursuit movements in the ipsilateral direction, via connections with the vestibular nuclei, cerebellum, and PPRF, as we will discuss in the section on reflex eye movements. The parieto-occipito-temporal cortex may provide some contribution to contralateral eye movements as well. Cortical descending control of eye movements is heavily influenced by visual inputs arriving at the primary visual cortex and visual association cortex (see Figure 13.14).

The basal ganglia also play a role in modulatory control of eye movements, and characteristic disorders of eye movements can be seen in basal ganglia dysfunction (see Chapter 16).

Lesions of the cerebral hemispheres normally impair eye movements in the contralateral direction, often resulting in a gaze preference toward the side of the lesion. This gaze preference is typically accompanied by weakness contralateral to the cortical lesion (if the corticofugal pathways are involved), so that the eyes look away from the side of the weakness (Figure 13.15A).

Certain clinical situations can cause the eyes to look toward the side of the weakness. This condition is called wrong-way eyes (Figure 13.15B). Causes of wrong-way eyes include seizure activity in the cortex, which can drive the eyes in the contralateral direction because of activation of the frontal eye fields (see Figure 13.14), while also causing abnormal or decreased movements of the contralateral side of the body because of involvement of motor association cortex and other structures. In addition, for unclear reasons, large lesions such as thalamic hemorrhage can disrupt the corticospinal pathways of the internal capsule, causing contralateral weakness, yet may also cause the eyes to deviate toward the side of the weakness. Lesions in the thalamic region causing wrong-way eyes are usually accompanied by deep coma. Finally, lesions of the pontine basis and tegmentum (see Figure 13.13; Lesions 2, 3; see also Figure 14.20C; Table 14.8) can cause wrong-way eyes because disruption of the corticospinal fibers causes contralateral hemiplegia, while involvement of the abducens nucleus or PPRF causes ipsilateral gaze weakness.

Cerebellar, Vestibular, and Spinal Control of Voluntary and Reflex Eye Movements

The cerebellum, vestibular nuclei, and spinal spinal proprioceptors influence ongoing voluntary eye movements and contribute to several forms of reflex eye movements. Two well-described forms of reflex eye movements are optokinetic nystagmus and the vestibulo-ocular reflex (VOR). The examiner can elicit optokinetic nystagmus (OKN) in the horizontal direction by moving a thick ribbon with vertical stripes (called an OKN step) horizontally in front of the eyes (see neuroexam.com/Video 34). The eyes alternate between smooth pursuit movements in the direction of stripe movement and backup corrective saccades opposite the direction of stripe movement in an attempt to stabilize the images. OKN is sometimes elicited in myoclonus because it can be observed in the eyes of fellow passengers as they watch the passing visual scene through an open window.

The slow phase, or smooth pursuit phase, of OKN is mediated by the ipsilateral posterior cortex (see Figure 13.14), with connections to the vestibular nuclei and flocculonodular lobe of the cerebellum projecting to the PPRF and abducens nuclei (see Figure 13.12). The fast phase, or saccadic phase, of OKN is mediated by the frontal eye fields projecting ultimately to the contralateral PPRF (see Figure 13.12). Therefore, lesions of the frontal cortex or anywhere in the saccadic pathways disrupt the fast phases of OKN, while the slow phases are disrupted by lesions in the smooth pursuit pathways. OKN testing is thus useful to check for subtle dysfunction in the eye movement pathways. OKN can also be elicited in the vertical direction.

The vestibulo-ocular reflex (VOR) stabilizes the eyes on the visual image during head and body movements. Inputs from the vestibular nuclei, especially the medial vestibular nuclei, travel in the M.tr to control the extranuclear nuclei (see Figure 12.18). The VOR can be tested with the oculocephalic maneuver (see neuroexam.com/Video 35) or with cold water calorics (see the section on the coma exam in Chapter 3). Proprioceptive inputs also help stabilize the eyes on the visual image, especially during head and neck movements.
CASE 13.1 DOUBLE VISION AND UNILATERAL EYE PAIN

**CHIEF COMPLAINT**
A 48-year-old woman came to the emergency room with worsening left eye pain and intermittent double vision.

**HISTORY**
Approximately 4 or 5 years previously, the patient had begun to have left frontal and left retro-ocular headaches that occurred intermittently at first, and then on an almost daily basis. An MRI scan was reportedly normal, and she was diagnosed with cluster migraine. The headaches continued to occur but were relieved by ibuprofen. One and a half years prior to presentation she began to have intermittent drooping of the left eyelid and dilation of the left pupil. She also noticed that her left eye occasionally drifted to the left, causing diplopia. This patient was very observant, and she noticed that her diplopia was worse when looking to the right. When covering each eye alternately, she reported that the two images did not overlap. In fact, the image from her left eye appeared to the right and slightly above the image from her right eye. These symptoms gradually progressed from intermittent to continuous, and her headaches were no longer relieved by up to 12 ibuprofen tablets per day, so she came to the emergency room.

**PHYSICAL EXAMINATION**
Vital signs: T = 98.7°F, P = 78, BP = 180/90.
Mental status: Alert and oriented x 3. Speech fluent, with intact naming and repetition. 3/5 words recalled after 5 minutes.
Neck: Supple with no bruits.
Lungs: Clear.
Heart: Regular rate with no murmurs.
Abdomen: Soft, nontender.
Neurologic exam:

- **Mental Status**: Alert and oriented x 3. Speech fluent, with intact naming and repetition. 3/5 words recalled after 5 minutes.
- **Ocular exam**: Visual fields full. Fundi normal. Right pupil 4 mm, constricting to 3 mm with direct and consensual light stimulation, and with accommodation. Left pupil 6 mm, with no direct or consensual response to light and no response to accommodation. Left eye had limited but not absent upgaze, downgaze, and adduction. Normal right eye movements. Left ptosis, with left palpebral fissure 6 mm and 9 mm. Corneal reflexes intact. Facial sensation intact. Face symmetrical, other than left prolapsed already described. Normal palate and tongue movements.
- **Motor**: No drift. Normal tone. 5/5 power throughout.

**Reflexes**:
- Oculocephalic (doll's eye) test:
  - Right gaze: Left eye-fixated (hyper deviation). Head did not turn.
  - Left gaze: Right eye-fixated (hypotropia). Head did not turn.

- **Coordination**: Normal on finger-to-nose and heel-to-shin testing.

- **Deep Tactile**: Not tested.

- **Sensory**: Intact light touch, pinprick, vibration, and joint position sense. Normal graphesthesia; no extinction.

**LOCALIZATION AND DIFFERENTIAL DIAGNOSIS**
1. On the basis of the symptoms and signs shown in bold above, where is the lesion?
2. What is the most likely diagnosis, and what are some other possibilities?

**Discussion**
1. The key symptoms and signs in this case are:
   - Left frontal and retro-orbital headaches
   - History of left eye drifting to the left, and diplopia with image from left eye above and to right of image from right eye, with diplopia worse when looking to the right
   - Left eye with limited but not absent upgaze, downgaze, and adduction, left ptosis, and a fixed dilated left pupil

   This patient has a history of diplopia and findings on exam that are compatible with an oculomotor nerve (CN III) palsy (see KCC 13.2, Figure 13.35). Her left pupil was dilated and unresponsive. Although left eye adduction, upgaze, and downgaze were decreased, they were not absent, suggesting a partial third-nerve palsy. In addition, there was no description of an abnormal eye position at rest. Headaches can have numerous causes (see KCC 5.1); when they are always on the same side, however, an intracranial abnormality on that side should be suspected.

   The most likely clinical localization is left oculomotor nerve (CN III).

2. Painful third-nerve palsy should be treated as an aneurysm until proven otherwise. The most common aneurysm causing CN III palsy occurs where the posterior communicating artery (PCom) branches off the internal carotid (see Figures 5.20, 13.2; KCC 5.6), although aneurysms of the internal carotid, posterior cerebral, and superior cerebellar arteries should also be considered. For other causes of CN III palsy, see KCC 13.2.

**Clinical Course and Neuroimaging**
A head CT (not shown) revealed an egg-shaped, 1 cm mass near the left edge of the posterior chiasmatic process (see Figure 12.3A) that enhanced with intravenous contrast. A cerebral angiogram was performed (Figure 13.16), showing a 1.5 cm aneurysm arising in the region where the PCom branches off the internal carotid (compare to Figure 4.16C). The PCom itself could not be seen on the angiogram. The aneurysm had a well-visualized neck, and its dome pointed posteriorly, along the course of the third nerve. The patient was taken to the operating room and underwent a left frontotemporal craniotomy. The left frontal and temporal lobes were carefully retracted and the left internal carotid artery visualized. Using an operating microscope, the aneurysm was identified and the neck of the aneurysm. The dome of the aneurysm was seen to project posteriorly and inferiorly under the edge of the tentorium cerebelli. A small PCom artery was found to arise from the internal carotid adjacent to the neck of the aneurysm. The neurosurgeons carefully placed a clip across the neck of the aneurysm, being cautious to avoid occluding any other small vessels such as the PCom. The dome of the aneurysm immediately became less tense and could be safely opened with microsurgical, and some blood was evacuated, leading to decompression of adjacent structures. Postoperatively the patient did quite well; 1 week after surgery her left pupil became nonreactive, but she had nearly full movement of the left eye, no diplopia, and no headaches.

CASE 13.2 A DIABETIC WITH HORIZONTAL DIPLOPIA

**MINICASE**
A 54-year-old man with a history of diabetes awoke one morning with horizontal diplopia that increased on gaze to the left and decreased on gaze to the right. He initially had some pain in the left periorbital area, which resolved after a few days. Exam was normal except for incomplete abduction of the left eye. He was able to move the left eye slightly past the midline toward the left; however, he was unable to fully "bury the sciera," as he could with the right eye when looking to the right. He had horizontal diplopia with no vertical component, which was worse on left gaze.

**LOCALIZATION AND DIFFERENTIAL DIAGNOSIS**
1. On the basis of the symptoms and signs shown in bold above, where is the lesion?
2. What is the most likely diagnosis, and what are some other possibilities?
**CASE 13.3 VERTICAL DIPLOPIA**

**MINICASE**
A 74-year-old man awoke one morning with vertical diplopia. The diplopia was relieved by covering either eye and did not vary in severity at different times of the day. He had no history of head trauma. Past medical history was notable only for hypertension. Exam was normal except for a right hypertropia and incomplete downgaze with the right eye when looking medially. He was tested with a red glass over the right eye (Figure 13.17) and had vertical diplopia, with the image from the right eye located below the image from the left eye. The diplopia worsened with downgaze and leftward gaze and improved with leftward head tilt.

**LOCALIZATION AND DIFFERENTIAL DIAGNOSIS**
1. On the basis of the symptoms and signs shown in bold above, where is the lesion?
2. What is the most likely diagnosis, and what are some other possibilities?

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**Discussion**
1. The key symptoms and signs in this case are:
   - Horizontal diplopia, worse on left gaze, with incomplete abduction of the left eye
   - This patient has dysfunction of the left lateral rectus muscle causing dysconjugate horizontal gaze, and diplopia (see Figures 13.1, 13.7, and 13.13). Possible causes of incomplete left eye abduction include dysfunction of the left abducens nerve (CN VI) or the lateral rectus muscle, or a mechanical problem in the orbit.
2. Given the patient's history of diabetes and the lack of any other associated findings, the most likely diagnosis is an isolated abducens nerve palsy, caused by neurovascular disease. Other possible causes of abducens nerve palsy and horizontal diplopia are discussed in KCC 13.1 and 13.4.

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**CASE 13.1 DOUBLE VISION AND UNILATERAL EYE PAIN**

**Figure 13.16 Left Posterior Communicating Artery (PComm) Aneurysm**
Angiogram from left internal carotid artery injection. Lateral view

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**Clinical Course**
A head CT was normal. When seen in follow-up 2 weeks later, the patient showed no change, but after 2 months his diplopia was less severe and he was able to bury the sciera almost completely on leftward gaze. Three months after presentation his exam was normal, and he had no symptoms except for occasional transient diplopia when looking in the distance to the left. Review Case 5 for another important cause of abducens palsy.

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**Discussion**
1. The key symptoms and signs in this case are:
   - Right hypertropia, and vertical diplopia worse with downward and leftward gaze and worse with rightward head tilt
   - The findings in this patient are compatible with a right trochlear palsy (see KCC 13.3; Figure 13.6). A disorder of the superior oblique muscle itself is also possible.
2. The most likely cause of the isolated trochlear palsy in this patient is, as in Case 13.2, an idiopathic neuropathy of presumed microvascular origin. For other possible causes of trochlear nerve palsy and vertical diplopia, see KCC 13.1 and 13.3.

**Clinical Course**
A head CT was normal. Tensilon test (see KCC 8.1) was negative, and hemoglobin A1c (an indicator of average blood glucose) was borderline, elevated at 7.7%, suggesting possible diabetes. The patient initially wore an eye patch over his right eye because this eliminated his diplopia and made it easier for him to function normally. He gradually improved, and 3 months later he no longer needed the eye patch and had diplopia only while reading, which involves looking down.

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**Figure 13.17 Results of Red Glass Testing**
Red glass was held over the patient's right eye.
CASE 13.4 LEFT EYE PAIN AND HORIZONTAL DIPLOPIA

MINICASE
A 27-year-old man with no previous medical problems came to the emergency room because of 1 week of crescendo left-sided headaches, left eye pain, and horizontal diplopia. He woke 1 week prior to presentation with a severe left frontal headache. Two days later the headache had moved to his left eye, and he began noticing horizontal diplopia on rightward gaze. He went to his primary medical doctor and had an MRI scan, which was reportedly normal. Because of continued symptoms, he finally decided to come to the emergency room for further evaluation, where he was seen by a neurology consult resident. Examination was normal except for mild erythema of the left orbital conjunctiva and slightly decreased adduction of the left eye on right lateral gaze. He had horizontal diplopia and left eye pain on rightward gaze, and the rightmost image vanished when the left eye was covered. There was also minimal horizontal diplopia on leftward gaze, with the leftmost image vanishing when the left eye was covered.

LOCALIZATION AND DIFFERENTIAL DIAGNOSIS
1. On the basis of the patient's symptoms and his findings on neurologie exam, what is the most likely localization for a lesion in this patient causing horizontal diplopia (see KCC 13.1 and 13.4)?
2. Given the pain and erythema of the left orbital conjunctiva, what are some possibilities for the diagnosis?

Discussion
1. The key symptoms and signs in this case are:
   - On right gaze: left eye pain, limited adduction, and horizontal diplopia, with the right image vanishing when the left eye was covered
   - On left gaze: mild horizontal diplopia, with the left image vanishing when the left eye was covered
   - Pain and erythema of the left orbital conjunctiva

   The examination reveals bilateral limitations of horizontal eye movement of the left eye, with more difficulty looking to the right. Relatively isolated dysfunction of both the left medial and lateral rectus muscles would be difficult to explain on the basis of nerve or CNS lesions (see Figure 13.13; Table 13.1; KCC 13.1, 13.4). In addition, the left eye pain that worsens with movement suggests a possible mechanical cause in the orbit. One possibility would be a lesion that restricts movement of the left lateral rectus muscle, limiting its ability to stretch on right lateral gaze and decreasing its ability to contract on left lateral gaze.

2. The differential diagnosis includes orbital trauma (although there was none based on history); thyroid disease (although pain in the periphery onset doesn't fit with this diagnosis); myasthenia gravis (since condition should not cause pain); or more likely, especially given the pain and erythema, an infection, inflammatory, or neoplastic disorder such as orbital cellulitis, orbital lymphoma, orbital myositis (orbital pseudotumor), sarcoidosis, Tolosa-Hunt syndrome, fungal infection, or cavernous sinus thrombosis.

Clinical Course and Neuroimaging
In the emergency room, the patient underwent a head CT scan. In addition, he had a lumbar puncture (see KCC 13.10), and cerebrospinal fluid studies were normal. On careful review of the CT scan, the lateral rectus muscle appeared slightly thickened. The patient was therefore admitted, and a brain MRI with gadolinium was done (Figure 13.18). The MRI revealed marked enhancement and thickening of the lateral rectus muscle, compatible with the diagnosis of orbital myositis (orbital pseudotumor), a relatively uncommon inflammatory condition of the extracocular muscles. The patient was treated with oral steroids and discharged home. His symptoms had improved when he was seen 1 week later in the outpatient office, but he was subsequently lost to follow-up because his insurance would not cover visits to a neurologist outside of his program.

CASE 13.5 UNILATERAL HEADACHE, OPHTHALMOPLEGIA, AND FOREHEAD NUMBNESS

CHIEF COMPLAINT
A 24-year-old woman with a history of pituitary adenoma suddenly developed severe headache, left forehead and cheek numbness, and inability to move the left eye.

HISTORY
The patient presented 2 years previously with Cushing's syndrome (see KCC 17.1) and underwent two operations to resect a pituitary adenoma. She did well until 2 weeks before admission, when she started having left frontal headaches, especially around the left eye and nose. An MRI scan showed recurrent pituitary adenoma, and radiation therapy was planned. Two days prior to admission, however, she had onset of horizontal diplopia and was found by her endocrinologist to have a left CN VI palsy. She was admitted to an outside hospital and treated with steroids to try to reduce swelling. However, the next day she had a sudden worsening of her headache, with pain and numbness involving the left cheek and forehead; a dilated, fixed left pupil; and almost no movement of the left eye. She was therefore urgently transferred to a tertiary care center for further evaluation and treatment.

PHYSICAL EXAMINATION
General appearance: Crying, anxious young woman in apparent pain.
Vital signs: T = 97°F, P = 92, R = 12/112.
Neck: Supple with no bruits.
Lungs: Clear.
Heart: Regular rate with no murmurs.
Abdomen: Benign.
Neurologic exam:
- MENTAL STATUS: Alert and oriented × 3.
- CN EXAM: Right pupil 3 mm, constricting to 2 mm.
- Left pupil 6 mm, with no direct or consensual response to light. Visual fields full. Fundi normal. Nor-

mal movements of the right eye, but the left eye had no extraocular movements and a marked left ptosis. She had diplopia in all directions of gaze. Sensation was slightly decreased to pinprick in the left forehead, eyelid, left bridge of the nose, and upper cheek (Figure 13.19). Face was symmetrical, aside from the left ptosis noted above. Shoulder shrug was normal, and tongue was midline.
- MOTOR: No pronator drift. 5-5 power throughout.
- REFLEXES: Not tested.
- COORDINATION: Normal on finger-to-nose testing.
- GAIT: Not tested.
- SENSORY: Intact light touch and pinprick sensation.

LOCALIZATION AND DIFFERENTIAL DIAGNOSIS
1. On the basis of the symptoms and signs shown in bold above, where is the lesion?
2. Given the patient's history of a pituitary adenoma and the sudden onset of her deficits, what is the most likely diagnosis? What are some other possibilities?

Discussion
1. The key symptoms and signs in this case are:
   - Initial left abducens palsy, evolving to ophthalmoplegia, ptosis, and a fixed dilated pupil
   - Pain, paresthesia, and decreased sensation to pinprick in the left forehead, eyelid, bridge of nose, and upper cheek

   This patient had dysfunction of the left CN III, IV, VI, and V1, constituting a left cavernous sinus syndrome (see KCC 13.7, Figure 13.11). Loss of involvement of the optic nerve suggests that the disorder was not in the orbital apex. Interestingly, the initial abnormal finding was an abducens palsy, suggesting a lesion that expanded from medial to lateral within the left cavernous sinus (see Figure 13.11).

   The most likely clinical localization is the left cavernous sinus.
2. This patient has a history of recurrent pituitary adenoma. The onset of her symptoms, however, is too rapid to be explained easily by extension of the tumor into the cavernous sinus. The sudden worsening of her symptoms could be explained by hemorrhage into the tumor, or pituitary apoplexy (see KCC 17.3). Interestingly, pituitary apoplexy often recurs in patients without a previously known history of adenoma. Other possibilities include cavernous carotid aneurysm or fistula, cavernous sinus thrombosis, or infection (see KCC 15.7).

**Clinical Course and Neuroimaging**

The tertiary care center to which the patient was transferred had an MRI scanner readily available. Therefore, an MRI was performed on an urgent basis because of the better resolution of MRI than CT for structures in the pituitary and cavernous sinus region (Figure 13.20). Figure 13.20A is a coronal T1-weighted image showing a large hemorrhage extending from the pituitary fossa into the left cavernous sinus. Note that the optic tract was not affected, and more anteriorly (not shown), the optic nerves were also spared. Figure 13.20B is an axial T2-weighted image, again showing the hemorrhage. The trigeminal nerve is nicely demonstrated in Figure 13.20B and can be seen to enter Meckel’s cave on both sides (compare to Figure 12.3A). Cerebrospinal fluid surrounding the trigeminal ganglion in Meckel’s cave appears white on T2-weighted images. Because of these findings, the patient was taken to the operating room for a transphenoidal resection (see KCC 17.1) of the hemorrhage and pituitary adenoma. Hemorrhagic tissue was removed from the left cavernous sinus, and hemostatic packing was inserted. By postoperative day 1, the patient had recovered some limited left extraocular movements and slight left pupillary responses. She was transferred back to the hospital closer to her home for the remainder of her recovery.

**CASE 13.6 PTOSIS, MIOIS, AND ANHYDROSIS**

**MINICASE**

A 17-year-old male got into an argument with his sister while intoxicated, and she hit him in the neck with a steel pellet gun. He was brought to the emergency room and treated for a left pneumothorax (collapsed lung). The emergency room physician noticed unequal pupils and called a neurology consult. On exam, the patient had an entry wound at the base of his neck just above the left clavicle (Figure 13.21). There was no neck swelling. The right pupil was 4 mm, constricting to 3 mm in response to light, and the left pupil was 2 mm, constricting to 1.5 mm. The left eyelid had 3 mm of ptosis compared to the right. The left forehead felt smoother than the right, suggesting decreased sweat production. When the right neck was pinched, the right pupil dilated (cilioparasympathetic reflex). Pinching the left neck caused no change in the left pupil. The remainder of the exam was normal.

**LOCALIZATION AND DIFFERENTIAL DIAGNOSIS**

1. On the basis of the symptoms and signs shown in bold above, where is the lesion?
2. What is the most likely diagnosis, and what are some other possibilities?

**Figure 13.21 Location of Entry Wound**

**Discussion**

- The key symptoms and signs in this case are:
  - Left ptosis
  - Small, reactive left pupil, with decreased cilioparasympathetic reflex
  - Decreased left facial sweating

This patient has Horner’s syndrome (see KCC 13.5, 13.6). Horner’s syndrome can be caused by a lesion anywhere in the sympathetic pathway to the eye (see Figure 13.20). However, given the history of a penetrating neck wound, the lesion is probably located in the sympathetic chain or sympathetic trunks of the carotid plexus. The entry wound was low in the neck (see Figure 13.21), making direct injury to the sympathetic in the carotid plexus unlikely (see Figure 13.10). In addition, impaired sweating is more common with preganglionic lesions. Nevertheless, the carotid artery may have been injured low in the neck, causing a carotid dissection (see KCC 10.6) extending superiorly, resulting in a Horner’s syndrome. A lesion of the upper thoracic nerve roots or spinal cord is unlikely, given the absence of any other neurologic findings, although the pneumothorax suggests the pellet traversed the region of the upper thoracic nerves.

Possible causes of Horner’s syndrome in this patient include direct traumatic injury to the sympathetic trunk in the neck (see Figure 13.21) or carotid dissection (see KCC 10.6).

In summary, the most likely clinical localization is left sympathetic chain in the vicinity of the lower neck or lung apex, or left carotid plexus.

**Clinical Course and Neuroimaging**

Because of the possibility of a carotid dissection, an angiogram was done (Figure 13.22). No dissection was seen. The steel pellet took a slightly downward course to lodge behind the carotid artery, at the level of the TI and TI nerve root exit points. Injury to the lower spinal or upper thoracic sympathetic trunk during the steel pellet’s trajectory through the neck was therefore the most likely diagnosis. Because of the pellet’s location adjacent to vital structures, it was not removed. Social services and psychiatry were consulted because of the circumstances of his injury. When seen 1 month later in follow-up, the patient was doing well, but his left ptosis and miosis remained essentially unchanged.

**Related Case.** Figure 13.23 (page 566) shows an MRI of the neck from a different patient with ptosis and miosis. This 43-year-old woman struck her head against the steering wheel in a car accident. She was well until 2 weeks later, when she developed pain over her right eye, with right ptosis and miosis. The T2-weighted MRI images in Figure 13.23 demonstrate a white crescent of clotified blood (see Table 4.3) in the false lumen of a carotid dissection (see KCC 10.6). In this case, the Horner’s syndrome was associated with a carotid dissection. She was treated with anticoagulation for several months to prevent emboli.
CASE 13.7 WRONG-WAY EYES

MINICASE
A 71-year-old man with a history of diabetes collapsed on the street and was unable to stand up, so he was brought to the emergency room by ambulance. On examination, he was awake but lethargic, had a rightward gaze preference, and was unable to move either eye past the midline toward the left. In addition, he had weakness of the right lower face and 2/5 strength in the right arm and leg, with an upgoing plantar response on the right. Examination was otherwise unremarkable.

LOCALIZATION AND DIFFERENTIAL DIAGNOSIS
1. Lesions in which locations can cause the constellation of symptoms and signs shown in bold above?
2. Given the patient's age and the time course of his presentation, what is the most likely diagnosis, and what are some other possibilities?

Discussion
1. The key symptoms and signs in this case are:
   • Lethargy
   • Rightward gaze preference, with inability to move either eye past the midline toward the left
   • Right face, arm, and leg weakness, with upgoing plantar response on the right

This patient has a combination of a left horizontal gaze palsy and right hemiparesis constituting so-called wrong-way eyes (see KCC 13.10; Figure 13.15). Wrong-way eyes can be caused by ongoing seizure activity in one of the central hemispheres, by lesions in the region of the thalamus, or by lesions in the pons affecting the corticospinal tract (contralateral hemiparesis) and abducens nucleus (ipsilateral gaze paresis). The patient's lethargy suggests possible mild involvement of brainstem activating systems (see Chapter 14). Lesions in the vicinity of the thalamus causing wrong-way eyes usually do in the setting of profound coma, which this patient did not have.

2. Given the patient's age and history of diabetes, the most likely diagnosis is an infarct in the left pons involving the left corticospinal and corticobulbar fibers as well as the left abducens nucleus (or PPRD). A hemorrhage in this location is also a possibility. Another possibility is that the patient could have ongoing seizure activity (focal status epilepticus) in the left hemisphere, causing the rightward gaze preference and right-sided weakness, but this is less likely given the history.

Clinical Course and Neuroimaging
The patient's CT scan showed an area of increased density at the top of the basilar artery, so he was taken for an emergency angiogram with a plan for intra-arterial thrombolyis (see KCC 13.4). However, the angiogram revealed a patent basilar artery, and it was concluded that the increased density seen in the basilar artery on CT scan was calcification rather than thrombus (see Table 4.1). He was therefore treated with intravenous heparin while an embolic evaluation was pursued (see KCC 10.4). An M.RI scan (Figure 13.24) revealed an area of increased T2 signal in the left pons consistent with an infarct from a penetrating vessel arising from the basilar artery (see KCC 13.5; Figure 14.20; Table 14.8). The patient was found to have panventricular atrial fibrillation and was treated with chronic oral anticoagulation and transferred to an inpatient rehabilitation facility. When seen in the office 4 months later, however, he still had severe 3/5 right hemiparesis and a left horizontal gaze palsy.

CASE 13.4: LEFT EYE PAIN AND HORIZONTAL DIPLOPIA

Figure 13.18 Orbital Pseudotumor Involving Left Lateral Rectus Muscle. T1-weighted axial MRI image with contrast gadolinium demonstrating abnormal enhancement and thickening of the left lateral rectus muscle compatible with orbital pseudotumor.

CASE 13.8 HORIZONTAL DIPLOPIA IN A PATIENT WITH MULTIPLE SCLEROSIS

MINICASE
A 25-year-old woman had a 2-year history of multiple sclerosis with relapsing and remitting episodes of weakness and sensory deficits in her extremities. Two weeks prior to evaluation, she had onset of horizontal diplopia. Compared to previous exams, the new findings consisted of an abnormality of rightward horizontal gaze such that the left eye did not adduct past the midline, and the right eye had sustained end gaze nystagmus on abduction. In contrast, when convergence was tested, the left eye was able to adduct past the midline. Leftward horizontal gaze was normal.

LOCALIZATION AND DIFFERENTIAL DIAGNOSIS
1. Draw the positions of this patient's eyes on leftward horizontal gaze, on rightward horizontal gaze, and during convergence.
2. What is the location of this patient's lesion, and which side is it on?
3. What is the most likely cause?

Discussion
1. The key symptoms and signs in this case are:
   • Left eye did not adduct past the midline
   • Right eye had sustained end gaze nystagmus on abduction

The positions of this patient's eyes during leftward and rightward gaze are shown in Figure 13.13B, lesion 4. Convergence was normal.

2. These findings constitute a left INO localized to the left MLF (see Figure 13.13A, lesion 4).
3. Given the patient's history, the most likely diagnosis is a multiple sclerosis plaque (see KCC 5.0) in the left MLF.

**Initial Clinical Course and Neuroimaging**

A brain MRI showed a new region of increased T2 signal along the floor of the fourth ventricle in the region of the left MLF (Figure 13.25).

### CASE 13.8 (CONTINUED)

During the next few days the patient gradually developed problems with leftward horizontal gaze as well, so neither eye would move past the midline when the midline when looking to the left. On rightward gaze, she continued to have no adduction of the left eye. Thus, the only remaining horizontal eye movement was right eye abduction, which continued to have end gaze nystagmus, as before.

**LOCALIZATION AND DIFFERENTIAL DIAGNOSIS**

1. Draw the positions of this patient's eyes on leftward horizontal gaze and on rightward horizontal gaze following her clinical worsening.
2. What is the location of this patient's lesion now?

**Discussion**

1. The key symptoms and signs in this case are:
   - Inability of either eye to move past the midline when looking to the left
   - No adduction of the left eye
   - End gaze nystagmus on right eye abduction

   The positions of this patient's eyes during leftward and rightward gaze are shown in Figure 13.13B, lesion 3.

2. These findings constitute a left INO plus a left horizontal gaze palsy, also called one-and-a-half syndrome (see KCC 13.6). Most likely her demyelinating plaque in the left MLF enlarged to involve the left abducens nucleus or PPRF (see Figure 13.13A, lesion 5).

**Clinical Course**

The patient was treated with steroids, and her eye movements and diplopia gradually improved. On follow-up examination she was able to move her eyes fully in all directions; in tests of saccades to the right, however, her right eye could be seen to move quickly to the right while her left eye moved more slowly to the right, lagging slightly behind. This is a way to test for a mild INO on physical examination (see KCC 13.8) and demonstrated a slight residual deficit in this patient.

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**CASE 13.5 Unilateral Headache, Ophthalmoplegia, and Forehead Numbness**

**Figure 13.20 Pituitary Apoplexy Causing Left Cavernous Sinus Syndrome**

(A) Coronal T1-weighted image demonstrating hemorrhage extending from the region of the pituitary fossa into the left cavernous sinus. (B) Axial T2-weighted image, again demonstrating hemorrhage in the left cavernous sinus, adjacent to Meckel's cave.
CASE 13.6 PTOSIS, MIOSIS, AND ANHIDROSIS

Figure 13.22 Steel Pellet in Region of the Sympathetic Trunk. Angiogram from aortic arch injection. Left anterior oblique view. The trajectory made by the steel pellet from the entry site to its final location traverses the region of the left T1 and T2 nerve roots and the junction between the thoracic and cervical portions of the sympathetic trunk (compare to Figure 13.10).

Marker placed at entry site
- Left common carotid artery
- Left vertebral artery
- Level of T1 nerve root
- Brachiocephalic artery
- Level of T2 nerve root
- Steel pellet
- Left subclavian artery
- Carotid in aortic arch

CASE 13.6 RELATED CASE

Figure 13.23 Right Carotid Dissection. Axial, T1-weighted MRI image through the neck and skull base reveals a crescent of blood in the right carotid, consistent with a right carotid dissection.

CASE 13.7 WRONG-WAY EYES

Figure 13.24 Infarct in Left Medial Pontine Basis and Tegmentum. Axial, T2-weighted MRI image. An infarct is present in the left pons in the region of the left corticospinal tract, PPN, and possibly the abducens nucleus.

CASE 13.9 HEADACHES AND IMPAIRED UPGAZE

MINICASE
A 23-year-old aerospace engineer developed mild headaches and difficulty looking up over the course of 3 weeks, so he went to see his family physician. On examination, his pupils were about 6 mm in diameter bilaterally and had minimal reaction to light, but they did contract during accommodation. He was unable to look upward at all past the horizontal plane, but he had otherwise full eye movements in other directions. When attempting to look upward, or after closing and opening his eyes, he had retraction of the upper eyelids and convergence-retraction nystagmus of both eyes. Examination was otherwise normal.

LOCALIZATION AND DIFFERENTIAL DIAGNOSIS
1. On the basis of the symptoms and signs shown in bold above, what syndrome does this patient have affecting his eye movements, and what is the usual localization of this syndrome?
2. What is the most likely diagnosis, and what are some other possibilities?

Discussion
1. The key symptoms and signs in this case are:
   - Headaches
   - Large pupils with minimal reaction to light but preserved reaction to accommodation (light-near dissociation)
   - Inability to look upward
   - Lid retraction and convergence-retraction nystagmus

   The patient has a classic Parinaud's syndrome (see KCC 13.9). Parinaud's syndrome is usually caused by compression of or lesions in the dorsal midbrain...
and prefrontal area. Impaired upgaze is probably caused by dysfunction of the upper portion of the vertical gaze center located in the dorsal part of the reticular midbrain medullar formation. Light-near dissociation probably occurs because fibers from the optic tract reaching the Edinger-Westphal nuclei travel via dorsal pathways including the posterior commissure and have been disrupted, while fibers descending from the visual cortex take a different route and are relatively spared (see KCC 13.5; Figure 13.8). Headaches of the kind seen in this patient can have many causes (see KCC 5.1) but also support the presence of intracranial pathology.

2. Given the presence of a gradually progressive Parinaud’s syndrome, the most likely diagnosis in this patient is a pineal region tumor (see KCC 5.8) that has enlarged to compress the dorsal midbrain. In young children before the cranial sutures close, hydrocephalus can present with Parinaud’s syndrome as the main abnormality. In an adult, however, if the hydrocephalus were severe enough to cause these findings, then intracranial pressure would likely be severely elevated as well, causing impaired consciousness (see KCC 5.3), which this patient does not have. Therefore, the most likely diagnosis is a primary neoplasm of the pineal region. Another, less likely possibility is that the patient has another lesion in this region, including metastatic tumor, infection, or vascular malformation.

Clinical Course and Neuroimaging

A brain MRI with intravenous gadolinium showed an enhancing lesion in the pineal region causing severe compression of the dorsal midbrain and prefrontal area (Figure 13.20). He was referred to a neurosurgeon and underwent a biopsy of the lesion performed stereotactically (see KCC 16.4). The pathologic diagnosis was uncertain, revealing either an intermediate-grade pineocytoma or a pineal teratoma. He was treated with multiple cycles of chemotherapy and with radiation therapy, with repeated worsening and temporary improvement in his symptoms, but he remained relatively stable at last follow-up, 2 years after initial presentation.

Additional Cases

Related cases can be found in other chapters for the following topics: abnormalities of eye movements or pupillary responses (Cases 5.2–5.7, 10.8, 10.10–10.12, 11.2, 14.1, 14.5–14.8, 15.3, 15.4, 16.2, 16.4, 16.3). Other relevant cases can be found using the Case Index.

Brief Anatomical Study Guide

1. There are six extraocular muscles for each eye, each with a different function (see Figure 13.1; Table 13.1). The medial and lateral rectus muscles move the eye medially and laterally, respectively. The superior and inferior rectus and superior and inferior oblique muscles are involved in vertical and torsional eye movements.

2. Three cranial nerves control eye movements: The ouculomotor nerve (CN III) supplies all extraocular muscles except the lateral rectus and superior oblique (see Table 13.1; Figure 13.2). In addition, it supplies the levator palpebrae superior muscle, which elevates the upper eyelid. The trochlear nerve (CN IV) innervates the superior oblique muscle, and the abducens nerve (CN VI) innervates the lateral rectus (see Table 13.1; Figure 13.4).
CASE 13.9 HEADACHES AND IMPAIRED UPGAZE

Figure 13.26 Pineal Region Tumor Compressing the Tectum. (A) Axial image demonstrating a large enhancing lesion in the pineal region. (B) Sagittal image showing the enhancing lesion compressing the dorsal midbrain and pretectal area.

1. The oculomotor nucleus is located in the rostral midbrain at the level of the superior colliculus and red nucleus (see Figures 13.2, 14.3A). Fascicles of the oculomotor nerve exit the midbrain ventrally in the interpeduncular fossa between the posterior cerebral and superior cerebellar arteries. The nerve then runs adjacent to the posterior communicating artery, where it is susceptible to compression by aneurysms or by downward herniation of the temporal lobe over the petrosal ridge.

2. The trochlear nucleus is located in the caudal midbrain at the level of the inferior colliculus and decussation of the superior cerebellar peduncles (Figure 13.4). Fascicles of the trochlear nerve decussate and exit the brainstem dorsally. The thin trochlear nerve is particularly susceptible to injury from shearing forces in head trauma.

3. The abducens nucleus, together with fibers of the facial nerve, forms the facial colliculus on the floor of the fourth ventricle in the midpons (see Figure 12.11). Fascicles of the abducens nerve travel ventrally to exit the brainstem at the pontomedullary junction (see Figure 12.2A). The abducens nerve then ascends a long distance along the clivus and over the petrous ridge (see Figure 13.4; see also Figure 12.1), making it susceptible to injury from downward traction in elevated intracranial pressure.

4. As the oculomotor, trochlear, and abducens nerves (CN III, IV, and VI) exit the cranial cavity, they travel through the cavernous sinus (see Figure 13.11) in close association with the ophthalmic division of the trigeminal nerve (CN V) and then enter the orbit via the superior orbital fissure (see Figure 12.3A). Lesions in the cavernous sinus or orbital apex can affect multiple cranial nerves involved in eye movement control.

5. The pupils are under both parasympathetic and sympathetic control. Parasympathetic pathways mediate pupillary constriction via the pathways summarized in Figure 13.8. Preganglionic parasympathetic fibers arise from the Edinger-Westphal nucleus. Note that the parasympathetic fibers travel with the oculomotor nerve, so damage to this nerve often produces an abnormally dilated pupil. Sympathetic pathways mediate pupillary dilation via pathways summarized in Figure 13.10. Sympathetic pathways can be interrupted at multiple levels from the brainstem to the nerve fibers ascending in the neck to the eye, resulting in Horner's syndrome (see KCC 13.5, 13.6).

6. Central pathways for control of eye movements that impinge on the oculomotor, trochlear, and abducens nuclei are referred to as supranuclear pathways. The pathways involve a distributed network including brainstem, cerebellar, basal ganglia, cortical, and other circuits. For horizontal eye movements, the final common pathway and main horizontal gaze center in the brainstem is the abducens nucleus, which controls horizontal gaze for both the ipsilateral and contralateral eyes through the medial longitudinal fasciculus (MLF) (see Figures 13.12, 13.13). The paramedian pontine reticular formation (PPRF) is another important horizontal gaze center with inputs to the abducens nucleus.
Brief Anatomical Study Guide (continued)

9. Vertical gaze is controlled by nuclei in the rostral midbrain and pretectal region, including the rostral interstitial nucleus of the MLF. Control of vergence eye movements probably arises from nuclei in the midbrain reticular formation. Descending cortical inputs from the frontal eye fields (see Figure 13.14) decussate to reach the contralateral PPRF, producing contralateral lateral horizontal gaze. However, descending cortical inputs from more posterior areas of the parieto-occipito-temporal junction tend to cause ipsilateral deviation of gaze.

10. Nystagmus refers to rhythmic alternating slow phases of eye movements that move in one direction, interrupted by fast phases of eye movements in the opposite direction. Nystagmus is abnormal when it occurs at rest (without changing visual or vestibular inputs). Normal nystagmus occurs during attempts to view a visual scene or a series of stripes moving in front of the eyes and is called optokinetic nystagmus (OKN). Vestibular inputs are relayed via the MLF to stabilize the eyes on a visual image during head and body movements. This is called the vestibulo-ocular reflex (VOR).

References

General References


Oculomotor, Trochlear, and Abducens Nerve Pathies


Cavernous Sinus and Orbital Apex Syndromes


Horner's Syndrome


Horizontal Gaze Disorders


Vertical Gaze Disorders and Parinaud's Syndrome


Brainstem III: Internal Structures and Vascular Supply

A 22-year-old woman felt her neck “snap” during treatment by a chiropractor. As she left the office, she felt dizzy and staggered out to her car, falling to the left. She also developed numbness and tingling on the left side of her face, a hoarse voice, a small left pupil, a drooping left upper eyelid, and decreased sensation on the right side of her body. This patient’s symptoms illustrate the complicated deficits that follow interruption of the blood supply to one part of the brainstem. In Chapter 10 we learned about the functions of various cortical regions and their blood supply. Here we will learn about the functions of brainstem nuclei and pathways, and the blood supply that is vital to each brainstem region.
ANATOMICAL AND CLINICAL REVIEW

No region of the nervous system inspires more awe in the clinician than the brainstem, perhaps because small lesions in this structure can have devastating consequences, or perhaps because of the elegant and complex anatomy of this compact structure juxtaposed between the cerebral hemispheres on the one hand and the spinal cord and cranial nerves on the other. Or finally, perhaps the brainstem inspires respect because it is the most evolutionarily ancient brain region (together with the basal forebrain), having back to the simpler nervous systems of our reptilian ancestors. Whatever the reason, a thorough knowledge of brainstem anatomy is essential for the clinician's ability to diagnose and treat the often life-threatening disorders of this region of the brain.

In the previous two chapters we discussed the role of the brainstem in cranial nerve function, eye movements, and pupillary control. In this chapter we will examine the inner workings of the brainstem in greater detail, including some important nuclei and white matter pathways. After introducing these structures, we will identify them in the traditional manner by reviewing a series of brainstem sections. Next, several brainstem structures not discussed in other chapters will be examined in greater depth, especially those contributing to the reticular formation and related structures. Finally, we will discuss the vascular territories of the brainstem, and the characteristic syndromes that result from damage to particular groups of brainstem structures located in close proximity to one another. Discussion of these vascular syndromes is diagnostically useful and also serves as an excellent review of regional brainstem neuroanatomy.

Main Components of the Brainstem

We can summarize the main components of the brainstem in a simplified manner, as shown in Figure 14.1, by using the following four functional groupings:

1. Cranial nerve nuclei and related structures
2. Long tracts
3. Cerebellar circuitry
4. Reticular formation and related structures

As would be expected from these functional groupings, brainstem lesions are often associated with cranial nerve abnormalities, long-tract findings, ataxia, and impairments related to reticular formation dysfunction such as impaired level of consciousness and autonomic dysregulation. It can be helpful to think of these four functional groupings when imaging the effects of lesions in different parts of the brainstem.

The cranial nerve nuclei and related structures were discussed in Chapters 17 and 18, the long tracts were discussed in Chapters 6 and 7, and the cerebellar pathways will be discussed in Chapter 15. In this chapter we will review these structures briefly and discuss the brainstem reticular formation and related structures in greater detail. The subcomponents of each grouping are listed in Table 14.1. Before proceeding further, let's identify these structures in the brainstem through the traditional, but so far unparalleled, method of examining stained brainstem sections.

Brainstem Sections

There is no substitute for learning brainstem anatomy, for examining its detailed structures in stained serial sections of the human brainstem. The sections in Figures 14.3, 14.4, and 14.5 were prepared with a stain for myelin, so that myelin appears dark and gray matter appears light. We will refer to these sections as we review different nuclei, pathways, and functional systems in this chapter. A useful technique for anatomical self-study and review is to follow a given structure or pathway from start to finish as it appears in multiple adjacent sections.

Recall that the brainstem consists of the midbrain, pons, and medulla oblongata (see Figure 12.1). As in the spinal cord, motor nuclei in the brainstem are located more ventrally, while sensory nuclei are located more dorsally. During development, the sensory and motor nuclei are demarcated by the sulcus limitans (see Figure 12.1). In the adult, the sulcus limitans is still visible along the lateral wall of the fourth ventricle, dividing motor nuclei ventromedially from sensory nuclei dorsolaterally.

Another set of terminology that is sometimes used in discussing the brainstem is "tectum," "tegmentum," and "basis" (Figure 14.2). The tectum, meaning "roof" in Latin, is obvious only in the midbrain and consists of the superior and inferior colliculi, which lie dorsal to the cerebral aqueduct. The tegmentum, meaning "covering," lies ventral to the cerebral aqueduct in the midbrain and ventral to the fourth ventricle in the pons and medulla. The tegmentum makes up the main body of the brainstem nuclei and reticular formation, which we will discuss in this chapter. The basis is the most ventral portion, where the large collections of fibers making up the cerebellar and corticobulbar tracts lie.

For overall orientation, let's review the brainstem sections briefly, proceeding from rostral to caudal. Functional details of the many structures mentioned here are discussed elsewhere. The midbrain is relatively short, and most axial sections cut through either the superior colliculi, which are more rostral (Figure 14.3A), or the inferior colliculi, which are more caudal (see Figure 14.3B). Sections at these two levels can be distinguished because sections through the superior colliculi also include the oculomotor nuclei and red nuclei (see Figure 14.3A), while sections through the inferior colliculi also include the

![Figure 14.1 Main Components of the Brainstem](image-url)
TABLE 14.1 Summary of Brainstem Structures

<table>
<thead>
<tr>
<th>MAIN FUNCTIONAL GROUPINGS</th>
<th>SUBCOMPONENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Cranial nerve nuclei</td>
<td>Somatic motor column (GSE)*</td>
</tr>
<tr>
<td>and related structures (see Chapters 12, 13)</td>
<td>Ocullomotor, trochlear, abducens, and hypoglossal nuclei</td>
</tr>
<tr>
<td>Branchial motor column (SVE)</td>
<td>Motor trigeminal, facial, ambiguous, and spinal accessory nuclei</td>
</tr>
<tr>
<td>Parasympathetic column (GVE)</td>
<td>Edinger-Westphal, superior and inferior salivatory nuclei, dorsal motor nucleus of CN X</td>
</tr>
<tr>
<td>General somatic sensory column (GSA)</td>
<td>Trigeminal nuclear complex</td>
</tr>
<tr>
<td>Special somatic sensory column (SSA)</td>
<td>Vestibular nuclei, cochlear nuclei</td>
</tr>
<tr>
<td>Vestibular sensory column</td>
<td>Nucleus solitarius: visceral portion (SVA); caudal portion (GVA)</td>
</tr>
<tr>
<td>Additional nuclei and pathways associated with eye movements</td>
<td>Periadenal area; superior colliculus; medial longitudinal fasciculus (MLF); central interstitial nucleus of the MLF; convergence center; paramedian pontine reticular formation; accessory hypoglossal nuclei</td>
</tr>
<tr>
<td>Additional nuclei and pathways associated with hearing</td>
<td>Superior olive; olivary nuclear complex; trapezoid body; lateral lemniscus; inferior colliculus</td>
</tr>
<tr>
<td>Other nuclei and pathways associated with cranial nerve functions</td>
<td>Reticular formation; central tegmental tract</td>
</tr>
<tr>
<td>2. Long tracts</td>
<td>Motor pathways</td>
</tr>
<tr>
<td>(see Chapters 6, 7)</td>
<td>Corticospinal and corticobulbar tracts; other descending somatotopic pathways; descending autonomic pathways</td>
</tr>
<tr>
<td>Sensory pathways</td>
<td>Posterior column; medial lemniscus system; anterolateral system</td>
</tr>
<tr>
<td>3. Cerebellar circuitry</td>
<td>Superior, middle, and inferior cerebellar peduncles</td>
</tr>
<tr>
<td>(see Chapter 15)</td>
<td>Pontine nuclei; red nucleus (parvocellular portion); central tegmental tract; inferior olivary nucleus</td>
</tr>
<tr>
<td>4. Reticular formation and related structures</td>
<td>Systems with widespread projections</td>
</tr>
<tr>
<td>Reticular formation; collicular region; pedunculopontine nuclei; substantia nigra; pontomesencephalic tegmental region; nucleus of the solitary tract; autonomic control, including heart rate and blood pressure; swallowing and vomiting; chemotactic trigger zone; autonomic control, including heart rate and blood pressure; sphencter control, including pontine micturition center</td>
<td></td>
</tr>
</tbody>
</table>

Note: The structures listed here reflect our interest in learning clinically relevant neuroanatomy. There are numerous additional brainstem structures beyond the scope of this text.

*GSA, general somatic afferent; GSE, general somatic efferent; GVA, general visceral afferent; GVE, general visceral efferent; SSA, special somatic afferent; SVA, special visceral afferent; SVE, special visceral efferent.
Figure 14.5 Myelin-Stained Sections of the Medulla and Cervical Spine
Axial planes of section are shown in the insets. (A) Cervical medulla (C5-6). (B) Caudal medulla (C6-8). (C) Cerebrospinal fluid (C6-8). (D) Posterior cervical spinal cord (C2). (E) Stylopharyngeal muscles (C2). (F) From Martin JH, 1990, Neuroanatomy: Text and Atlas, 2nd Ed. McGraw-Hill, New York; D from the University of Washington Digital Anatomist project.)
Now that we have reviewed the overall architecture of the brainstem, we are ready to discuss each of the four main functional groupings (see Table 12.3) in more detail.

**Cranial Nerve Nuclei and Related Structures**

As discussed in Chapter 12, the cranial nerve motor nuclei are located ventral to the sulcus limitans, and the sensory nuclei dorsal to the sulcus limitans. In an arrangement similar to that of the spinal cord (see Figure 12.4), there are three longitudinal columns of motor nuclei and three columns of sensory nuclei, covered in detail in Chapters 12 and 13 (see Figure 12.5; Tables 12.3, 12.4). We will review these nuclei again briefly here, and identify them in the brainstem sections. Knowing the locations of these nuclei in the brainstem is essential for localizing brainstem lesions, as we will discuss later in this chapter.

The somatic motor nuclei (CSN) are the oculomotor, trochlear, abducens, and hypoglossal nuclei, all of which remain adjacent to the midline. The oculomotor nuclei (CN III) are in the rostral midbrain, the trochlear nuclei (CN IV) in the caudal midbrain; both nuclei lie just ventral to the periaqueductal gray (see Figure 14.3A,B). The medial longitudinal fasciculus (MLF) forms the ventral border of the oculomotor and trochlear nuclei, and interconnects these nuclei, the abducens nuclei, and the vestibular nuclei. The abducens nuclei (CN VI) help form the facial colliculus on the floor of the fourth ventricle in the mid- to lower pons (see Figure 14.4C). As we discussed in Chapter 13, several other brainstem regions are important for the supranuclear control of movements, including the paramedian pontine reticular formation (see Figure 13.12), the rostral interstitial nucleus of the MLF, and the convergence center. The hypoglossal nuclei (CN XII) form the hypoglossal triceps on the floor of the fourth ventricle in the middle to lower pons (see Figure 14.5A; see also Figure 12.28B) and have a longitudinal sausage shape continuing into the caudal medulla (see Figure 14.5B). As can be seen in these sections, three sausage-shaped nuclei border a central space through which the nuclei run along the wall of the ventricle or central canal of the medulla. These are, from medial to lateral, the hypoglossal, dorsal motor X, and solitary nuclei (see Figure 14.5A,B; see also Figure 12.5).

The branchial motor nuclei (SVN) are the trigeminal motor nucleus (CN V), facial nucleus (CN VII), nucleus ambiguus (CN IX, X), and spinal accessory nucleus (CN XI; also known as the accessory spinal nucleus). Recall that the branchial motor nuclei initially lie just lateral to the somatic motor nuclei, but they gradually migrate ventrolaterally to the tegmentum (see Figure 12.4). The trigeminal motor nucleus is located in the upper to midpons (see Figure 14.4B), just ventral to the chief trigeminal sensory nucleus, near the level where the trigeminal nerve exits the brainstem. The facial nucleus is located more caudally in the pontine tegmentum (see Figure 14.4C) and gives rise to the loopings of the fibers of the facial colliculus. The nucleus ambiguus is difficult to distinguish from the surrounding brainstem (see Figure 14.5A,B). It runs longitudinally through the medulla in a similar position to the facial nucleus. The spinal accessory nucleus (also known as the accessory spinal nucleus), as its name implies, is located not in the brainstem, but rather in the upper five segments of the cervical spinal cord (see Figure 14.5D). It protrudes laterally between the dorsal and ventral horns of the spinal cord central gray matter.

The parasympathetic nuclei (CVE) are the Edinger–Westphal nuclei (CN III), superior (CN VII) and inferior (CN IX) salivatory nuclei, and dorsal motor nucleus of CN X. The Edinger–Westphal nuclei form a V-shaped cap as they fuse in the midline and curve over the dorsal and rostral aspect of the occipital motor nuclei (see Figure 14.3A; see also Figure 13.3). The superior and inferior salivatory nuclei lie in the pontine tegmentum (see Figure 12.5), and do not form discrete, easily visible nuclei on standard sections. The dorsal motor nucleus of CN X runs from the rostral to the caudal medulla, just lateral to the hypoglossal nucleus (see Figure 14.5A,B). It forms the vagal trigone on the floor of the fourth ventricle, just lateral to the hypoglossal trigone (see Figure 12.2B).

General somatic sensory (GSA) inputs from the cranial nerves (CN V, VII, IX, X) all travel to the trigeminal nucleus complex. The trigeminal sensory complex runs from the midbrain to the upper cervical spinal cord (see Figures 14.3–14.5) and consists of three nuclei: the mesencephalic, chief sensory, and spinal trigeminal nuclei (see Table 12.6). The mesencephalic trigeminal nucleus and tract, subserving proprioception, run along the lateral edge of the periaqueductal gray matter of the midbrain (see Figures 14.3, 14.4A). The chief trigeminal nucleus (CN V1) is located in the upper to midpons, just dorsalateral to the trigeminal motor nucleus (see Figure 14.4B). The spinal trigeminal nucleus and spinal trigeminal tract run the length of the lateral pons and medulla (see Figures 14.4C, 14.5A–C). It should be clear from reviewing Figure 14.5C and D that the spinal trigeminal nucleus is the rostral extension of the dorsal horn of the spinal cord. Recall that these systems are analogous, subserving pain and temperature sensation for the face and body (see Table 12.6). Similarly, the chief trigeminal nucleus (see Figure 14.4B) is analogous to the dorsal column nuclei (see Figure 14.5B) in that both subserve fine discriminative touch.

Special somatic sensory (SSS) inputs for hearing and vestibular sense (CN VIII) reach the cochlear and vestibular nuclei, respectively. The dorsal and ventral cochlear nuclei wrap around the lateral aspect of the inferior cerebellar peduncle at the pontomedullary junction (see Figure 12.17C). After entering the brainstem, the hearing pathways decussate at multiple levels, as discussed in Chapter 12. Many fibers from the cochlear nuclei decussate in the trapezoid body in the caudal pons (see Figure 14.4C; see also Figures 12.16, 12.17B). Some fibers synapse in the superior olivary nuclear complex of the pons (see Figure 14.4C). Auditory information then ascends in the lateral lemniscus (see Figures 14.3B, 14.4) to reach the inferior colliculus (see Figure 14.3B). From there, fibers ascend via the brachium of the inferior colliculus to the medial geniculate nucleus of the thalamus, located just lateral to the superior colliculus of the midbrain (see Figure 14.3A). Information then continues in the auditory radiations to the primary auditory cortex (see Figure 12.18).

There are four vestibular nuclei—superior, inferior, medial, and lateral—on each side of the brainstem, lying on the lateral floor of the fourth ventricle, in the pons and rostral medulla (see Figures 14.4B,C, 14.5A; see also Figure 12.18). As we discussed in Chapter 12, the vestibular nuclei convey perception of head position and acceleration to the cerebral cortex via relays in the ventral posterior thalamus. However, most functions of the vestibular nuclei are in the level of conscious perception. Thus, the medial and lateral vestibulospinal tracts (see Figure 6.11D) are involved in posture and muscle tone, and they arise primarily from the medial and lateral vestibular nuclei, respectively. The medial vestibular nucleus is the largest of the vestibular nuclei (see Figure 14.5A). The inferior vestibular nucleus is also relatively easy to identify be-
cause fibers of the lateral vestibular nucleus traverse the inferior vestibular nucleus as they descend to the spinal cord, giving the inferior vestibular nucleus a characteristic "checkerboard" appearance on myelin-stained sections (see Figure 14.5A).

As we mentioned earlier in this section, the MLF is an important pathway connecting the vestibular nuclei and nuclei involved in extracranial movements (see Figure 12.18). The MLF can be identified as a heavily myelinated tract running near the midline in each side, just under the floor of the fourth ventricle in the midline of the pons (see Figure 14.4), and just under the oculomotor and trochlear nuclei in the midbrain (see Figure 14.3). Fibers arising from the medial vestibular nucleus, with additional contributions mainly from the superior vestibular nucleus, ascend in the MLF to the oculomotor, trochlear, and abducens nuclei, mediating vestibulo-ocular reflexes (see Chapter 13). Finally, as we will discuss in Chapter 15, the vestibular nuclei have numerous important reciprocal connections with the cerebellum, primarily with the inferior cerebellar vermis and flocculonodular lobes.

All visceral afferents, whether special or general, travel to the nucleus solitarius (see Figure 14.5A,B), located just lateral to the dorsal motor nucleus of CN X. Note that the nucleus solitarius has a unique appearance in myelin sections, with the heavily stained central solitary tract surrounded by the lightly stained tube-shaped (donut-shaped in cross section) solitary nucleus. Special visceral afferents (SVA) for taste (CN VII, IX, X) reach the rostral nuclei solitarius, also known as the gustatory nucleus, while general visceral afferents (GVA) from the cardioregulatory (and gastrointestinal) systems (CN IX, X) reach the caudal nucleus solitarius, also known as the cardiorespiratory nucleus. As discussed in Chapter 12, the taste pathway continues rostrally via the central tegmental tract (see Figures 12.12, 14.3, 14.4) to reach the ventral posterior nucleus (VPM) of the thalamus, which projects to the cortical taste area in the parietal operculum and insula.

**Long Tracts**

The major long tracts that pass through the brainstem were discussed in Chapters 6 and 7. The major descending motor pathways are summarized in Figure 6.11 and Table 6.3. Recall that the corticospinal and corticobulbar tracts travel in the middle third of the cerebral peduncles in the midbrain (see Figure 14.2; see also Figure 6.10B). The other portions of the cerebral peduncles carry predominantly corticoreticular fibers involved in cerebellar circuitry (see Chapter 15). The corticospinal fibers continue from the midbrain cerebral peduncles to run through the basis pontis (see Figure 14.4) and then emerge as the pyramids in the ventral medulla (see Figure 14.5A,B). The pyramidal decussation occurs at the cervico-medullary junction (see Figure 14.5C), giving rise to the lateral corticospinal tract (see Figure 14.2D).

The major ascending somatosensory pathways are summarized in Figures 7.1 and 7.2, and in Table 7.1. Recall that axons in the posterior columns, serving vibration, joint position sense, and fine touch, synapse onto neurons in the posterior horn nucleus, consisting of the more medial nucleus gracilis for the legs, and the more lateral nucleus cuneatus for the arms (see Figure 14.5B-D). The posterior column nuclei give rise to the internal arcuate fibers, which cross to the opposite side (see Figure 14.5B) and then ascend through the brainstem as the medial lemniscus (see Figures 14.3, 14.4, 14.5B-D) to reach the VPFL (ventral posterior lateral nucleus) of the thalamus (see Figure 7.1). The anterolateral systems, including the spinthalamic tract, subserves pain, temperature, and crude touch. The anterolateral systems decussate in the spinal cord—not the brainstem—and they assume a fairly fixed, lateral position as they ascend through the brainstem (see Figures 14.3–14.5).

One additional descending pathway that is clinically relevant is the descending sympathetic pathway running through the lateral brainstem in close proximity to the interstitial nuclei (see Figure 13.10). Recall that damage to this pathway can cause Horner’s syndrome (see KCC 13.5).

**KEY CLINICAL CONCEPT: LOCKED-IN SYNDROME**

Patients who have absent motor function but maintain intact sensation and cognition are said to be "locked-in." The usual cause is an infarct in the ventral pons (see KCC 14.3) affecting the bilateral corticospinal and corticobulbar tracts. The spinal cord and cranial nerves receive no input from the cortex, and the patient is unable to move. Sensory pathways and the brainstem reticular activating systems are spared. Patients are thus fully aware and able to feel, hear, and understand everything in their environment. This condition can mimic—in but should be carefully distinguished from—coma, which is discussed later in this chapter (see KCC 14.2).

As we saw in Chapter 13, vertical eye movements and eyelid elevation are controlled by a region in the tegmentum of the rostral midbrain. Horizontal eye movements, however, depend on pontine circuits (see Figure 13.12). Therefore, locked-in syndrome often spares vertical eye movements and eye opening. Patients with this syndrome can thus communicate using eye movements. Special computer interfaces based on eye movements have been developed for patients with locked-in syndrome. The French editor Jean-Dominique Bauby ever wrote an entire book (Le Scaphandre et le Papillon, or The Diving Bell and the Butterfly) after becoming locked in, spelling out one letter at a time to a transcriber by using eye movements. The prognosis is generally poor: About 60% of patients eventually succumb to respiratory infection or other complications of paralysis. Some patients, however, do regain some motor function over time, and rarely, a near-complete recovery can occur.

In addition to bilateral ventral pontine infarcts, other lesions in the ventral pons, such as hemorrhage, tumor, encephalitis, multiple sclerosis, or central pontine myelinolysis can also occasionally cause locked-in syndrome. Less commonly, lesions in the bilateral cerebral peduncles of the midbrain, or in the internal capsules, can be the cause. In addition, a locked-in condition can result from severe disorders of motor neurons, peripheral nerves, muscles, or the neuromuscular junction (see KCC 8.1).
largest of the cerebellar peduncles (see Figure 14.4B,C). It contains massive inputs to the cerebellum arising from the pontine nuclei scattered through the basis pontis (see Figure 14.4). The pontine nuclei, in turn, receive inputs from the corticopontine fibers of the cerebral peduncles (see Figure 14.3). The inferior cerebellar peduncle mainly carries inputs to the cerebellum from the spinal cord (see Figure 14.5A). In addition to the pontine nuclei, several other brainstem nuclei participate in cerebellar circuitry. We will mention only a few of these here. As we have just discussed, the red nucleus receives inputs from the superior cerebellar peduncle (see Figure 14.3A). The rostral (parvocellular) portion of the red nucleus sends fibers via the central tegmental tract (see Figures 14.3B, 14.4) to reach the inferior olivary nucleus in the rostral medulla (see Figure 14.5A), which in turn sends fibers back to the cerebellum via the inferior cerebellar peduncle. Interruption of this circuit from cerebellum to brainstem and back to cerebellum results in a characteristic, though rare, movement disturbance called palatal myoclonus, which is characterized by continuous rhythmic clicking movements of the palate. In addition, as mentioned earlier, the vestibular nuclei are intimately interconnected with the cerebellum.

Reticular Formation and Related Structures

The reticular formation is a central core of nuclei that runs through the entire length of the brainstem (Figure 14.6). It is continuous rostrally with certain diencephalic nuclei, and caudally with the intermediate zone of the spinal cord. Simplifying somewhat, we can say that these rostral and caudal extensions highlight the two main functions of the reticular formation. Thus, the rostral reticular formation of the mesencephalon and upper pons function together with diencephalic nuclei to maintain an alert conscious state in the forebrain. Meanwhile, the caudal reticular formation of the pons and medulla works together with the cranial nerve nuclei and the spinal cord to carry out a variety of important motor, reflex, and autonomic functions. Although there are numerous exceptions, this simplified rostral and caudal conceptualization can be heuristically and clinically useful. Definitions vary as to which nuclei to include in the reticular formation. The reticular formation has no obvious nuclear divisions when viewed with conventional histological staining. In addition, as we will discuss shortly, some neurons in the reticular formation have very widespread projection patterns, adding to the impression that this structure is diffusely organized. With more refined techniques, however, numerous specific nuclei can be identified within the reticular formation, some of which have quite precisely organized projection patterns. In addition, some cranial nerve nuclei, such as the superior and inferior salivatory nuclei, or the nucleus ambiguus, lie buried within the reticular formation. For our purposes, we will define the reticular formation as simply that portion of the brainstem tegmentum in which clearly defined nuclei are not generally visible with conventional staining.∗

In addition to the reticular formation, the brainstem tegmentum contains numerous other nuclei that we refer to here simply as related structures (see Table 14.1). These include the periaqueductal gray matter in the midbrain, which is involved in pain modulation, and the chemosensitive trigger zone in the medulla, involved in causing nausea.

∗Clearly visible subnuclei do appear in some regions, for example, the nucleus reticularis gigantocellularis, which is located in the medial medullary glossopharyngeal and vagus).
TABLE 14.2 Widespread Projection Systems in the Nervous System

<table>
<thead>
<tr>
<th>PROJECTION SYSTEM</th>
<th>LOCATION(S) OF CELL BODIES</th>
<th>MAIN TARGET(S)</th>
<th>NEUROTRANSMITTER RECEPTORS</th>
<th>FUNCTION(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reticular formation</td>
<td>Midbrain and retrolimbic pons</td>
<td>Thalamus intralaminar nuclei, hypothalamus, basal forebrain</td>
<td>Unknown (glutamate?)</td>
<td>Alertness</td>
</tr>
<tr>
<td>Intrapallidal nuclei</td>
<td>Medial thalamic nuclei</td>
<td>Cortex, striatum</td>
<td>GABA (GABAergic)</td>
<td>Alertness</td>
</tr>
<tr>
<td>Dopaaminergic</td>
<td>Midbrain substantia nigra pars compacta and ventral tegmental area</td>
<td>Striatum, limbic cortex, amygdala, nucleus accumbens, prefrontal cortex</td>
<td>DA, D2, D3</td>
<td>Mood elevation, movement, reward, emotional, working memory</td>
</tr>
<tr>
<td>Serotoninergic</td>
<td>Midbrain and raphe nuclei</td>
<td>Entire CNS</td>
<td>5-HT, 5-HT2A, 5-HT2C, 5-HT1A</td>
<td>Mood elevation, sleep, memory, pain, nausea</td>
</tr>
<tr>
<td>Histaminergic</td>
<td>Hypothalamic tuberomammillary nucleus; midbrain, reticular formation</td>
<td>Entire brain</td>
<td>H1</td>
<td>Alertness</td>
</tr>
<tr>
<td>Acetylcholinergic</td>
<td>Basal forebrain, nucleus basalis, medial septal nucleus, and nucleus of diagonal band</td>
<td>Cerebral cortex</td>
<td>Muscarinic (M1, M2), nicotinic subtypes</td>
<td>Alertness, memory, planning, arousal</td>
</tr>
<tr>
<td>Pontomesencephalic region: pedunculopontine tegmental nucleus and lateral tegmental nuclei</td>
<td>Thalamus, cerebellum, pons, medulla</td>
<td>Muscarinic (M1, M2), nicotinic subtypes</td>
<td>Alertness, memory, emotional, autonomic, motivational</td>
<td></td>
</tr>
</tbody>
</table>

*Many of the neurotransmitters releasing the neuromodulatory transmitters listed here also release a variety of peptides, which are likely to play a neuromodulatory role as well.
*Several of the receptor subtypes listed here have been cloned, and additional receptor subtypes are constantly being added.
*Functions listed are highly simplified here; see text and references for additional details.

Figure 14.7 Ascending Reticular Activating System (ARAS). (A) Coronal view; (B) Frontal view. Widespread projections from the pontomesencephalic reticular formation course via the thalamic intralaminar nuclei, basal forebrain, and hypothalamus, projecting over targets including large regions of the nervous system. In others, the system as a whole has widespread projections, but individual neurons have very specific projections, enabling focal control of specific targets. Together, these projection systems are essential for maintaining an alert conscious state, and for regulating attention, sleep-wake cycle, emotional balance. In the sections that follow, we will discuss the major widespread projection systems—some with identified neurotransmitters, and others for which the neurotransmitters are still under investigation.

**Brainstem Reticular Formation and Thalamus**

The pontomesencephalic reticular formation forms a circuit together with certain thalamic nuclei that is critical to maintaining normal consciousness (Figure 14.7). On the basis of animal experiments and human patients studied in the 1960s and 1970s, it was found that lesions in the rostral brainstem reticular formation and caudal diencephalon can cause coma, while stimulation of the same regions can lead to behavioral and electrophysiological arousal from mesencephalic. Moruzzi and Magoun named these regions of the brain the ascending reticular activating system (ARAS). Although it has subsequently been found that these systems are not all ascending descending cor-
The pontomesencephalic reticular formation projects to the thalamic intralaminar nuclei (see Figure 14.7). The neurotransmitters for these projections have not been identified with certainty, although many neurons in this pathway contain glutamate. The thalamic intralaminar nuclei have numerous reciprocal connections with the basal ganglia (see Table 7.3; Figure 7.7). In addition, however, the intralaminar nuclei, particularly the rostral intralaminar nucleus (central lateral, paracentral, and central medial nuclei) have widespread projections to the cerebral cortex (see Figure 7.8). These projections, together with widespread projections from the thalamic nuclei, such as those arising from the adjacent midline thalamic nuclei (see Figure 7.6), are thought to be important for maintaining normal alertness. In addition to projections to the intralaminar nuclei, the pontomesencephalic reticular formation projects to the hypothalamus and basal forebrain (see Figure 14.7). Widespread projections from these regions, in turn, may also participate in the alerting functions of the pontomesencephalic reticular formation.

What activates this system of behavioral arousal and alertness? The reticular formation gets inputs from sensory pathways, especially the anterolateral system spinothalamic pathway involved in pain transmission (Figure 14.8; see also Figure 7.2). In addition, numerous regions of association cortex and limbic cortex project to the pontomesencephalic reticular formation (as well as to the intralaminar nuclei). Thus, brainstem and cortical processes and emotions, respectively, can lead to an increased level of alertness through this system. Other circuits that may play a role in attentional mechanisms include the superior colliculus, corellubum, and lateral reticular nucleus, as we will discuss in Chapter 19. These mechanisms are still under active investigation.

Identified Neurotransmitter Systems

Aside from the brainstem formation and certain thalamic nuclei, several identified neurotransmitter systems that project in a rostral direction to innervate the forebrain arise from the midbrain and rostral pons, while those that project to the brainstem, cerebellum, or spinal cord arise from the lower pons or medulla. In addition, some neurotransmitter systems that project rostrally have their main source outside the brainstem in the hypothalamus (histamine) or basal forebrain (acetylcholine).

As we discussed in Chapter 2 (see Table 2.2), neurotransmitters have two general types of functions. One is to mediate communication between neurons through fast excitatory or inhibitory postsynaptic potentials acting in the millisecond time range. The main excitatory and inhibitory neurotransmitters in the central nervous system are glutamate and gamma-aminobutyric acid (GABA), respectively. The second function is neurotrans modulation, generally occurring over slower time scales. Neurotransmodulation includes a broad range of cellular mechanisms involving signaling cascades that regulate synaptic transmission, neuronal growth, and other functions. Neurotransmodulation can either facilitate or inhibit the subsequent signaling properties of the neuron. The neurotransmitters of the diffuse projection systems, including acetylcholine, dopamine, noradrenaline, serotonin, and histamine, have a mainly neurotransmodulatory role in the central nervous system. In addition, it is likely that a variety of peptides, small molecules, and other, as yet unidentified, transmitters participate as well. Depending on the specific receptors present, these transmitters can have a facilitatory or inhibitory effect on neuronal signaling. Some neurotransmitters even have both a facilitatory and an inhibitory neurotransmodulatory effect at different synapses or different receptor sites. The functional effects of these transmitters also depend on the region of the brain in which they are found, and on the level of consciousness, sleep--wake cycle, emotional state, motor behavior, and many other diverse factors. Some of these neurotransmodulatory actions are beyond the scope of this text (see the references at the end of this chapter for more information). Here, we will focus instead on the anatomical distribution of these neurotransmitter systems and their functional roles only in the most general terms.

Note that, unlike gross lesions of the pontomesencephalic reticular formation, lesions or pharmacological blockades of the individual projecting neurotransmitter systems discussed in this section do not result in coma. Lesions or blockades of some neurotransmitter systems, especially acetylcholine and histamine, can cause profound confusion and disorientation, but not coma. Thus, it appears unlikely that maintenance of the normal awake state does not depend on a single projection system. Rather, it probably depends on intact functioning of multiple anatomical and neurotransmitter systems acting in parallel, including the pontomesencephalic reticular formation and other brainstem projection pathways, as well as bilateral thalamic intralaminar nuclei, and bilateral cerebral cortex. The individual neurotransmitter systems discussed here do play an important role in attentional mechanisms, memory, and emotional states, as will be discussed.

ACETYLCHOLINE. Acetylcholine is the major efferent neurotransmitter of the peripheral nervous system, found at the neuromuscular junction, preganglionic autonomic synapses, and postsynaptic ganglionic sympathetic synapses (see Chapter 6). Cholinergic neurons play a more limited role in the central nervous system, functioning primarily in neurotransmodulation rather than neurotransmission (recall that the major excitatory neurotransmitter of the central nervous system is glutamate). Neurotransmodulatory cholinergic neurons with widespread projections are found mainly in two locations (Figure 14.9): the pontomesencephalic region of the brainstem, and the basal forebrain. Neurons of the brainstem cholinergic projection system are found mainly in the pedunculopontine tegmental nuclei and the laterodorsal tegmental nucleus (see Figure 14.9). These nuclei are located, respectively, in the lateral portion of the reticular formation and periaqueductal gray, at the junction between the mid-
Classically, the main cholinergic receptor type in the central nervous system is muscarinic (see Table 14.2). However, nicotinic receptors may play an important role in the central nervous system as well. The main functions of acetylcholine in the central nervous system are attention, memory, and learning. Pharmacological blockade of central cholinergic transmission causes delirium (see KCC 14.2, 19.15) and memory deficits. Degeneration of cholinergic neurons in the basal forebrain may be one of the mechanisms for memory decline in Alzheimer’s disease (see KCC 19.16). The effects of cholinergic blockade on striatal neurons in movement disorders are discussed in Chapter 16.

Dopamine. Dopamine is found mainly in neurons located in the ventral tegmental area and the substantia nigra pars compacta and the nearby ventral tegmental area (see Figures 14.3, 14.10). Three projection systems have been described arising from these nuclei in the mesencephalon. The mesostriatal (nigrostriatal) pathway arises mainly from the substantia nigra pars com-

![Image of brain structures with annotations](image-url)

**Figure 14.9** Cholinergic Projection Systems. See also Table 14.2. (A and B sections modified from Martin JH. 1996. Neuroanatomy: Text and Atlas, 2nd Ed. McGraw-Hill, New York.)

- Brain and pons. Cholinergic projections from this region travel to the thalamus, including the intralaminal nuclei, which in turn project to widespread regions of the cortex (see Figure 14.7). Acetylcholine has different effects on different regions of the thalamus. In addition to its possible role in arousal, the pedunculopontine nucleus has a role in motor systems, and it is sometimes referred to as the mesencephalic locomotor region. Electrical stimulation of this region in animals causes coordinated locomotor movements. In this capacity, the pedunculopontine and laterodorsal tegmental nuclei have extensive connections with the basal ganglia, tectum, deep cerebellar nuclei, pons, medulla, and spinal cord.

- Cholinergic inputs to the thalamus generally have an arousing effect mediated indirectly by facilitation of excitatory projections from the thalamus to the cortex. However, direct cholinergic inputs to the cortex do not arise from the brainstem to any significant extent; instead, they come mainly from the basal forebrain (see Figure 14.9). The nucleus basalis (of Meynert) contains cholinergic neurons that project to almost the entire cerebral cortex. Cholinergic projections to the hippocampal formation arise from the medial septal nuclei and from the nucleus of the diagonal band (of Broca). Cholinergic effects on the cortex and hippocampus are generally facilitatory. The cholinergic projections to the hippocampus are involved in generating a rhythmic oscillation, called the hippocampal theta rhythm, that has been postulated to play a role in the memory functions of this brain region.

- In addition to cholinergic neurons with long-range projections, the central nervous system also contains cholinergic interneurons with more short-range local connections. Such cholinergic interneurons are found in the striatum (see Figure 16.7) and, to a more limited extent, in the cerebral cortex. There is also a cholinergic projection from the medial habenula to the interpeduncular nucleus.

![Image of brain structures with annotations](image-url)

**Figure 14.10** Dopaminergic Projection Systems. See also Table 14.2.
Norepinephrine. Neurons containing norepinephrine (noradrenaline) were once thought to be located exclusively in the locus ceruleus, meaning “blue spot,” located near the fourth ventricle in the rostralpons (see Figures 14.4A, 14.11). However, norepinephrine neurons with similar projections to the locus ceruleus are also found scattered in the lateral tegmental area of thepons and medulla. Ascending noradrenergic projections from the locus ceruleus and rostral lateral tegmental area reach the entire forebrain (see Figure 14.11).

The effects of norepinephrine on the cortex are inhibitory or excitatory, but effects on the thalamus are generally excitatory. Some of the better-known receptor types are listed in Table 14.2. Functions of the ascending norepinephrine projection system include modulation of attention, sleep–wake states, and mood. Attention-deficit disorder is often treated with medications that enhance noradrenergic transmission. Firing of locus ceruleus neurons increases in the awake state and decreases dramatically during sleep. However, lesions of the locus ceruleus do not cause somnolence. On the other hand, norepinephrine, a sleep disorder characterized by excessive daytime sleepiness, often responds to treatment with noradrenergic-enhancing medications. Norepinephrine appears to be important, together with serotonin, in mood disorders such as depression and manic-depressive disorder, and in anxiety disorders including obsessive-compulsive disorder (see KCC 18.3).

The locus ceruleus and lateral tegmental area also supply norepinephrine to the cerebellum, brainstem, and spinal cord. Noradrenergic neurons in the lateral tegmental area of the caudal pons and medulla are involved in sympathetic functions such as blood pressure control. In addition to norepinephrine, the related catecholamine epinephrine (adrenaline) is found in a small number of brainstem neurons. The role of these neurons has not been established, but it may also be related to blood pressure control.

Serotonin. Serotonin is found in neurons of the raphe nuclei of the midbrain,pons, and medulla (Figure 14.12). “Raphe” means “seam” in Greek, and it refers to the midline semilunar appearance of the brainstem in some areas where these nuclei are located (see Figures 14.12B, 14.4). The rostral raphe nuclei of the midbrain and rostral pons project to the entire forebrain, including the cortex, thalamus, and basal ganglia (see Figure 14.12). Both excitatory and inhibitory effects of serotonin have been described, even within the same structure. Serotonergic pathways are believed to play a role in several psychiatric syndromes (see also KCC 18.3), including depression, anxiety, obsessive-compulsive disorder, aggressive behavior, and certain eating disorders. The caudal raphe nuclei of the caudal pons and medulla project to the cerebellum, medulla, and spinal cord. Projections to the spinal cord and medulla are involved in pain modulation (see Figure 7.8). In addition to the raphe nuclei, a small number of serotonergic neurons have been identified in other brainstem regions, including in the area postrema and caudal locus ceruleus, and around the interpeduncular nucleus.

Histamine. Histamine is found mainly in neurons of the posterior hypothalamus in the tuberomammillary nucleus (Figure 14.13), although there
are some scattered histaminergic neurons in the midbrain reticular formation as well. Most histamine in the body is found outside the nervous system in mast cells, where it plays a role in immune responses and allergic reactions. Only relatively recently were histaminereceivingleurons identified in the nervous system. Divergent histaminergic projections from the tuberomammillary nucleus to the forebrain may be important in maintaining the alert state. Histamine has excitatory effects on thalamic neurons, and both inhibitory and excitatory effects on cortical neurons. Anti-histamine medications, used to treat allergies, are thought to cause drowsiness by blocking CNS histamine receptors.

As we will discuss shortly, the histaminergic neurons of the tuberomammillary nucleus participate in a circuit with the hypothalamic neurons that regulate sleep and arousal (see Figure 14.15A). Inhibitory neurons, especially located in the ventrolateral preoptic area of the anterior hypothalamus, project to the tuberomammillary nucleus, inhibiting histamine release and promoting sleep.

OTHER PROJECTING SYSTEMS. In addition to the systems already listed, a variety of other neuropeptides or projecting pathways that may play a role in alertness, mood regulation, memory, and other functions have been described or are still under investigation. These include peptides and small-molecule neurotransmitters. For example, adenosine is another putative neurotransmitter that may be important in mechanisms of alertness. Adenosine receptors are found in both the thalamus and the cortex, and adenosine generally has an inhibitory effect on these structures. The sources of adenosine in the nervous system have not been well characterized. Interestingly, concentrations of adenosine vary in a circadian manner, reaching a maximum just before sleep begins. One important mechanism for the increase in alertness produced by caffeine may be the blockade of adenosine receptors.

The inhibitory neurotransmitter GABA is found throughout the nervous system. Although well known for its role in inhibitory local interneurons, GABA also participates in long-range inhibitory projections. For example, GABAergic projection systems have been described in the basal forebrain projecting to widespread cortical areas, and in the reticular nucleus of the thalamus projecting to other thalamic nuclei, as well as to the medial brainstem reticular formation. The functional roles of these GABAergic projection systems are still under investigation, but they may be crucial for gating information flow in the nervous system and for regulating oscillatory electrophysiological activity underlying sleep and arousal.

Anatomy of the Sleep-Wake Cycle

The sleep-wake cycle involves a complex interplay of neural circuits, many located in the brainstem. In adult humans, there are five stages of sleep (Figure 14.14). Normally, sleep begins with stages 1 through 4 of progressively deeper nonREM (non-rapid eye movement) sleep. NonREM sleep is followed by REM (rapid eye movement) sleep, during which most dreaming typically occurs. The cycle then repeats several times through the night (see Figure 14.14). REM sleep is sometimes called "paradoxical sleep." This name is used because in some ways REM is a deeper stage of sleep than stage 4, while in other ways it more closely resembles the awake state. For example, general muscle tone and brainstem monoaminergic neurotransmission are lower during REM sleep than during any other stage. On the other hand, the electroencephalogram (EEG; see Chapter 4) during REM sleep in some ways resembles that of awake activity (a low-voltage mixture of relatively fast activity), while the EEG of stages 3 and 4 nonREM sleep more closely resembles coma (high-voltage slow activity). It is also easier to awaken an individual from REM sleep than from stages 3 and 4 of nonREM sleep.

Sleep is not, as was once thought, a passive process arising from decreased stimulation of the nervous system. Several neural circuits interact to generate sleep, including many of the circuits described earlier in this chapter. Interestingly, whereas classic transcranial stimulation in cats at the midbrain level produces coma, demonstrating the importance of the reticular formation in maintaining the awake state, stimulation at the level of the lowerpons markedly reduces sleep in cats. This result suggested the presence of sleep-promoting regions in the medulla, which have subsequently been postulated to be located in the medullary reticular formation and nucleus solitaryis (Figure 14.15A). In fact, lesions in certain regions of the medulla, as well as in the anterior hypothalamus and basal forebrain, can markedly reduce sleep. These regions are especially important for promoting nonREM sleep. For example, GABAergic neurons in the ventrolateral preoptic area of the anterior hypothalamus and in nearby regions send inhibitory projections to histaminergic neurons in the posterior hypothalamus (see Figure 14.15A). Some of these anterior hypothalamic neurons are called nonREM-on cells. One mechanism by which these cells promote nonREM sleep is inhibition of histaminergic activating systems that project to the forebrain (see Figure 14.13). In addition, inhibition of histaminergic excitatory input to brainstem activating systems, such as those mediated by acetylcholine (ACh), leads to a further reduction in arousal (see Figure 14.15A).

A different set of brainstem circuits is thought to control REM sleep (see Figure 14.15B). Several classes of REM-on cells are located in the pontine reticular formation. Activity in GABAergic REM-on cells during REM sleep inhibits neuropeptides (NE) release from the locus ceruleus and lateral segmental area, and inhibits serotonin (5-HT) release from the raphe nuclei (see Figure 14.15B).

Noradrenergic and serotonergic REM-off cells show progressively reduced activation during sleep, leading to the inhibition of REM sleep. It is thought that the level of activation of these REM-off cells may be the key factor in determining the amount of REM sleep an individual experiences. This idea is supported by the findings that some conditions, such as sleep deprivation, lead to increased REM sleep, while other conditions, such as REM sleep deprivation, lead to decreased REM sleep.

The precise locations of these sleep-promoting regions in the brainstem have not been confirmed electrophysiologically.
Brainstem Circuits Important for Sleep Regulation

(A) During nonREM sleep, GABAergic neurons (in the ventral lateral preoptic area of the anterior hypothalamus) inhibit histaminergic neurons (in the tuberomammillary nucleus). This removes histaminergic activation from the forebrain and from brainstem cholinergic neurons (in the pedunculopontine nucleus and in the laterodorsal tegmental nucleus). Certain regions of the medulla may also play a role in nonREM sleep. (B) During REM sleep, REM-on cells and REM-waking-on cells in the pontine reticular formation interact with other brainstem circuits to activate cholinergic inputs to the thalamus, inhibit tonic muscle activity, activate phasic eye movements, and activate other phasic motor activity. (Spinal cord section modified from DeArmond SJ, PARSONS MM, Maynard MD. 1989. Structure of the Human Brain: A Photographic Atlas, 3rd Ed. Oxford, New York.)

REM sleep

Non-REM sleep

Hypocretinergic neurons

Histaminergic neurons

Medially thalamic formation and nucleus reticularis

Facial motor nuclei

Medullary reticular formation and nucleus reticularis

GABAergic neurons

(A) Non-REM sleep

(B) REM sleep

Which of the following brainstem neurotransmitter systems is most strongly activated during nonREM sleep? During REM sleep?

- Histamine
- Acetylcholine (Ach)
- NE
- 5-HT

(see Figure 14.15)

Review Exercise

1. Excessive daytime sleepiness
2. Cataplexy (sudden loss of muscle tone from the awake state, often in response to an emotional stimulus)
3. Hypnagogic (while falling asleep) or hypnopompic (while waking) dreamlike hallucinations
4. Sleep paralysis (awaking, but remaining unable to move for several minutes)

Discovery of the hypocretin/orexin peptides raises the hope that ongoing investigations will explain these phenomena in cellular and molecular terms, which may lead to improved treatments for this disorder.

The most commonly accepted definition of coma, as proposed by Plum and Posner, is unarousable unresponsiveness in which the patient lies with eyes closed. Coma can perhaps be best understood if it is contrasted with various similar-appearing states, as in Table 14.3.

Brain death might be considered an extreme form of coma. As discussed in Chapter 3, brain death is defined on the basis of clinical examination demonstrating no evidence of forebrain or brainstem function, including no brainstem reflexes. When an EEG is done as a confirmatory test in brain death, it shows
TABLE 14.3 Definitions of Coma and Related States

<table>
<thead>
<tr>
<th>STATE</th>
<th>PURPOSEFUL RESPONSES TO STIMULI?</th>
<th>BRAINSTEM REFLEXES</th>
<th>SLEEP-WAKE CYCLES OCCUR</th>
<th>EEG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain death</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Flat (-2 microvolts)</td>
</tr>
<tr>
<td>Coma</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Various fixed patterns (not flat, often slow); usually does not vary over time, including no sleep-wake cycles</td>
</tr>
<tr>
<td>Stupor, obtundation, lethargy</td>
<td>Yes, at times</td>
<td>Yes</td>
<td>Variable</td>
<td>Various patterns (not flat, often slow)</td>
</tr>
<tr>
<td>Persistent vegetative state</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Various patterns (not flat, often slow); sleep-wake cycles occur</td>
</tr>
<tr>
<td>Akinesia, abulia, catalepsy</td>
<td>Yes, at times</td>
<td>Yes</td>
<td>Yes</td>
<td>Various patterns (not flat, often slow); sleep-wake cycles occur</td>
</tr>
<tr>
<td>Sleep</td>
<td>Yes, at times</td>
<td>Yes</td>
<td>Yes</td>
<td>Normal sleep patterns</td>
</tr>
<tr>
<td>Status epilepticus</td>
<td>Variable</td>
<td>Variable</td>
<td>Seizure activity</td>
<td>Normal EEG</td>
</tr>
<tr>
<td>Locked-in syndrome</td>
<td>No*</td>
<td>Yes*</td>
<td>Yes*</td>
<td>Normal EEG</td>
</tr>
<tr>
<td>Dissociation, somnambulant</td>
<td>Yes, at times</td>
<td>Yes</td>
<td>Yes</td>
<td>Normal EEG</td>
</tr>
</tbody>
</table>

* Some patients may have preserved vertical eye movements, or other slight movements under volitional control.

* Mild abnormalities, such as slight background slowing, may be present.

"electroencephalograph," or a flat pattern, less than 2 microvolts in amplitude. Cerebral perfusion and metabolism are likewise reduced to zero in brain death. In contrast, during coma, many simple or even complex reflexes may occur. "Unresponsiveness" in coma refers to psychologically meaningful or purposeful responses mediated by the cortex, which are absent (see Table 14.3). For example, in coma a patient may show reflex eye movements (such as the vestibulo-ocular reflex; see Chapter 3, "Coma Exam"), or may exhibit posturing (see Figure 3.5), or even intermittent stereotyped spontaneous movements. However, purposeful (as opposed to reflex) withdrawal from noxious stimuli and other responses demonstrating volition do not occur in coma.

In coma, cerebral metabolism is typically reduced by at least 50%, in agreement with the lack of significant cortical functions. The EEG (see Chapter 4) is usually abnormal in coma, but it can show many different patterns, including large-amplitude slow waves, burst-suppression, triphasic waves, spindle waves, or even alpha activity (a pattern seen in normal wakefulness). The most consistent abnormality of the EEG in coma is that it is typically monotonous, with little variability over time, unlike the normally varying EEG seen in different sleep stages (see Figure 14.14). Sleep differs from coma (see Table 14.3) in that patients in coma are unresponsive regardless of the stimulus, and as already noted, patients in coma do not undergo cyclical variations of state seen during sleep.

There is a wide continuum of levels of consciousness between coma and the fully awake state. A variety of more poorly defined terms—lethargy, obtundation, stupor, semicoma, and so on—are sometimes used to describe different states along this continuum. Although definitions for these terms exist, use of these terms alone, without further details, can be confusing to other physicians when they need the chart and try to assess the patient's progress. Therefore, as described in Chapter 3 in the section on the coma exam, it is essential to document the patient's level of alertness with a specific statement of what the patient can do in response to specific stimuli. For example, if pressure applied to a nail bed or to the supraorbital ridge causes a patient to briefly open their eyes, moan, and push away the examiner one hand before lapsing back into unresponsiveness, the patient is not in coma. Documenting impaired consciousness and the specific response elicited is the most practical way to follow changes in patients of this kind. Other states along the continuum of impaired alertness, attention, and cognition, such as delirium (global confusional states) and dementia, are discussed further in Chapter 19 (see KCC 19:14-19.16).

Several weeks after an initial catastrophic brain insult causing coma, many patients emerge into a perplexy stage in which they remain sleep-wake cycles and other primitive orienting responses and reflexes mediated by the brainstem and hypothalamus, but remain unconscious. This vegetative state can also occur in certain degenerative or congenital disorders, and if it lasts for more than one month it is called a persistent vegetative state (PVS) (see Table 14.9). As in coma, patients in PVS have no meaningful responses to stimuli, and they do not have diffuse cortical dysfunction evidenced by over 50% reduction in cerebral metabolism. However, patients in PVS do open their eyes and arouse in response to stimulation, and they may turn their eyes and heads toward auditory or tactile stimuli, presumably through brainstem-mediated pathways. Patients in PVS do not track visual stimuli, although visual tracking is often the earliest sign of recovery from PVS to a slightly milder form of brain dysfunction. Specific clinical criteria have been established for PVS by a multisociety task force (see the references at the end of this chapter for more information). Terms such as "coma vigil" or "aplastic syndrome" were used in the past for PVS and similar states, but they are imprecise and are not generally used today.

Several states of profound apathy, in the extreme, can resemble coma or PVS. These include akinesis mutism, abulia, and catalepsy (see Table 14.3). These disorders have in common the dysfunction of circuits involving the frontal lobes, mesencephalon, and ascending dopaminergic projections (see Figure 14.10) important to the initiation of motor and cognitive activity. In akinesis mutism, the patient appears fully awake, and unlike patients in PVS, such patients visually track the examiner. However, they usually do not respond to any commands. Akinesis mutism can be viewed as an extreme form of abulia, often resulting from frontal lesions, in which patients usually sit passively but may occasionally respond to questions or commands after a long delay. In some patients, abulia or akinesis mutism can be reversed with dopaminergic agonists. Abulia is discussed further in Chapter 19 (see KCC 19:14.11). Catalepsy is a similar akinesic state that can occasionally be seen in advanced cases of schizophrenia. Again, frontal-lobe and dopaminergic dysfunction have been implicated. Other related akinetic-apathetic states include advanced parkinsonism (see KCC 16.2), severe depression, and neuropsychiatric malignant syndrome.

An important consideration in the differential diagnosis of coma is status epilepticus, meaning continuous seizure activity (see KCC 18.2). Often seizure activity is clinically obvious. However, sometimes only subtle twitching or no motor activity at all is present. Studies in which EEGs were performed indiscriminately in a series of patients in coma revealed that unrecognized status epilepticus was present in up to 25% of cases. Therefore, whereas the cause of coma cannot be found, when there is a history of seizures, an EEG should be performed promptly so that anticonvulsant therapy can be initiated when needed.

The locked-in syndrome discussed in KCC 14.3 can sometimes be mistaken for coma (see Table 14.3). Unlike coma, however, these patients are conscious and may be able to communicate through vertical eye movements or eye blinks. Several psychiatric disorders can cause patients to appear as if in
a coma. In addition to catatonia and severe depression, pa-
tients may be unresponsive when in a dissociative state,
often resulting from severe emotional trauma. Some diseases
or, as in the case of drug, somatization disorder, disor-
der, or facility disorder can also sometimes produce states
resembling coma, sometimes called "pseudocoma." Often
these can be distinguished from coma by a carefully per-
formed neurological examination (see Chapter 3), although in some
cases the diagnosis may not be obvious.

**Transcendental loss of consciousness**, as we discussed in
KCC 10.3, is usually caused by cardiac or other medical con-
ditions, and is much less commonly caused by neurological
diseases such as seizures or brainstem ischemia.

**Clinical Approach to the Patient in Coma**

Coma is a neurological emergency because many causes of coma are reversible if treated promptly but can cause per-
manent damage that becomes progressively severe as time goes on. Some important causes of coma are listed in
Table 14.4. As in any other emergency situation, the initial priorities are to ensure that there is an unobstructed
airway, that the patient is breathing, and that there is normal circu-
lation function. When it is clinically apparent, the patient
should be intubated, and cerebral revascularization initiated.
Establishing prompt intravenous access is also essential.

**Intravenous Thiamine, Electrolyte, and Analgesics**

When the condition is confirmed, thiamine deficiency, hypoglycemia, and opiate overdose are readily treatable causes of coma. Additional doses are needed when these conditions are confirmed.

Hypoglycemia can also be given, if benzodiazepine overdose is suspected. Next, a more detailed assessment should be performed, including history, exam, blood tests, and other di-
agnostic tests, to find specific treatable causes of coma.

**Reticular Formation Motor, Reflex, and Autonomic Systems**

in this chapter we have so far emphasized the role of the reticular formation in modulation of alertness, attention, and consciousness. However, many circuits, particularly of the caudal reticular formation, serve crucial functions in motor, reflex, and autonomic function, including basic "life support" systems such as respiration and cardiovascular control.

**Respiration involves a network of control systems acting at multiple levels.** Usually, respiratory rhythms occur automatically under the control of cir-
cuits in the medulla. The importance of the medulla was demonstrated when animals transected at or above the pontomedullary junction continued to breathe. However, other regions of the nervous system have strong modula-
tory influences on the respiratory pattern. Respiratory rhythms can also be sus-
pended temporarily by voluntary control mediated by the forebrain. Some
important brainstem regions involved in respiration are shown in Figure 14.16. There are numerous inputs to respiratory circuits, including chemoreceptors for blood oxygen level and pH, many of which project to the cardiorespiratory portion of the nucleus solitarius. In addition, there are inputs from stretch re-
ceptors located in the lungs. The pacemaker for respiration is thought to lie in the pre-Bötzinger complex located in the medulla. Other nuclei in the medulla participate in respiratory rhythms, and as shown in Figure 14.16, some
are active during inspiration, while others are active during expiration. Ulti-
mately, these nuclei project to spinal cord (lower motor neurons in cervical spinal segments C2 to C8) to excite thoracic nerve fibers that contract the diaphragm during inspiration, or to lower motor neurons at thoracic levels controlling thoracic inspiratory and expiratory muscles.

Lesions of the medulla disrupt respiratory circuits and can cause respiratory arrest and death. Other abnormal respiratory patterns are sometimes seen with lesions of the central nervous system. Proceeding from caudal to rostral, lesions of the medulla that do not cause respiratory arrest can lead to an ominous pattern of very irregular breathing, called apneustic respiration, which is ultimately fatal to respiratory arrest. Lesions of the reticular pontine area located dorsal to the motor nucleus of CN V (see Fig-
ure 14.16) can cause a peculiar breathing pattern called apneustic respiration,
in which the patient has brief 2- to 3-second pauses at full inspiration. Midbrain lesions, as well as lesions in other regions, often lead to hypopneal ventilation. Fi-
ally, in Cheyne-Stokes respiration, breathing becomes progressively deeper
then shallower with each breath to the point of apnea. The cycle then repeats, and breathing gradually becomes deeper again, in a continual crescendo-decrescendo pattern. This breathing pattern is not typi-
cally harmful in and of itself. Cheyne-Stokes respiration is usually seen in bi-
 lateral lesions at or above the level of the upper pontine (including lesions of the
cerebral cortex), but it can also be seen in non-
cilin and in medical conditions such as
cardiac failure.

Control of heart rate and blood pressure
are likewise mediated by circuits at multiple
levels in the nervous system. Inputs to the 
caudal nucleus of the solitary tract (CNS),
also known as the cardiopulmonary
nucleus, are a major source of input to the
nearby medullary reticular formation. The
nucleus receives inputs from barorecep-
tors in the carotid body and aortic arch
nerve (CN X and X, respectively (see
Figure 12.19, 12.20). Control of heart rate and
cardiovascular pressure is then mediated by circuits, many of
which project directly from the nucleus solitaris to sympa-
thetic preganglionic neurons in the brainstem and spinal cord
(see Figure 6.13). Preganglionic neurons in the
cerebral ventralmedulla project to sympa-
thetic preganglionic neurons in the spinal cord (see KCC 7.2). Interestingly, the
cardiovascular portion of the nucleus solitaries may also project to the forebrain, largely via
the parabrachial nucleus of the medulla (see Figure 14.4A). Inputs from the nucleus
solitaries to the limbic system (see Chapter 18)
can, for example, be important in mediating emotional responses to altered
cardiovascular function, and they have been postulated to play a role in trig-
ner's syndrome. Information travels in the other direction as well, so an
effective state manifested as limbic system activity has a strong effect on aut-
onomic function through connections to the brainstem reticular formation.

The reticular formation is involved in many complex motor tasks. Experi-
mental animals in which the brainstem has been disconnected from higher
structures can still perform numerous motor tasks, including orienting toward
stimuli, maintaining posture, and even locomotion. Motor systems arising
from the brainstem, discussed in Chapter 6, include the reticulospinal,
vestibulospinal, tectospinal, and rubrospinal tracts (see Figure 6.11). In addi-
tion, the substantia nigra and pedunculopontine tegmental nucleus play important
roles in basal ganglia circuits, and parts of the reticular formation are integral to the
tropical cortical function.

Abnormal flexor (decoration) posturing or extensor (decrebrate) post-
turing (see Figure 3.5) are mediated largely by brainstem circuits. Regions of the
tegmental formation adjacent to cranial nerve nuclei are crucial for coordi-
nating activity and mediating neural involvement in spinal nerves, such as
the cervical reflex, eye movements, and many other activities (see Chapters 12 and
13). Behaviors such as coughing, hiccuping, sneezing, yawning, shivering,
gagging, gagging, vomiting, and crying are all housed in the brainstem, and lesions
of circuits in the pontomedullary reticular formation. Lesions of the
brainstem can interfere with these behaviors or cause them to emerge abnor-
nally. For example, patients with pontine infarcts can exhibit abnormal sponta-
neous shivering, lesions of the medulla can produce hiccuping, and lesions of

descending white matter pathways can produce abnormal spontaneous
pseudobulbar laughter and crying (see KCC 12.8).

In the region of the area postrema, located along the caudal wall of the
turritum in the medulla, is a region called the chemoreceptor trigger zone
(see Figure 5.15). In this region, the blood-brain barrier is incomplete,
allowing endogenous substances or exogenous toxins in the bloodstream to
trigger nausea and vomiting. Nausea and vomiting can also be triggered by a
stimulus at the start of the release of serotonin (5-HT) from cells in the stom-
ach and small intestine walls in response to emetic agents. 5-HT stimulates
the endings of afferent fibers traveling with the vagus to reach the nucleus
solitarius in the brainstem. Vagal afferents also project to the nearby area
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a role in the nausea and vomiting seen in disorders of the vestibular system
or cerebellum, and in elevated intracranial pressure, although the mechanisms
are still under investigation.

The pontine micturition center and other regions of the reticular formation
are involved in maintaining sphincter control (see Figure 7.11). As we discussed
in Chapter 7, the periaqueductal gray functions together with other regions in
the brainstem and spinal cord to modulate pain transmission (see Figure 7.5).

**Brainstem Vascular Supply**

The blood supply to the posterior fossa structures arises from the verteobasilar
system (Figure 14.17; see also Figure 10.2). The paired vertebral arteries arise
from the subclavian arteries at the base of the neck, and then ascend through the
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the brainstem and spinal cord to modulate pain transmission (see Figure 7.5).
Figure 14.17 Brainstem Blood Supply
(A) Ventral view. (B) Lateral view.

Several types of smaller branches arise from these main arteries and provide the blood supply to the brainstem (Figure 14.18). Paramedian branches tend to respect the midline, with individual branches supplying either the right or left paramedian regions. They extend a variable distance from the ventral surface of the brainstem, with the longest branches reaching all the way to the ventral surface of the medulla (see Figure 14.17A). The main vascular territories of the brainstem are shown in Figures 14.19 and 14.20. The medial medulla is supplied by paramedian branches of the anterior spinal artery in more rostral regions, and by paramedian branches of the vertebral arteries in more caudal regions (see Figure 14.20(D)). Recall that the anterior spinal artery arises from each vertebral artery, runs along the ventral surface of the medulla (see Figure 14.17A), and continues out of the cranial vault to supply the ventral spinal cord (see Figure 6.5). The lateral medulla is supplied by penetrating branches from the vertebral artery and the PICA (see Figures 14.19, 14.20(D)). The medial pons is supplied by paramedian branches of the basilar artery (see Figures 14.19, 14.20(L)). The lateral pons is supplied by circumferential branches of the basilar artery. In the more caudal regions, the lateral pons is supplied by the AICA (see Figures 14.19, 14.20(C)). The inner ear is supplied by the internal auditory (labyrinthine) artery (see Figure 14.17B), which usually arises as a branch of the AICA, but occasionally comes directly off the basilar artery. The more rostral lateral pons is sup-
piled mainly by small circumferential branches of the basilar artery called linear pontine arteries. (See Figure 14.17.) A small variable region of the superior dor-solateral pons receives some blood supply from the SCA (see Figures 14.19, 14.20B), but this artery supplies mainly the superior cerebellum rather than the brainstem. The midbrain is supplied by penetrating branches arising from the top of the basilar artery and from the proximal PCAs (see Figures 14.17, 14.18, and 14.20A). Recall that arteries supplying the thalamus also arise mainly from the top of the basilar artery and proximal PCAs (see Figure 10.8A). Paramedian branches arising from the top of the basilar artery and from the interpeduncular cistern may supply the medial midbrain and thalamus (see Figure 14.17A). Sometimes these arteries bifurcate after their origin, giving rise to the so-called arteries of Percheron, which supply the bilateral medial midbrain and thalamus. Occlusion of an artery of Percheron before it bifurcates can lead to bilateral medial midbrain or thalamic infarcts.

Tables 14.7, 14.8, and 14.9 list important structures lying in each of the main brainstem vascular territories. Clinical syndromes associated with these territories will be discussed in the next section.

Because the brainstem is so essential for maintaining consciousness and vital life functions, it is crucial for the physician to be familiar with the major vascular territories of the posterior circulation. We will first discuss general features of vertebrobasilar vascular disease and then review syndromes involving specific vascular territories.

### General Features of Posterior Circulation Disease

As discussed in Chapter 10, infarcts can occur by a variety of mechanisms, including **embolism**, often of cardiac origin; or in situ **thrombosis**, often occurring on a nidus of preexisting atheroma, acute or chronic; and **lacunar disease**, often resulting from small-vessel occlusion in the setting of chronic hypertension. These mechanisms and the others discussed in Chapter 10 (see KCC 10.4) can all occur in the posterior circulation. It is important to recognize the differences in symptoms associated with the vertebrobasilar system and the basilar system and their branches. Because the vertebrobasilar system supplies posterior fossa structures, including the brainstem, warning signs of vertebrobasilar ischemia can be very common. Therefore, when patients report these symptoms, they should always be brought to immediate medical attention in an effort to avoid life-threatening brainstem infarction, coma, and death.

### TABLE 14.6 Common Warning Signs of Vertebrobasilar Ischemia

<table>
<thead>
<tr>
<th>SYMPTOM</th>
<th>ISCHEMIC STRUCTURES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness (vertigo), nausea</td>
<td>Vertebrobasilar nucleus, cerebellum, or inner ear</td>
</tr>
<tr>
<td>Diplopia, disconjugate gaze</td>
<td>Supranuclear infratentorial eye movement pathways (see Chapter 13)</td>
</tr>
<tr>
<td>Blurred vision, or visual disturbances</td>
<td>Eye movement pathways, or visual cortex</td>
</tr>
<tr>
<td>Vertigo (ataxia)</td>
<td>Cerebellum or cerebellar pathways</td>
</tr>
<tr>
<td>Unsteadiness</td>
<td>Corticobulbar pathways or brainstem nuclei</td>
</tr>
<tr>
<td>Dysarthria, dysphagia</td>
<td>Long somatosensory pathways or trigeminal system</td>
</tr>
<tr>
<td>Nummings and tingling, particularly bilateral or perioral</td>
<td>Corticospinal tract</td>
</tr>
<tr>
<td>Hemiparesis, quadriparesis</td>
<td>Pontomesencephalic reticular formation or bilateral thalamus</td>
</tr>
</tbody>
</table>

**Symptoms of vertebrobasilar ischemia are listed in Table 14.6.** These warning signs can be attributed to ischemia of specific anatomic components of the brainstem (see Figure 14.17), such as the cranial nerve nuclei and their interconnections, long sensory and motor tracts, cerebellar circuits, and the reticular activating systems— or to ischemia of the occipital lobes (PCA territory).

In addition to these clues from the patient's history, certain findings on neurologic examination can often help distinguish brainstem ischemia from ischemia of the cerebral hemispheres. Features strongly suggestive of brainstem involvement rather than hemispheric involvement include **crossed signs**, such as crossed sensation on one side of the face and contralateral body or weakness on one side of the face and contralateral body, and **cranial nerve abnormalities**, especially those causing eye movement abnormalities, such as **disconjugate gaze, wrong-way eyes** (see Figure 13.13), **pupillary abnormalities**, or **skiagram** (see Chapter 13). For example, involvement of the midbrain, which supply the bilateral medial midbrain and thalamus. Occlusion of an artery of Percheron before it bifurcates can lead to bilateral medial midbrain or thalamic infarcts.

Once brainstem ischemia is suspected, certain rules of thumb can be helpful in further localizing brainstem vascular disease or other lesions to the midbrain, pons, or medulla. Signs of **midbrain dysfunction** include third-nerve palsies, unilateral or bilateral pupil dilation ataxia, flocus (dysconjugate) pursuit, and impaired consciousness. Signs of **pontine dysfunction** include bilateral Rubini's signs, generalized weakness, perioral numbness (see Figure 12.9), "scl and pepper" (pins and needles) facial tingling, bilateral or lower visual loss or blurring (usually caused by impaired blood flow from the basilar artery to both PCAs), irregular or apneic respirations (described earlier), ocular bobbing (eyes dip downward quickly and then return gradually to mid position before dipping again), shivering, palatal myoclonus (central temporal tract described earlier), abducens palsy or horizontal gaze palsy, bilateral small but reactive pupils (dissipation of descending sympathetic fibers), extensor (deacrebrate) posturing, and impaired consciousness. Signs of **medullary dysfunction** include vertigo, ataxia, nystagmus, nausea, vomiting, respiratory arrest, autonomic instability, and hiccup. Specific vascular syndromes of different brainstem regions are discussed in greater detail in the next section.

Treatment of vertebrobasilar disease is similar to treatment of ischemic stroke in the anterior circulation and depends on the mechanism of ischemia (see KCC 10.4). As with anterior circulation disease, transient ischemic attacks (TIAs) sometimes provide a warning prior to ischemic infarction (see KCC 10.3). Patients with an initial ischemic event should undergo an evaluation as described in KCC 10.4 to search for a mechanism for the ischemia. Anticoagulation therapy is used to treat thrombembolic disease caused by atrial fibrillation or mechanical cardiac valves. As discussed in KCC 10.6, **vertebral dissection**, often following minor head or neck trauma, is another important source of embolic disease, usually treated with anticoagulation. Occasionally an erratic or fusiform basilar artery aneurysm (see Figure 5.26) can form thrombus that embolizes intermittently to distal branches. Much more commonly, an arterotemeric or giant aneurysm of the basilar artery or basilar tip results in embolic disease from evolving small vessel lacunes, which can also cause waking and warning symptoms but do not involve stenosis of major blood vessels. To prevent life-threatening **vertebral or basilar thrombosis**, vertebrobasilar arteries are treated with anticoagulation therapy. Although such therapy has not been proven effective by randomized trial. In addition, this blood pressure-lowering medications should be used cautiously or avoided to prevent worsening of hypertension. Systemic administration of the thrombolytic agent t-PA can improve outcome if given within 4 hours of onset or stroke, although there is an increased risk of hemorrhage. Intratral administration of thrombolytic agents locally at the site of the clot using interventional neuroradiological techniques has also been beneficial in the treatment...
gional setting. Unlike carotid stenosis (see KCC 10.5), vertebral and basilar stenosis have not been successfully treated with endarterectomy, although angioplasty has been tried experimentally with some success. Finally, as with anterior circulation stroke (see KCC 10.4), it is essential to treat the patient with a multidisciplinary approach, with careful attention to other coexisting medical conditions and potential complications, both during the acute stage and during recovery.

Specific Clinical Syndromes of the Vertebralbasilar Territory. The discussion in this section focuses on infarcts in several specific territories of the posterior circulation (Tables 14.7–14.9). In addition to being clinically useful, review of these vascular territories and the anatomical structures affected in each territory serves as a useful review of the regional anatomy of the brainstem, and can help consolidate knowledge acquired in this and the preceding two chapters. After discussing these focal syndromes, we will review several multifocal or bilateral brainstem syndromes, such as basilar thombofus, top-of-the-basilar syndrome, and pontine hemorrhage.

Of all the focal brainstem vascular syndromes that we will discuss here (see Tables 14.7–14.9), only two are common: the lateral medullary syndrome, usually caused by vertebral thombofus and medial basis pontis infarct, usually caused by lacunar disease. Medial medullary syndrome and SCA syndrome are less common. The other syndromes listed are relatively rare when occurring in isolation.

Proceeding from caudal to rostral, vascular syndromes of the medulla are listed in Table 14.7 (see Figure 14.20D). The medullary medullary syndrome is caused by occlusion of paramedian branches of the anterior spinal or vertebrobasilar arteries. Infarction of the pyramidal tract results in contralateral arm and leg upper motor neuron weakness (see Figure 6.14C). Sometimes the contralateral arm is involved as well, although usually less than the arm and leg. Often, there is ipsilateral tongue weakness from infarction of the existing CN XII fascicles or, depending on how far the infarct extends from the ventral surface of the medulla, from infarction of the hypoglossal nucleus. Also depending on how far dorsally the infarct extends, there may be contralateral decreased vibration and joint position sense caused by infarction of the medial lemniscus.

Lateral medullary syndrome, or Wallenberg’s syndrome, is a relatively common brainstem infarct. In addition to being clinically important, this is the one syndrome that students should memorize because understanding the clinical features and anatomical structures involved serves as a helpful reference point for understanding all other brainstem syndromes as well. Because the syndrome affects the lateral tegmentum, motor involvement is usually not prominent and prognosis is generally good. Lateral medullary syndrome is usually caused by thrombofus rather than emboli. Vertebral thrombofus is the most common cause. Isolated involvement of the PICA is a less common cause.

The most disabling features of lateral medullary syndrome are ipsilateral signs caused by infarction of the inferior cerebellar peduncle, and vertigo caused by infarction of the vestibular nuclei (see Figure 14.20D). Unsteady gait, horizontal or rotary nystagmus, nausea, and vomiting are common associated features. There is often decreased pain and temperature sensation of the ipsilateral face (spinal trigeminal nucleus and tract) and of the contralateral body (spinothalamic tract; see Figure 7.9B). In some cases, facial sensory loss is contralateral, possibly because of the involvement of crossing fibers, or sometimes ipsilateral facial paresthesias or heightened sensitivity may occur, particularly shortly after onset. Other variants include sensory loss in just the upper or lower contralateral body, probably due to only partial involvement of the spinothalamic tract. Involvement of the descending sympathetic fibers, which run in the lateral tegmentum of the brainstem near the spinothalamic tract, causes an ipsilateral Horner’s syndrome (see KCC 13.5; Figure 13.10), with ptosis, miosis, and, less commonly, anhidrosis. Infarction of the nucleus ambiguus and exiting fascicles of CN X causes breathy hoarseness and dysphagia (see KCC 12B). The gag reflex is often decreased on the side of the lesion, and laryngoscopy shows ipsilateral vocal cord paralysis. Finally, involvement of the nucleus solitarius can occasionally be demonstrated by tests for decreased taste sensation on the ipsilateral tongue. As already noted, motor involvement is not commonly present. In some cases, however, there may be ipsilateral facial weakness, possibly due to fibers of the facial nerve that loop caudally into the medulla before exiting at the pontomedullary junction. In addition, when infarcts extend somewhat more medially and reach the pyramidial tract, contralateral hemiparesis may be present, and combined lateral and medullary infarcts can sometimes occur. An uncommon but interesting manifestation of lateral medullary infarcts is loss, in some patients, of vertical orientation, making them suddenly feel as if the whole world has turned upside down or sideways.

Many clinical features of lateral medullary syndrome also occur in other lesions of the lateral brainstem tegmentum, such as AICA syndrome, and sometimes in SCA syndrome as well (see Table 14.8; Figure 14.20C). The presence of hoarseness or loss of taste sensation helps localize the syndrome to the medulla rather than the pons. In addition, the presence of ipsilateral hearing loss suggests AICA involvement rather than lateral medullary syndrome.

Vascular Syndromes of the Pons are listed in Table 14.8 (see Figure 14.20B,C). Like lateral medullary syndrome, medial pontine syndromes are also relatively common and clinically important. Because the paramedian pontine

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**TABLE 14.7 Focal Vascular Syndromes of the Medulla**

<table>
<thead>
<tr>
<th>REGION</th>
<th>SYNDROME NAME</th>
<th>VASCULAR SUPPLY</th>
<th>ANATOMICAL STRUCTURE(S)</th>
<th>CLINICAL FEATURES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lateral medulla</td>
<td>Wallenberg's syndrome</td>
<td>Vertebral artery (more commonly than PICA)</td>
<td>Inferior cerebellar peduncle, vestibular nuclei</td>
<td>Ipsilateral ataxia, vertigo, nystagmus, nausea</td>
</tr>
<tr>
<td></td>
<td>(lateral medullary syndrome)</td>
<td></td>
<td>Trigeminal nucleus and tract</td>
<td>Ipsilateral facial decreased pain and temperature sense</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sphenothalamic tract</td>
<td>Ipsilateral body decreased pain and temperature sense</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Descending sympathetic fibers</td>
<td>Ipsilateral Horner's syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Nucleus ambiguus</td>
<td>Hoarseness, dysphagia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Nucleus solitarius</td>
<td>Ipsilateral decreased taste</td>
</tr>
</tbody>
</table>

*Eponymous names for vascular syndromes listed in Tables 14.7–14.9 (Weber's syndrome, Claude's syndrome, etc.) need not be memorized, since their exact meanings have varied historically.*
### TABLE 14.9 Focal Vascular Syndromes of the Midbrain

<table>
<thead>
<tr>
<th>REGION</th>
<th>SYNDROME NAMED</th>
<th>VASCULAR SUPPLY</th>
<th>ANATOMIC STRUCTURES</th>
<th>CLINICAL FEATURES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midbrain basis (see Figure 14.20A)</td>
<td>Weber’s syndrome</td>
<td>Branches of PCA and top of basilar artery</td>
<td>Oculomotor nerve fasciculi</td>
<td>Ipsilateral third-nerve palsy</td>
</tr>
<tr>
<td>Midbrain tegmentum (see Figure 14.20B)</td>
<td>Claude’s syndrome</td>
<td>Branches of PCA and top of basilar artery</td>
<td>Cerebral peduncle</td>
<td>Contralateral hemiparesis</td>
</tr>
<tr>
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<td>Beneckit’s syndrome</td>
<td>Branches of PCA and top of basilar artery</td>
<td>Oculomotor nerve fasciculi</td>
<td>Ipsilateral third-nerve palsy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cerebral peduncle</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Red nucleus, superior cerebellar peduncle fibers</td>
<td>Contralateral hemiparesis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Oculomotor nerve fasciculi</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Contralateral ataxia</td>
<td></td>
</tr>
</tbody>
</table>

*Eponymous names for vascular syndromes listed in Tables 14.7–14.9 (Weber’s syndrome, Claude’s syndrome, etc.) need not be memorized, since their exact meanings have varied historically.*

*More dorsal lesions involving the midbrain tegmental formation cause impaired consciousness.*

### REVIEW EXERCISE

Cover the labels on the left side of Figure 14.20. For each of the following brainstem regions and vascular territories, name the structures affected and the expected deficits:

14.20A: Midbrain basis and tegmentum (PCA and top-of-basilar branches) (See Table 14.8)
14.20B: Caudal pontine basis (paramedian branches of basilar, ventral territory) (See Table 14.8)
14.20C: Lateral inferior pons (AICA) (See Table 14.8)
14.20D: Medial medulla (paramedian branches of vertebral and spinal arteries) (See Table 14.7)
14.20E: Lateral medulla (vertebral artery and PCA) (See Table 14.7)

Rostrolateral pons may also be involved, occasionally causing some features of lateral tegmental syndrome.

**Vascular syndromes of the midbrain** are listed in Table 14.9 (see Figure 14.20A). **Midbrain infarcts** result from the occlusion of penetrating vessels arising from the top of the basilar artery and proximal PCAs. Infarcts in this territory often occur in the setting of an embolus lodged at the top of the basilar artery (top-of-basilar syndrome) causing infarcts in multiple other locations as well, but midbrain infarcts can occasionally be seen in isolation. Midbrain syndromes have been described involving different regions of the basis, tegmentum, or both. Infarction of the cerebral peduncles in the midbrain basis causes contralateral hemiparesis; infarction of the third-nerve nucleus or fasci- 
cides causes an ipsilateral third-nerve palsy; and infarction of the red nucleus and fibers of the superior cerebellar peduncle (above the decussation) causes a contralateral tremor and ataxia. Larger infarcts of the midbrain that affect the midbrain reticular formation cause impaired consciousness, although when this occurs, other territories are often involved as well.

In addition to these specific territories (see Tables 14.7–14.9), posterior circulation infarcts can sometimes occur that involve multiple territories. In **basilar thrombosis**, there are often catastrophic bilateral infarctions of multiple regions of the pons and other regions supplied by the basilar artery, including the cerebellum, midbrain, thalamus, and occipital lobes. Basilar thrombosis usually results from thrombosis of a previously narrowed basilar artery in the setting of atherosclerotic disease. Patients often develop multiple cranial nerve abnormalities, long-tract signs, and coma, typically with a poor prognosis.

**Top-of-the-basilar syndrome** is usually caused by an embolus that lodges in the distal basilar artery, also causing infarcts of multiple vascular territories.

Clinical features include visual disturbances resulting from infarcts of the visual cortex; memory disturbances from infarcts of the bilateral medial thalami; eye movement abnormalities from infarction of the oculomotor nucleus and third-nerve fascicles in the midbrain; somnolence, delirium, or vivid visual hallucinations ("peduncular hallucinosis") caused by infarction of the midbrain reticular formation; and ataxia resulting from cerebellar infarcts. Of note, pontine involvement is often relatively mild in top-of-the-basilar syndrome. Sometimes, as an embolus migrates up the basilar artery toward the top, it occludes various perforator arteries in the pons, producing a series of transient deficits referred to as the **basilar scapula syndrome**.

Another important vascular syndrome of the brainstem is **pontine hemorrhage**. This is most commonly seen in the setting of chronic hypertension causing fragility of small penetrating blood vessels (see KCC 5.6). Pontine hemorrhage usually involves the paramedian branches of the basilar artery, at the junction between the tegmentum and basis pontis. Although small hemor- rhages can cause relatively mild deficits, pontine hemorrhages are often large and bilateral, resulting in catastrophic bilateral cranial nerve deficits, long-tract signs, coma, and a poor prognosis. Hemorrhage in other regions of the brainstem is relatively uncommon and is usually caused by vascular malformations rather than hypertension.
CASE 14.1 FACE AND CONTRALATERAL BODY NUMBNESS, HOARSENESS, HORNER'S SYNDROME, AND ATAXIA

CHIEF COMPLAINT
A 22-year-old woman suddenly developed left posterior neck pain, vertigo, ataxia, left facial numbness, and hoarseness after chiropractic neck manipulation.

HISTORY
The patient had been well until 4 months previously, when she injured her neck in a car accident. She saw a chiropractor daily for neck pain. On the day of admission, after her neck was "snapped," she suddenly felt increased pain in the left posterior neck region. As she left the chiropractor's office, she felt dizzy and nauseated and staggered out to her car, falling toward the left. She noticed her vision becoming or swaying (oscillopsia) but had no diplopia. She vomited twice, and when she reached home her husband noticed that her voice sounded hoarse. She also felt a numbness and tingling on the left side of her face. The symptoms did not improve after a brief nap, so she came to the emergency room.

PHYSICAL EXAMINATION
Vital signs: T = 90°F; P = 60; BP = 126/64.
Neck: No bruits.
Lungs: Clear.
Heart: Regular rate with no murmurs or gallops.
Abdomen: Soft, nontender.
Extremities: Normal.

Neurologic exam:
Cranial Nerves: Left pupil 2.5 mm, constricting to 1 mm. Right pupil 3.5 mm, constricting to 2 mm. Visual fields full. Right-beating horizontal and counterclockwise rotary nystagmus, which increased with rightward gaze. Patient reported an associated perception of the visual field moving back and forth (oscillopsia). Extraocular movements full. Left ptosis. Decreased pinprick and temperature sensation in left ophthalmic, maxillary, and mandibular divisions of CN V (Figure 14.21). Decreased left corneal reflex. Face symmetrical. Taste not tested. Hearing intact. Voice hoarse. Decreased palate elevation on the left, and decreased left gag reflex. Normal sternomastoid and trapezius strength. Tongue midline.

Motor: No drift. Normal tone. 5/5 power throughout.
Reflexes:
Coordination: Mild ataxia on finger-to-nose testing on the left. Toe tapping on the left was irregular in rhythm (dysrythmoc).
Gait: Unable to stand because of severe dizziness.
Sensory: Decreased pinprick and temperature sensation in the right limbs and trunk below the neck (see Figure 14.21). Intact light touch, vibration, and joint position sense.

LOCALIZATION AND DIFFERENTIAL DIAGNOSIS
1. On the basis of the symptoms and signs shown in bold above, where is the lesion?
2. Given the sudden onset of deficits and neck pain following neck manipulation, what is the most likely diagnosis? What are some other possibilities?

Discussion
1. The key symptoms and signs in this case are:
   • pain in the left posterior neck region
   • Unsteady gait, falling toward the left
   • Left ataxia and dysrythmoc
   • Dizziness and nausea with right-beating nystagmus
   • Decreased pinprick and temperature sensation in the left face
   • Decreased left corneal reflex
   • Decreased pinprick and temperature sensation in the right limbs and trunk below the neck
   • Left ptosis, with small, reactive left pupil
   • Hoarseness, with decreased palate elevation on the left and decreased left gag reflex

   This patient had virtually all the clinical features of lateral medullary syndrome, or Wallenberg's syndrome. Review the structures in the lateral medulla involved, as well as the corresponding deficits that produce this characteristic constellation of findings (see Figure 14.21D; Table 14.7; see also Figure 7.9B).

2. Lateral medullary syndrome is usually caused by thrombosis, most often involving the vertebral artery, and less often the PICA in isolation (see KCC 14.3), resulting in a lateral medullary infarct. Given the patient's recent neck manipulation, neck pain, young age, and lack of other stroke risk factors, vertebral dissection should be strongly considered (see KCC 10.6). Other, much less likely causes of lateral medullary dysfunction in this patient include hemorrhage into a vascular malformation, abscess, or demyelinating disease.

   The most likely clinical localization and diagnosis is, therefore, left lateral medullary syndrome, with left lateral medullary infarct caused by left vertebral dissection.

Clinical Course and Neuroimaging

Initial brain CT and conventional MRI scans did not show an infarct (Figure 14.22A). However, diffusion-weighted MRI on the day of admission suggested left lateral medullary infarct (not shown), and this was confirmed by following conventional MRI 5 days later (Figure 14.22B). An MRA performed on the day of admission showed loss of flow in the left vertebral artery. Axial T1-weighted MRI sections through the vertebral arteries demonstrated a bright region of thickening in the wall of the left vertebral artery consistent with intramural clot from a left vertebral dissection (Figure 14.22C). The patient was treated with intravenous heparin anticoagulation for a week, and then switched to Coumadin (Warfarin). On follow-up 11 days after presentation, she no longer had nausea, vertigo, or nystagmus, and she was able to walk well, with only slight leftward veering on tandem gait. She still had a left Horner's syndrome, mildly decreased pinprick sensation in the left face and right body, and trace appendicular ataxia on the left side.
CASE 14.2 HEMIPARESIS SPARING THE FACE

MINICASE
A 53-year-old man with a history of cigarette smoking and hypercholesterolemia was driving home from the airport at 7:00 A.M. one morning and had a 1-hour episode of pins and needles in his right perioral area, arm, and leg. He reached home, and at 10:00 A.M., while he was walking the dog, these symptoms recurred, together with difficulty walking and clumsiness of the right arm and leg. On exam in the emergency room, he had decreased tone and 3/5 to 4/5 strength in the right arm and leg, an upgoing toe on the right, and decreased vibration and joint position sense in the right arm and leg. There was only a trace decrease in the right nasolabial fold at rest, and his smile was asymmetrical. Tongue was midline.

LOCALIZATION AND DIFFERENTIAL DIAGNOSIS
1. On the basis of the symptoms and signs shown in bold above, what is the most likely location for the lesion?
2. What is the most likely diagnosis?

Discussion
1. The key symptoms and signs in this case are:
   - 3/5 to 4/5 weakness of the right arm and leg with a right Babinski's sign
   - Trace decreased right nasolabial fold
   - Right body paresthesias, and decreased vibration and joint position sense

Right arm and leg upper motor neuron weakness sparing the face could be caused by a lesion in the left medulla or in the right cervical spinal cord (see SCC 6.5, Figure 6.18C). Similarly, paresthesias and decreased vibration and joint position sense in the right body could be caused by a lesion in the left brainstem involving the medial lemniscus (see Figure 7.9C), or in the right cervical spinal cord involving the posterior columns (see Figure 7.10B). The fact that some subtle right facial weakness was present makes the spinal cord location less likely. Since the face was nearly spared, however, the lesion is unlikely to lie above the facial nerve exit point (posterior medullary junction) because if it did, more prominent facial involvement would be expected. This leaves the medial medulla as a likely location (see Table 14.7, Figure 14.20D), involving the corticospinal fibers in the medullary pyramid, and the left medial lemniscus. The lack of tongue motor involvement (hypoglossal nerve) is interesting, but according to the published literature on medial medullary syndrome, the tongue is involved only 50% of the time or less.

The most likely clinical localization is left medial medulla, involving the pyramidal and medial lemniscus, but sparing the hypoglossal nucleus and CN XII fascicles.

2. Given the patient's age, and vascular risk factors of cigarette smoking and hypercholesterolemia, the most likely diagnosis is left medial medullary infarction. This is usually caused by occlusion of paramedian branches of the vertebral or anterior spinal arteries (see SCC 14.3, Table 14.7, Figure 14.20D). The right peritotal pins and needles experienced by this patient suggests some possible ischemia affecting the spinal trigeminal nucleus or trigeminal thalamic fibers (see Figures 12.8, 12.9). Although this symptom is more common in pontine ischemia, it can occasionally be seen in medial medullary syndrome.

Clinical Course and Neuroimaging
Conventional MRI was initially negative, but diffusion-weighted MRI revealed a left medial medullary infarct (Figure 14.23). Several days later this was visible on conventional MRI as well. The patient was admitted and treated with intravenous heparin. Workup, including MRA, echocardiogram, and a Holter monitor, did not reveal an obvious embolic source (see SCC 10.4). However, an MRA revealed an irregular region of signal loss in the distal left vertebral artery, just prior to the vertebralbasilar junction.

Because of the possibility of vertebral dissection (see SCC 10.6) or vertebral ste INITIATION (see SCC 14.3), a conventional vertebral angiogram was done. The angiogram confirmed occlusion of the distal left vertebral artery just beyond the left PICA takeoff point but did not reveal a dissection. This suggests that the patient's medial medullary infarct was caused by occlusion of paramedian vessels arising from the distal left vertebral artery (see Figure 14.20D). The vertebral occlusion may have been embolic from an unknown source, or could have been caused by thrombosis superimposed on a stenosed atherosclerotic vertebral artery. The patient was switched from intravenous heparin anticoagulation to oral anticoagulation with Coumadin. His weakness gradually improved, and he was discharged to an inpatient rehabilitation facility to continue his recovery.

CASE 14.1 FACE AND CONTRALATERAL BODY NUMBNESS, HOARSENESS, HORNER'S SYNDROME, AND ATAXIA

Figure 14.22 Left Laterally Medullary Infarct Caused by Vertebral Dissection Axial MRI images of the brain and cervical spine. (A) T2-weighted MRI done on admission does not show infarct, but does show absence of the flow void in the left vertebral artery. (B) Follow-up T2-weighted MRI done 5 days after admission shows increased signal in the left lateral medulla compatible with infarction (compare to Figure 14.20D). (C) T1-weighted images of the neck done on the day of admission show the left vertebral artery to have a thickened wall with a bright appearance compatible with dissection and coagulation of blood in the wall of the left vertebral artery (see Table 4.4).

(Medulla)
CASE 14.2 HEMIPARESIS SPARING THE FACE

Figure 14.23 Left Medial Medullary Infarct. Diffusion-weighted MRI images of the brain. (A) Axial section through the medulla. (B) Coronal section.
CASE 14.3 DYSARTHRIA AND HEMIPARESIS

MINICASE
A 74-year-old woman with a history of hypertension and atrial fibrillation had acute onset one morning of slurred speech and right-sided weakness. On exam, she had right facial weakness sparing the forehead, dysarthric speech, decreased palate elevation on the right, and tongue deviation to the right. In addition, her right arm had leg decreased tone and 0/5 to 2/5 weakness, and she had increased reflexes on the right and a right Babinski's sign.

LOCALIZATION AND DIFFERENTIAL DIAGNOSIS
1. On the basis of the symptoms and signs shown in bold above, what is the most likely location for the lesion?
2. What is the most likely diagnosis?

Discussion
1. The symptoms are strongly suggestive of brainstem dysfunction, possibly localized to the pons (see KCC 14.3; Table 14.6). Review each of this patient's symptoms and their localization in Table 14.6.
1. Given the patient's vascular risk factors and the fact that the episodes occur in situations that may lower the patient's systemic blood pressure (standing up), the most likely diagnosis is TIAs in the vertebrobasilar system, possibly caused by basilar stenosis. This is a potentially life-threatening situation, and the patient should be brought to immediate medical attention. An MRI should be performed and anticoagulation considered if a significant stenosis is found.

CASE 14.4 CONTINUATION

HISTORY, CONTINUED
The patient did not seek medical attention for his symptoms. On a Friday night 3 days prior to admission, the patient abruptly developed right facial numbness, decreased hearing in the right ear, slurred speech, right hand clumsiness (occasionally dropping things), and unsteady gait. When he returned to work at the garage on Monday, he had trouble working on the car, so he finally came to the emergency room.

PHYSICAL EXAMINATION
Vital Signs: T = 96.7°F; P = 14.
Orthostatic testing:
Supine: P = 80, BP = 120/80.
Standing: P = 88, BP = 122/76.
Neck: Supple with no bruits.
Lungs: Clear.
Heart: Regular rate with no murmurs.
Abdomen: Soft, nontender; normal bowel sounds.
Extremities: Normal.
Neurologic exam:
MENTAL STATUS: Alert and oriented x3. Naming and repetition intact. Mildly decreased attention; for example, skipped November when naming months backward. Recalled 1/3 words after 5 minutes, but got 3/3 with prompting.
CRANIAL NERVES: Pupils 4 mm, constricting to 2.5 mm bilaterally. Fundi normal. Extraocular movements full, with fine horizontal nystagmus (direction of fast phase was not specified). Light touch and pinprick sensation slightly decreased in right V3 and V4 distribution. Right corneal reflex decreased.
FACE symmetrical. Hearing decreased on the right. On the Weber test (see KCC 12.5) sounds were louder on the left. Speech slightly slurred. Normal palate elevation. Shoulder shrug and sternomas-toid normal. Tongue midline.
MOTOR: No drift. Normal tone. 3/5 power throughout.

REVIEW:
COORDINATION: Mild dysmetria on finger-to-nose testing on the right. Right finger tapping and foot tapping were slightly slow and dysmetric.
Gait: Slightly wide based. Able to do only two or three steps of tandem gait because of unsteadiness. When the patient stood or walked during the exam, he did not have symptoms of the transient episodes described above.
SPEECH: Intact light touch, pinprick, vibration, and joint position sense.

LOCALIZATION AND DIFFERENTIAL DIAGNOSIS
1. On the basis of the symptoms and signs shown in bold above, what is the most likely location for the lesion? Which blood vessel(s) may be involved?
2. What is the most likely diagnosis?

Discussion
1. The key symptoms and signs in this case are:
   • Decreased hearing in the right ear, with Weber test also eliciting decreased right hearing
   • Light touch and pinprick sensation slightly decreased in right V3 and V4 distribution, with decreased right corneal reflex

CASE 14.4 UNILATERAL FACE NUMBNESS, HEARING LOSS, AND ATAXIA

CHIEF COMPLAINT
A 56-year-old male auto mechanic had 1 month of episodic diplopia and unsteadiness, and then suddenly developed persistent right face numbness, hearing loss, and right-sided clumsiness.

HISTORY
Past history was notable for severely elevated cholesterol and cigarette smoking. About 1 month prior to admission, the patient developed transient episodes consisting of light-headedness, nausea, unsteadiness "staggering like I was drunk," diagonal diplopia with the right image higher than the left, periorbital numbness, and a generalized headache. The episodes were precipitated by his standing up and walking around, lasted 5 or 6 minutes, and occurred up to four or five times per day. The episodes gradually improved over time and nearly stopped.

INITIAL LOCALIZATION, DIFFERENTIAL DIAGNOSIS, AND MANAGEMENT
1. On the basis of the symptoms shown in bold above, what general brain region is most likely involved?
2. Given this patient's history, what diagnosis should be seriously considered, and what should be done?
Right dysmetria and dysarthria, with slurred speech, horizontal nystagmus, and unsteady, wide-based gait

The patient has findings compatible with a right lateral caudal pontine syndrome, most likely caused by a right AICA infarct (see Table 14.8, Figure 14.20C). Decreased hearing of somatosensory origin based on the Weber test (see KCC 12.5: neuroexam.com Video 42) may be due to involvement of the labyrinthine artery (see Figure 14.21A); impaired right facial sensation may be due to infarction of the right trigeminal nucleus and tract; and right-sided appendicular ataxia, gait ataxia, slurred speech, and nystagmus may be caused by involvement of the right middle cerebellar peduncle and vestibular nuclei (see Figure 14.20C). The patient also had mildly decreased attention, which is a non-specific finding that could have many causes, including brainstem ischemia (see KCC 19.14).

The most likely clinical localization is right caudal lateral pons, AICA territory.

2. The patient's vascular risk factors and antecedent episodes of transient symptoms make infarction in the right AICA territory the most likely diagnosis.

Clinical Course and Neuroimaging

An MRI revealed an infarct in the right lateral caudal pons in the territory of the AICA (Figure 14.25A); see also Figure 14.20C). An MRA showed a striking lack of flow in the entire vertebrobasilar system (see Figure 14.23B). This finding suggests that the patient most likely had long-standing disease of the posterior circulation, and that he developed collateral flow through vessels not visible on the MRA to supply his brainstem. In this tenuous situation, artery-to-artery embolus or thrombus of the AICA could have caused infarction in the right AICA territory.

The patient was admitted to the hospital and treated with intravenous heparin anticoagulation, and then switched to Coumadin. After 5 days, at the time of discharge, he had no nystagmus, his right hearing was improved, facial sensation was normal except for a small area around the right side of his mouth, (see Figure 12.9) he was able to perform tandem gait, and the right arm and leg ataxia was improved but not completely gone. In addition, his attention (possibly reflecting poor flow in the vertebrobasilar system) had returned to normal.

Five days later he returned to the emergency room with nausea causing decreased eating and drinking, and he had recurrent symptoms of light-headedness when standing, without other symptoms. Exam was unchanged, except that on orthostatic testing his pulse and blood pressure, respectively, went from 76 and 147/98 supine, to 110 and 124/96 standing (an increase in heart rate of greater than 10 beats per minute, or a decrease in systolic blood pressure of greater than 10 mm Hg is considered abnormal). Blood tests confirmed that his Coumadin anticoagulation was adequate, and there was no evidence of bleeding as the cause of orthostasis, so he was admitted for intravenous hydration and observation. Again he did well, gradually tolerated the upright position better, and was discharged. He quit smoking, started taking daily walks, began a low-cholesterol diet, and later began taking a cholesterol-lowering drug. At follow-up 1 month and again 4 months later, he was without symptoms, and exam was normal except for decreased pinprick sensation in a small area around the right tip and trace dysarthria of right finger and toe tapping.

Discussion

The symptoms are strongly suggestive of brainstem dysfunction, possibly from vertebrobasilar disease (see KCC 14.3: Table 14.6). Review the localization of each of these symptoms in Table 14.6. Of note, inflammatory bowel disease can sometimes cause hypercoagulability, so incipient thrombosis in the vertebrobasilar system should be strongly considered.

CASE 14.5 LOCKED IN

MINICASE

A 57-year-old woman with a history of Crohn's disease was walking in a mall and suddenly had to sit down because she felt sweaty and the left side of her face felt "funny." Her husband noticed a "lazy eye" on the left. She was taken to an outside hospital, where on initial exam she had slurred speech with good comprehension. She also had weakness and decreased sensation of the left face, arm, and leg, and this was asymetrical (side not specified). She was admitted to the hospital, but because of concerns about increased bleeding risk with Crohn's disease, she was not anticoagulated.

INITIAL LOCALIZATION AND DIFFERENTIAL DIAGNOSIS

On the basis of the symptoms and signs shown in bold above, what is the most likely general location for the lesion? Given this patient's history, what diagnosis should be seriously considered?

Discussion

The symptoms are strongly suggestive of brainstem dysfunction, possibly from vertebrobasilar disease (see KCC 14.3: Table 14.6). Review the localization of each of these symptoms in Table 14.6. Of note, inflammatory bowel disease can sometimes cause hypercoagulability, so incipient thrombosis in the vertebrobasilar system should be strongly considered.

CASE 14.5 (CONTINUED)

HISTORY, CONTINUED

That evening at 9:00 p.m., the patient suddenly had a respiratory arrest requiring intubation, and she was found to have decerebrate posturing (see Figure 3.48). The next morning she was transferred to a tertiary care center. On exam, she was intubated and unable to move her extremities, but she was awake and able to answer yes/no questions appropriately by using eye blinks or vertical eye movements. She had no horizontal eye movements, even with oculocephalic maneuvers, but she did have voluntary vertical eye movements. She also had ocular bobbing (faster phase down, slow phase up), and a skew deviation, with the left eye higher than the right. There was no movement of the limbs in response to commands. In response to pain, the left arm did not move, the right arm had extensor (decerebrate) posturing, and both legs had triple flexion (see Figure 3.40). Reflexes were absent, and both toes were upgoing.

LOCALIZATION AND DIFFERENTIAL DIAGNOSIS

1. On the basis of the symptoms and signs shown in bold above, what is the most likely localization?
2. What is the most likely cause, and what are some other possibilities? What is the name of this clinical syndrome?

Discussion

1. The key symptoms in this case are:
   - Respiratory arrest
   - Decerebrate horizontal eye movements
   - Ocular bobbing and a skew deviation
   - Ability to answer yes/no questions appropriately using eye blinks or vertical eye movements
   - No voluntary movements, with only decerebrate posturing, triple flexion, and bilateral Babinski's signs

2. The findings suggest possible medullary involvement (see Figure 14.16). The other findings—including lack of horizontal eye movements, ocular bobbing, skew deviation, and bilateral upper motor neuron-type paralyses with extensor posturing—all suggest extensive bilateral involvement of the pons (see KCC 14.3: Figure 14.20B,C). The fact that consciousness and vertical eye movements were preserved suggests that the midbrain was spared.
2. This clinical picture is compatible with locked-in syndrome (see KCC 14.1) caused by extensive bilateral pontine and possibly medullary infarcts, sparing the midbrain.

**Clinical Course and Neuroimaging**

An MRI revealed massive bilateral infarcts of the pons, extending downward to the medulla (Figure 14.26A, B). The midbrain (including the midbrain reticular formation) was not involved (see Figure 14.26C). An MRA showed absent flow in the vertebrobasilar system similar to that exhibited by the patient in Case 14.4 (see Figure 14.25B). The lack of vertebrobasilar flow suggests that this patient had developed a basilar artery thrombosis, but that unlike the patient in Case 14.4, she did not have sufficient collateral flow to supply much of her brainstem. She was treated with intravenous heparin but made no significant improvements during her hospitalization. Eventually, her left arm also developed decerebrate posturing. The patient and family decided to continue the mechanical ventilator; however, they requested no resuscitation in the event of cardiac arrest. A speech therapist worked with the patient to facilitate communications using picture and letter cards and other devices, and she remained able to communicate, but unable to move except for looking up and down or blinking (levator palpebrae superior). She developed several infections that were treated with antibiotics, and when last seen, two and a half months after onset, her exam remained unchanged.

**Related Cases.** Locked-in syndrome (see KCC 14.1) is usually caused by bilateral ventral pontine lesions, but rarely it can be caused by lesions in other locations. For example, Figure 14.27 shows an MRI scan from a 50-year-old mathematician with a stroke in the areas of the left cerebral cortex, insula, and basal ganglia. The midbrain was spared, indicating that the lesion was limited to the thalamus and basal ganglia. He remained in a locked-in state, communicating with eye movements only, for the next year and a half and eventually succumbed to an overwhelming pulmonary infection.

Atherosclerotic basilar stenosis with superimposed basilar thrombosis is a life-threatening neurologic emergency requiring prompt treatment. The two cases of locked-in patients described here, as well as other cases in this chapter, demonstrate the potentially dire consequences of basilar insufficiency. Figure 14.28 shows a pathology specimen from a patient who died of basilar thrombosis. This patient was a 67-year-old man who, over 2 days, gradually became sedated, weak, and quadriplegic, eventually lapsing into coma with no eye movement. An MRI showed massive infarction of the pons, midbrain (including the reticular formation), thalamus, and cerebellum (B) supplied by the basilar artery; see Figures 14.17, 14.19). Postmortem examination revealed severe atherosclerotic narrowing of the basilar artery (see Figure 14.28), with superimposed thrombus.

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**CASE 14.3 DYSARATHRIA AND HEMIPARESIS**

Figure 14.24 Left Pontis Infarct Axial T2-weighted MRI image through the pons.

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**CASE 14.4 UNILATERAL FACE NUMBNESS, HEARING LOSS, AND ATAXIA**

Figure 14.25 Right AICA Infarct and Basilar Insufficiency (A) Axial T2-weighted MRI image through the pons demonstrating increased signal in the right doro-lateral pons and middle cerebellar peduncles, compatible with right anterior inferior cerebellar artery (AICA) Infarct (compare to Figure 14.20B). (B) MRA demonstrating absence of visible flow in the vertebral or basilar arteries. This suggests severe narrowing of the basilar artery.
CASE 14.6 (CONTINUED)

**LOCALIZATION AND DIFFERENTIAL DIAGNOSIS**

On the basis of the symptoms and signs shown in bold above, what is the most likely localization? What is the most likely diagnosis?

**Discussion**

The key symptoms and signs in this case are:
- Bilateral frontal and retro-orbital headaches
- Nausea
- Blurred vision
- Generalized weakness: gait difficulty; transient episode of right-sided weakness; weakness of left face sparing the forehead, left arm, and left leg, with left leg triple flexion, and bilateral Babinski's signs; progression to bilateral right greater than left extensor posturing
- Decreased responsiveness, progressively worsening
- Dysarthria; inability to protrude tongue
- Right horizontal gaze palsy; limited upgaze
- Shivering movements

This patient had symptoms and signs suggestive of waxing, waning, and then sudden worsening dysfunction of several bilateral regions supplied by the vertebrobasilar system (see KCC 14.3, Table 14.6). Blurred vision could be the result of occipital lobe involvement or diplopia. The alternating right, then left, and then right hemiparesis with bilateral Babinski's signs is strongly suggestive of basilar artery stenosis affecting the bilateral basal poors. The presence of wrong-way eyes (see Table 14.8; see also KCC 13.10; Figure 13.35; Case 13.7) at the time of initial examination (left weakness with left gaze preference) suggests extension to the right pontine tegmentum (see Figure 14.20C). Limited upgaze and impaired consciousness suggest impaired function of the midbrain tegmentum. Shivering is characteristic of pontine dysfunction, and the headaches, nausea, and dysarthria are also suggestive of brainstem dysfunction resulting from ischemia (see KCC 14.3, Table 14.6). Given the patient's vascular risk factors, the overall picture is most compatible with evolving basilar thrombosis, possibly in the setting of preexisting basilar stenosis.

**Clinical Course and Neuroimaging**

The patient's initial head CT revealed no infarcts or hemorrhages (Figure 14.29A). Interestingly, there was a region of increased density in the basilar artery with Hounsfield units (HU) of 60 to 70 compatible with clotted blood (see Table 4.1). Intravenous heparin was started, and in an experimental treatment for basilar thrombosis, the patient was then taken for an immediate angiogram (see Figure 14.29B). When the left vertebral artery was injected with dye, flow stopped after the proximal basilar artery just after the PCA, and the dye refluxed down into the contralateral right vertebral artery during the injection (see Figure 14.29B). Urokinase, a thrombolytic agent, was then infused through a catheter directly into the basilar artery at the region of the occlusion. The result was successful lysis of a clot that had blocked a very narrow region of the basilar artery (see Figure 14.29C). After the lysis, the injected dye no longer refluxed significantly into the contralateral (right) vertebral artery, but instead continued distally, demonstrating...
restored flow in the distal basilar artery, PCA, and SCAs (see Figure 14.29c). Follow-up head CT no longer showed a bright clot in the basilar artery with HU (see Table 4.1) measured at 40 (compare to Case 13.7).

On exam that evening, the patient was alert, following commands, with slightly limited right gaze and upgaze. He had extensor posturing on the left side, purposeful movements on the right and bilaterally upgoing toes. The next day he had full eye movements except for slightly limited right eye abduction. 4+/5 strength on the left side, and bilateral equivocal plantar responses. He was changed over from heparin to Coumadin, and an MRA just before discharge (2 weeks after onset) showed persistent focal stenosis of the midbasilar artery. MRI showed no evidence of infarction. By the time of discharge, the patient had a completely normal neurologic exam, and he walked out of the hospital with no deficits.

**CASE 14.5 LOCKED IN**

Figure 14.26 Bilateral Pontine Basis Infarcts Causing Locked-in Syndrome Axial T2-weighted MRI images: (A) Rosstral medulla with small bilateral regions of increased signal, compatible with infarcts. (B) Pons with extensive bilateral infarcts destroying the corticospinal and corticobulbar pathways. (C) Midbrain is spared, including the midbrain reticular formation, allowing preserved consciousness.
CASE 14.5 RELATED CASES

Figure 14.27 Bilateral Midbrain Basis Infarcts Causing Locked-in Syndrome

(A) Medulla, (B) Pons. (C) Midbrain, with bilateral T2-brigh regions in the cerebral peduncles, compatible with infarcts.

(A) Medulla
(B) Pons
(C) Midbrain

Figure 14.28 Basilar Artery Stenosis

Pathology specimen from a patient who died of basilar thrombosis. A severe narrowing of the midbasilar artery can be seen (arrow), caused by atherosclerotic disease. This resulted in the superimposed basilar thrombosis.
**CASE 14.6** WRONG-WAY EYES, LIMITED UPGAZE, DECREASED RESPONSIVENESS, AND HEMIPARESIS WITH AN AMAZING RECOVERY

Figure 14.29 Basilar Artery Thrombosis Treated with Intra-arterial Thrombolysis. (A) Head CT on admission showing bright signal in the basilar artery, suggesting thrombosis. No infarct or hemorrhage was seen. (B) Angiogram done following left vertebral artery injection, demonstrating lack of flow in the basilar artery post the anterior inferior cerebellar arteries (AICA). Left anterior oblique view (C) Repeat angiogram after intra-arterial thrombolysis, demonstrating restored flow in the distal basilar artery territory. A mid-basilar artery narrowing can be seen just distal to the AICAs. Left anterior oblique view following injection of the left vertebral artery, as in B.

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**CASE 14.6 (CONTINUED)**

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**CASE 14.7** DIPLOPIA AND UNILATERAL ATAXIA

MINICASE

A 72-year-old man with a history of hypertension and hypercholesterolemia was watching TV one night and suddenly saw two faces on the screen diagonally displaced. This diploria went away when he covered one eye. In order not to alarm his wife, he quietly made his way to bed, but the next morning the diploria was unchanged, and he also noticed gait unsteadiness with staggering to the right. He tried using a friend's walker, but then also noticed that his right hand was clumsy. For example, he had difficulty picking up a credit card from the table with his right hand. On exam, his left eye would elevate by only 1 mm, adduct by only 2 mm, and depress by only 3 mm (Figure 14.30B). Left eye abduction was normal. He had diagonal diploria, which was tested with a red glass over the right eye, as shown in Figure 14.30D. There was a left piosis, with the palpebral fissure measuring 4 mm on the left and 9 mm on the right (see Figure 14.30C). The left pupil had a slightly irregular shape (see Figure 14.30D).
CASE 14.7 (CONTINUED)

14.20A but reacted normally to light. The patient also had mild right ataxia on finger-to-nose and heel-to-shin testing, and an unstable gait, tending to list to the right. The remainder of the exam was normal, except for the right plantar response, which was equivocal.

LOCALIZATION AND DIFFERENTIAL DIAGNOSIS
1. What is the cause of the eye movement abnormalities summarized in Figure 14.29 (review KCC 13.1, 13.2)?
2. A lesion in what region of the brain could cause these abnormalities along with right ataxia?
3. What is the most likely diagnosis?

Discussion
The key symptoms and signs in this case are:
- Diagonal diplopia, and left eye movements with only 1 mm elevation.
- 2 mm adduction, 3 mm depression and normal abduction with left ptosis.
- Right arm and leg ataxia.
- Equivocal right plantar response.
- Unsteady described as "like firecrackers going off in front of my eyes," associated with multiple other vague complaints, including episodic, pleuritic, and back pain, which were attributed to fibrositis or stress. There was a strong family history of migraine.

The most likely clinical localization is left midbrain tegmentum, including the oculomotor nerve fascicles and superior cerebellar peduncles fibers (Claude's syndrome; see Table 14.9).

3. Given the sudden onset of symptoms in a man in his 70s with a history of hypertension and elevated cholesterol, the most likely diagnosis is left midbrain infarct, caused by occlusion of the penetrating vessels at the top of the basilar artery and proximal left PCA (see Figure 14.17A, 14.20A). A far less likely possibility is a small hemorrhage in this region.

Clinical Course and Neuroimaging
An MRI revealed subtle increased T2 signal in the midbrain tegmentum (not shown). Diffusion-weighted MRI confirmed the presence of an acute infarct in the left midbrain tegmentum (Figure 14.31; compare to Figure 14.20A). The patient was admitted and treated with intravenous heparin. MRA was unremarkable, but a Holter monitor revealed intermittent atrial fibrillation, and echocardiogram showed an enlarged left atrium. He was therefore transferred to Courmadin and discharged home with a persistent left third-nerve palsy and mild right ataxia.

Related Case. Figure 14.32 shows an MRI from another patient with a slightly larger midbrain infarct. The infarct involved the right midbrain tegmentum and right cerebral peduncle, resulting in a right CN III palsy, left-sided ataxia, and left hemisensory (Benedikt's syndrome) (see Table 14.9, Figure 14.20A). Compare Case 14.7 and this related case with Case 13.1.

CASE 14.8 INTERMITTENT MEMORY LOSS, DIPLOPIA, SPARKLING LIGHTS, AND SONOMENCE

MINICASE
A 40-year-old retired businesswoman was sent to the emergency room by her physician because of 2 months of worsening episodes of memory loss, sparkling lights, and blurry or double vision. Her past medical history was notable for anticoagulopathy (antiphospholipid antibody syndrome, a condition causing hypercoagulability; see Table 10.5), including elevated anti- phospholipid antibodies (IgG 2407, IgM 38, IgA < 10), a first-trimester miscarriage, left subclavian stenosis, and Raynaud's phenomenon. She had been treated in the past with Coumadin, but she elected to take aspirin instead. She also had a long history of brief, 1- to 2-minute, episodes of migrainelike visual distortions (see KCC 5.1) that she described as "like firecrackers going off in front of my eyes," associated with multiple other vague complaints, including episodic, pleuritic, and back pain, which were attributed to fibrositis or stress. There was a strong family history of migraine. The patient's sister had died 2 months prior to admission, and shortly afterward the patient began having recurrent episodes of memory loss lasting several minutes each, along with worsening of all her other complaints. She was somewhat evasive and vague in describing the episodes, and her physicians initially believed them to be psychosomatically based. Memory lapses included forgetting whether her sister had been buried or cremated, and forgetting a real estate deal she had recently completed.

On the day of admission, she saw her physician because of a new complaint she had developed a few days earlier of blurred and then double vision to the point where it was difficult for her to stand up and walk. On initial examination she was alert and fluent but had mildly reduced attention, able to repeat only 57 digits forward, and recalling 23 objects after 3 minutes. Her right pupil was slightly enlarged at 4 mm, constricting sluggishly to 2.5 mm, and her left pupil was 3 mm, constricting briskly to 2 mm. She had limited upward gaze with both eyes. In addition, medial gaze was reduced with the right eye, and she had a right ptosis. Exam was otherwise unremarkable.

Her physician sent her to the emergency room, where she was examined by a neurologist, but by the time she arrived she had normal eye movements, with the only abnormality on exam being a mild residual anisocoria. She was admitted for further evaluation, and the next morning she was found again to have limited upgaze bilaterally, right ptosis, and right limited medial gaze, with a somewhat dilated right pupil. Anticoagulation with intravenous heparin was initiated; however, during the subsequent days she had waning and waning somnolence and delirium to the point of being unarousable at times. At other times, despite being transferred to the intensive care unit, she would wake up, pull out all her intravenous lines, and walk down the hallway to use the bathroom. Her eye movement abnormalities persisted, and in addition she developed bilateral ataxia on finger-to-nose testing (when she was awake enough to cooperate) and decreased blink to visual threat on the left side.

LOCALIZATION AND DIFFERENTIAL DIAGNOSIS
1. How can the eye movement abnormalities in this patient be summarized?
2. Dysfunction in what location can cause these eye movement abnormalities along with an impaired level of consciousness and ataxia?
3. Given the history of hypercoagulability and the addition of a left visual field deficit, as well as episodes of memory loss, what vascular syndrome (specify blood vessels involved) can cause this combination of deficits (see KCC 14.3)?

Discussion
The key symptoms and signs in this case are:
- Episodes of memory loss
- Mildly reduced attention evolving to wakening and waning somnolence and delirium
- Limited upward gaze with both eyes
- Double vision with limited right medial and upward gaze, enlarged right pupil, and right ptosis
- Bilateral ataxia on finger-to-nose testing
- Sparkling lights, blurry vision, and later decreased blink to visual threat on the left side.

Summary of eye movement abnormalities: The patient had limited upgaze bilaterally. In addition, she had findings compatible with right third-nerve dys-
function, including right ptosis, a large right pupil with decreased reactivity to light, and reduced right eye adduction in addition to the limited upgaze.

2. Localization of eye movement abnormalities, skew deviation, and ataxic Dysfunction in the midbrain tegmentum (see Figure 14.20A) could cause (1) vertical gaze abnormalities through involvement of the rostral interstitial nucleus of the MLF in the rostral midbrain (see the Chapter 13 section on vertical eye movements), (2) right third-nerve dysfunction through involvement of the right third-nerve fascicles or nucleus (a right third-nerve nucleus lesion involving the ipsilateral, superior rectus nucleus, and contralateral crossing fibers, could also cause bilateral impairment of upgaze; see Table 13.2; Figure 13.3); (3) skew deviation through involvement of the rectus formation (see KCC 14.2); and (4) bilateral ataxia through involvement of the superior cerebellar peduncle fibers.

3. Vascular localization and diagnosis: Given this patient’s history of hypercoagulability, a thromboembolic disorder is likely. The above deficits can be localized to the midbrain tegmentum, which is supplied by small penetrating vessels arising from the top of the basilar artery and proximal PCAs (see Figures 14.17A, 14.19, 14.20A). The left visual field defect could be explained by an infarct of the right occipital lobe, which is supplied by the right PCA. In addition, the episodes of memory loss could have been caused by TIAs involving the bilateral medial thalami or medial temporal lobes (see KCC 18.1) and these structures are also supplied by the PCAs (see Figures 10.5, 10.8). Therefore, the above deficits could all be caused by vascular insufficiency at the top of the basilar artery and proximal PCAs, known as top-of-the-basilar syndrome (see KCC 14.3; Figure 14.17). Top-of-the-basilar syndrome is usually caused by an embolus or thrombus lodged at the top of the basilar artery. Another, less likely possibility is thrombosis of the more proximal basilar artery, although in that case pontine dysfunction generally occurs, including corticospinal, horizonttal gaze, proprioceptive, and other dysfunctions not seen in this patient.

Clinical Course and Neuroimaging

As already noted, despite anticoagulation the patient’s condition continued to worsen and worsen. MRI and head CT scans demonstrated multiple bilateral infarcts in the territory of vessels arising from the top of the basilar artery (Figure 14.33), including the midbrain tegmentum, bilateral medial thalami, and right occipital lobe. An angiogram was performed because of concerns that, given her rheumatological history, she might have CNS vasculitis (see Table 10.5) which would require a different treatment (immunosuppressive therapy). The angiogram was negative for changes suggestive of vasculitis. However, a filling defect was seen at the top of the basilar artery, most likely due to a thrombus that had embolized to that location from a remote source such as the heart, or less likely, due to a thrombus that had formed locally (Figure 14.34). Of note, the PCAs did not fill from the basilar artery (compare to Figure 4.17B). However, when the internal carotid arteries were injected (not shown), the PCAs did fill, via the posterior communicating arteries, except for the distal right PCA. This result suggests that the midbrain and thalamic infarcts were caused by the occlusion of small penetrating vessels arising from the top of the basilar artery and proximal PCAs (see Figure 14.17A), while the right occipital infarct was probably caused by an embolus that broke off from the top of the basilar region and migrated up into the distal right PCA (see Figure 14.19).

During the course of her hospital stay, the patient’s condition initially waxed and waned as already noted, but she later developed right hemiparesis and lupus into a coma (see KCC 14.2). A week later, she began to regain some responsiveness to stimulation and to commands, and an MRA revealed that some flow had been restored through the distal basilar artery. She was eventually discharged on Coumadin to a rehabilitation facility.

**CASE 14.7 DIPLOPIA AND UNILATERAL ATAXIA**

Figure 14.31 Left Midbrain Infarct in Region of Third Nerve Fascicles and Superior Cerebellar Peduncle

*Diffusion-weighted MRI images. (A) Axial image through the midbrain. (B) Coronal image.*
CASE 14.7 RELATED CASE

Figure 14.32. Right Midbrain Infarct in Region of Cerebral Peduncle, Superior Cerebellar Peduncle, Red Nucleus, and Third-Nerve Fascicles. Axial T2-weighted MRI image through the midbrain.

Posterior cerebral artery

Infarct

Superior sagittal sinus

Temporal lobe

Posterior cerebral artery

Central peduncle

Midbrain tegmentum

Occipital lobe

Discussion
The key symptoms and signs in this case are:
- Bilateral retro-orbital headache
- Intractable hiccups

Headache can have many causes, but it may be associated with intracranial pathology (see KCC 5.1). Hiccups can be caused by lesions of the posterior fossa, particularly in the medulla (see KCC 14.3). Given the occurrence of symptoms possibly related to brainstem dysfunction many years earlier, a chronic or recurrent lesion of the brainstem, especially the medulla, is the most likely diagnosis. Some possibilities would include demyelination, a low-grade tumor, or a small recurrent hemorrhage in an arteriovenous malformation or cavernous angioma, vertebral-basilar migraine, and vasculitis or immune-mediated disorders of the CNS (CNS lupus, Behçet's syndrome, sarcoidosis, etc.).

Clinical Course and Neuroimaging

A brain MRI was performed (Figure 14.33). The MRI revealed a small bright region on unenhanced T1-weighted images, consistent with subacute hemorrhage (see Table 4.4), located in the dorsal portion of the rostral pons in the region of the obex. The patient was admitted briefly for observation and then was discharged home with an appointment for an angiogram approximately 1 month later, once the bleed had resolved, to look for an arteriovenous malformation. The angiogram was negative, and it was felt that the patient most likely had a cavernous angioma (see KCC 5.6). A follow-up MRI scan 3 to 4 months later revealed resorption of the hemorrhage (see Figure 14.33).

Treatment of cavernous angiomas is controversial; however, because of concerns about the potential high risk if another bleed should occur in this location, the decision was made to treat the angioma by surgical resection. The lesion was resected during a long, delicate operation in the posterior fossa. Pathologic examination of the resected tissue confirmed cavernous angioma (see KCC 5.6). She made a complete recovery without any deficits.

CASE 14.9 INTRACTABLE HICCUPS

MINICASE
A 50-year-old woman developed a bilateral retro-orbital headache associated with nasal discharge 2 weeks prior to presentation. She was treated with oral antibiotics for presumed sinusitis, and her symptoms resolved. On review of her past history, she described an episode 14 years previously of vertigo, nystagmus, and dysarthria with a negative workup done in 1977, before MRI was available. Because of these previous symptoms, an MRI scan was scheduled; however, she then suddenly developed intractable hiccups lasting 5 days, causing her to come back to her physician's office. General exam and neurologic exam were entirely normal.

Localizer and Differential Diagnosis
Although hiccups (singultus) are usually benign, persistent hiccups can be caused by a variety of systemic or gastrointestinal disorders, as well as by CNS lesions. Lesions in what general region of the CNS are associated with hiccups? Assuming that this patient's previous neurologic symptoms are related to her present complaints, what are some possibilities for the diagnosis?

Additional Cases
Related cases can be found in other chapters for the following topics: brainstem internal structures and vascular supply (Cases 5.2-5.6, 10.3, 10.11, 12.8, 13.7-13.9, 15.4, 15.5). Other relevant cases can be found using the Case Index.
CASE 14.8 INTERMITTENT MEMORY LOSS, DIPLOPIA, SPARKLING LIGHTS, AND SOMNOLENCE

Figure 14.33 Infarcts Caused by Top-of-the-Basilar Syndrome
- Axial CT scan images: (A) Hypodensity in midbrain tegmentum and right occipital lobe compatible with infarcts. (B) Section slightly higher than in (A), showing bilateral medial thalamic and right occipital infarcts.

(A) Temporal lobe
- Infarct in midbrain tegmentum
- Pals cerebi
- Right occipital infarct
- Movement artifact
- Infarct in medial thalamic nucleus
- Calcified pinales
- Calcified choroid plexus

(B) Superior cerebellar artery
- Posteriorinferior cerebellar artery (PICA)
- Anterior inferior cerebellar artery (AICA)
- Distal basilar artery
- Superior cerebellar artery (SCA)
- Basilar artery
- Posterior artery
- Anterior inferior cerebellar artery (AICA)

Figure 14.34 Top-of-the-Basilar Syndrome
- Angiogram following injection of the left vertebral artery: (A) Left lateral view. Note filling defect in the distal basilar artery, and lack of filling of the bilateral posterior cerebral arteries (PCAs).
- (B) Anteroposterior view (compare to Figure 4.17).
CASE 14.9 INTRACTABLE HICCUPS

In this chapter we focused on the four main components of internal brainstem structures shown in Figure 14.1, namely: cranial nerve nuclei and related structures; long tracts; cerebellar circuitry; and reticular formation and related structures. We will describe two strategies for reviewing this material here. First, we will take a functional approach and use the myelin-stained brainstem sections shown in Figures 14.3-14.5 to identify functional pathways and functional groupings of nuclei that are distributed throughout these sections and beyond. Second, we will take a regional approach and use the vascular territories shown in Figure 14.20 to identify clinically relevant constellations of deficits that occur with focal brainstem infarcts.

1. To begin the functional review, use Table 14.1 to recall each of the six functional columns of cranial nerve nuclei, and follow these columns through the brainstem sections in Figures 14.3-14.5, identifying each of the component nuclei (all nuclei can be identified on these sections except for the salivatory nuclei and the cochlear nuclei) (see also Figure 12.5). As you trace structures through adjacent brainstem sections, be sure to note their spatial relationships to nearby structures as well.

2. Next, review the auditory pathway by following the lateral lemniscus through the sections from the caudal pons to the inferior colliculus (see Figures 14.3-14.4); using Figures 12.16 and 12.17 as a guide. Identify the MLF in each brainstem section (see Figures 14.3-14.5), and recall its functions (see Figures 12.18, 13.12). Follow the taste pathway from the nucleus solitarius rostrally toward the thalamus by following the central tegmental tract from the medulla up through the midbrain (see also Figure 12.12).

3. Next, follow each of the long tracts (see Figures 6.18, 7.3, 7.2) through the brainstem sections, proceeding from rostral to caudal to trace the route of the corticospinal tract, and from caudal to rostral to trace the posterior column–medial lemniscal system and the anterolateral (spinothalamic) system (see Figures 14.3-14.5). Cerebellar circuitry is discussed in detail in Chapter 15, but as an initial orientation, use the stained brainstem sections in Figures 14.3-14.5 to identify each of the structures listed under cerebellar circuitry in Table 14.1.

4. The reticular formation was simplified in this chapter as containing rostral and caudal regions with different primary functions (see Figure 14.6). The rostral reticular formation, located in the midbrain and upper pons, includes several widespread projection systems involved primarily in behavioral and cognitive arousal (see Table 14.2; Figures 14.6-14.13). Lesions in the pontomesencephalic reticular formation often cause coma. Other circuits of the reticular formation located mainly in the more caudal pons and medulla are important for control of respiration, heart rate, blood pressure, and other autonomic functions, as well as for motor control, posture, muscle tone, locomotion, and a variety of other relatively stereotyped motor activities.

5. By reviewing brainstem vascular syndromes, we will complete a regional overview of internal brainstem structures and also enhance our clinical knowledge. The major blood vessels of the posterior circulation are shown in Figures 14.17-14.20. Paramedian penetrating bran-
Brief Anatomical Study Guide (continued)

Ches supply medial regions of the brainstem, while lateral regions are supplied by penetrators arising from both small-caliber circumferential branches (see Figure 14.18) and the larger vessels shown in Figure 14.17.

6. Proceeding from caudal to rostral, identify each vascular territory on the right half of Figure 14.20. Cover the labels and name the vessels that supply each territory (these are also listed in Tables 14.2-14.6). Next, name the structures within each territory that would be affected by occlusion of the blood supply to that territory, and name the associated clinical symptoms and signs. By proceeding in this way through the vascular territories of the medulla, pons, and midbrain, you should gain a full appreciation of the elegance of brainstem anatomy and its clinical importance.

References

Anatomical and Clinical Review


Coma


Pereset JR. 1982. The Diagnosis of Stroke and Coma. 3rd Ed. FA Davis, Philadelphia.


Brainstem Vascular Supply and Vertebrobasilar Disease


ANATOMICAL AND CLINICAL REVIEW
Cerebellar Lobes, Peduncles, and Deep Nuclei
Microscopic Circuitry of the Cerebellum
Cerebellar Output Pathways
Cerebellar Input Pathways
Vascular Supply to the Cerebellum

KCC 15.1 Cerebellar Artery Infarcts and Cerebellar Hemorrhage
KCC 15.2 Clinical Findings and Localization of Cerebellar Ataxia
KCC 15.3 Differential Diagnosis of Ataxia

CLINICAL CASES
15.1 Sudden Onset of Unilateral Ataxia
15.2 Walking Like a Drunkard
15.3 A Boy with Headaches, Nausea, Slurred Speech, and Ataxia
15.4 Nausea, Progressive Unilateral Ataxia, and Right Face Numbness

Additional Cases

BRIEF ANATOMICAL STUDY GUIDE

Cerebellar lesions can cause abnormalities in movement of the body and eyes and can affect balance by disrupting vestibular function. A 13-year-old boy with a lesion in the cerebellum developed gradually worsening headaches, nausea, vomiting, and unsteadiness over the course of 2 months. His headaches were worse at night and were mainly in the left occipital area. A neurologic examination revealed bilateral papilledema, nystagmus, mildly slurred speech, and irregular, ataxic movements that were worse on the left side than the right. In this chapter we will learn about the anatomy and functions of the cerebellum, including network interactions with other parts of the nervous system, and we will see examples of cases in which these functions have been impaired.
ANATOMICAL AND CLINICAL REVIEW

The cerebellum integrates massive sensory and other inputs from many regions of the brain and spinal cord. This information is used by the cerebellum to smoothly coordinate ongoing movements and to participate in motor planning. Like the basal ganglia, discussed in Chapter 16, the cerebellum has no direct connections to lower motor neurons, but instead exerts its influence through connections to motor systems of the cortex and brainstem (see Figures 2.17, 6.6).

The cerebellum is organized into different regions with specialized functions (see Table 15.1). The inferior vermis and flocculonodular lobes regulate balance and eye movements through interactions with the vestibular circuitry. These regions, together with other parts of the vermis, are involved in control of the medial motor systems discussed in Chapter 6 (proximal trunk muscles). More lateral cerebellar regions control the lateral motor systems (distal appendicular muscles). Finally, large regions of the most lateral cerebellar hemispheres are important in motor planning.

Although cerebellar circuitry is complex, the effects of lesions on the cerebellum are relatively easy to understand based on these different cerebellar regions, as we will see. Cerebellar lesions typically result in a characteristic type of irregular uncoordinated movement, called ataxia. Cerebellar lesions can often be localized on the basis of just a few simple principles (see also KCC 15.2d):

1. Ataxia is ipsilateral to the side of a cerebellar lesion.
2. Midline lesions of the cerebellar vermis or flocculonodular lobes mainly cause unsteady gait (truncal ataxia) and eye movement abnormalities, which are often accompanied by vertigo, nausea, and vomiting.
3. Lesions lateral to the cerebellar vermis mainly cause ataxia of the limbs (appendicular ataxia).

It is also important to recognize that because of the multiple reciprocal connections between the cerebellum, brainstem, and other regions, ataxia may be seen with lesions in these other locations as well. In addition, cerebellar pathways participate in several other functions, including articulation of speech, respiratory movements, motor learning, and possibly certain higher-order cognitive processes.

In this chapter, we will begin our tour of the cerebellum by discussing its overall structure. Next we will discuss the microscopic circuitry and input/output connections of the cerebellum. Finally, we will review the vascular supply to the cerebellum and the clinical effects of lesions on cerebellar networks.

Cerebellar Lobes, Peduncles, and Deep Nuclei

The cerebellum is the largest structure in the posterior fossa (Figure 15.1). It is attached to the dorsal aspect of the pons and rostral medulla by three white matter peduncles (feet) and forms the roof of the fourth ventricle (Figures 15.1, 15.3). The cerebellum consists of a midline vermis, named for its worm-like appearance, and two large cerebellar hemispheres (see Figure 15.3A).

There are numerous fissures, the deepest of which is called the primary fissure (see Figures 15.1, 15.3A), separating the cerebellum into an anterior lobe and a posterior lobe. If the cerebellum is removed from the brainstem by cutting the cerebellar peduncles (Figure 15.2), the ventral surface of the cerebellum becomes visible (see Figure 15.3C). On the ventral surface, the posterolateral fissure separates the posterior lobe from the flocculonodular lobes, a region with important connections to the vestibular nuclei.

The two flocculi are connected to the midline structure called the nodulus by thin pedicles (see Figure 15.3C). The nodulus is the most inferior portion of the cerebellar vermis. Another important landmark on the inferior surface consists of the cerebellar tonsils (see Figures 15.1, 15.3C). Mass lesions of the cerebrum or cerebellum, or brain swelling with severely elevated intracranial pressure, can cause the tonsils to herniate (see KCC 5.4) through the foramen magnum (see Figure 15.1; see also Figure 5.18), compressing the medulla and causing death because of impingement on medullary respiratory centers.

The two flocculi are connected to the midline structure called the nodulus by thin pedicles (see Figure 15.3C). The nodulus is the most inferior portion of the cerebellar vermis. Another important landmark on the inferior surface consists of the cerebellar tonsils (see Figures 15.1, 15.3C). Mass lesions of the cerebrum or cerebellum, or brain swelling with severely elevated intracranial pressure, can cause the tonsils to herniate (see KCC 5.4) through the foramen magnum (see Figure 15.1; see also Figure 5.18), compressing the medulla and causing death because of impingement on medullary respiratory centers.
Table 15.1 Functional Regions of the Cerebellum

<table>
<thead>
<tr>
<th>REGION</th>
<th>FUNCTIONS</th>
<th>MOTOR PATHWAYS INFLUENCED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lateral hemispheres</td>
<td>Motor planning for extremities</td>
<td>Lateral corticospinal tract</td>
</tr>
<tr>
<td>Intermediate hemispheres</td>
<td>Deltal limb coordination</td>
<td>Lateral corticospinal tract, rubrospinal tract</td>
</tr>
<tr>
<td>Vermis and</td>
<td>Proximal limb and trunk coordination</td>
<td>Anterior corticospinal tract, reticulospinal tract, vestibulospinal tract, tectospinal tract</td>
</tr>
<tr>
<td>floculonodular lobe</td>
<td>Balance and vestibulo-ocular reflexes</td>
<td>Medial longitudinal fasciculus</td>
</tr>
</tbody>
</table>

The cerebellum can be divided into three functional regions, from medial to lateral, based on their input and output connections (see Figure 15.3A, Table 15.1):

1. The **vermis** and **floculonodular lobes** are important in control of proximal and trunk muscles, and in vestibulo-ocular control, respectively.
2. The **intermediate part** of the cerebellar hemisphere is mainly involved in control of more distal appendicular muscles in the arms and legs.
3. The largest part of the cerebellum is the **lateral part** of the cerebellar hemisphere, which is involved in planning the motor program for the extremities. Interestingly, a large portion of the lateral cerebellar hemisphere can be removed **unilaterally** without severe deficits.

The deep cerebellar nuclei and vestibular nuclei also fit with this medial to lateral functional organization (Figure 15.4). All inputs to the cerebellum are relayed by these nuclei (Figure 15.5). In addition, these nuclei receive colateral fibers from cerebellar inputs on their way to the cerebellar cortex. The

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On midsagittal section (see Figure 15.1), the beautiful branching pattern of the central cerebellar white matter and cortical gray matter can be appreciated, to which the term “arbor vitae,” meaning “tree of life,” has been applied. Instead of gyri, the small ridges that run from medially to lateral on the surface of the cerebellum are called folia, meaning “leaves” (see Figures 15.1, 15.3A).

Removing the cerebellum from the brainstem (Figure 15.3B,C) reveals the three cerebellar peduncles (superior, middle, and inferior), which form the walls of the fourth ventricle. The superior cerebellar peduncle carries mainly inputs from the cerebellum, while the middle cerebellar peduncle and inferior cerebellar peduncle carry mainly outputs. The superior cerebellar peduncle decussates in the midbrain at the level of the inferior colliculus (see Figure 14.3B). Because of the striking conjunction of fibers in this decussation, another name for the superior cerebellar peduncle is the brachium conjunctivum. Because of its massive connections to the pons, an alternative name for the middle cerebellar peduncle is brachium pontis. The alternative name for the inferior cerebellar peduncle is restiform body, meaning “rope-like body.”
deep cerebellar nuclei, or roof nuclei, are from lateral to medial, the de
tate nucleus, emboliform nucleus, globus nucleus, and fastigial nucleus (see
Figure 15.4). A mnemonic is "Don't Eat Greasy Foods" (Dentate, Embo-
lliform, Globosus, Fastigial). The dentate nuclei are the largest of the
deprecated cerebellar nuclei, and it receives projections from the lateral cerebellar
hospers. The emboliform and globosus nuclei are together called the in-
terposed nuclei, and they receive input from the intermediate part of the
cerebellar hemispheres. Interestingly, experimental recordings have shown
that the dentate nucleus to be active just before voluntary movements, while
the interposed nuclei are active during and in relation to the movement.
The fastigial nuclei receive input from the vermis, and a small input from the
occipital lobe. Most fibers leaving the interior vermis and fissures project
to the vestibular nuclei (see Figures 12.18, 15.4) which function in
ways the mitral deep cerebellar nuclei.

**Microscopic Circuitry of the Cerebellum**

The cerebellar cortex has three layers (Figure 15.6). The granule cell layer
is tightly packed with small granule cells so numerous that they rival the total
number of cerebellar nuclei in the remainder of the nervous system. The Purkinje cell
layer contains the cells bodies of large, flask-shaped Purkinje cells. The mol-
ecular layer consists of the unmyelinated granule cell axons, Purkinje cell
dendrites, and several types of interneurons.

There are primarily two kinds of synaptic inputs to the cerebellum (see
Figures 15.5, 15.7). One kind is provided by mossy fibers, which arise from
numerous regions, as will be discussed shortly in the section on cerebellar
input pathways. Mossy fibers ascend through the cerebellar white matter to
form excitatory synapses onto dendrites of the granule cells. Granule cells,
in turn, send axons into the molecular layer, which bifurcate, forming paral-
lel fibers that run parallel to the folia (see Figure 15.7). The parallel fibers
run perpendicular to the elongated fan-like dendritic trees of the Purkinje cells
During its course, each parallel fiber forms excitatory synaptic contacts with
numerous Purkinje cells. All output from the cerebellar cortex is carried
by the axons of Purkinje cells into the cerebellar white matter. The Purkinje
cells form inhibitory synapses onto the deep cerebellar nuclei and vestibular
cells, which then convey outputs from the cerebellum to other regions
through excitatory synapses (see Figure 15.5).

The other kind of synaptic input to the cerebellar cortex is carried by
climbing fibers. Climbing fibers arise exclusively from neurons in the cor-
trolateral inferior olivary nucleus (see Figure 14.5A). They wrap around
the body and proximal dendritic tree of Purkinje cells (Figure 15.7), forming
powerful excitatory synapses. A single climbing fiber will branch to supply
about 10 Purkinje cells; however, each Purkinje cell is excited by just one
climbing fiber. Climbing fiber inputs have a strong modulatory effect on the
response of Purkinje cells, causing a sustained decrease in their response to
synaptic inputs from parallel fibers.

The cerebellar cortex contains several classes of inhibitory interneurons
(see Figures 15.7, 15.8). Basket cell, stellate cells, and small cells are located in the mol-
ecular layer. These cells are excited by synaptic inputs from the granule cell
parallel fibers. They then give rise to processes that travel in a rostral-caudal
direction, perpendicular to the parallel fibers, to release GABA 
the cellular inhibition of adjacent Purkinje cells. The stellate cells terminate on Purkinje cell
dendrites, while basket cells are named for the strong inhibitory basketlike con-
nections they form on Purkinje cell bodies. GoGi cells are found in the
granule cell layer.

The Golgi cells receive excitatory inputs from granule cell parallel fibers
in the molecular layer, where they then provide feedback inhibition onto the gran-
ule cell dendrites. This inhibitory feedback tends to shorten the duration of
excitatory inputs to the granule cells (enhanced signal resolution in the time
domain). Moreover, inhibitory lateral connections from stellate and basket
fibers to adjacent Purkinje cells tend to narrow the spatial extent of excitatory inputs
to Purkinje cells (enhanced signal resolution in the spatial domain).

Complex synaptic interactions occur in the granule cell layer in a specialized
region called the cerebellar glomerulus (Figure 15.8). Cerebellar glomeruli are visible as
small clearings among the granule cells (see Figure 15.8); they contain axons and dendrites encapsulated in a glial sheath. Glomeruli contain two types of inputs (large mossy fiber aceptors and
Golgi cell axon terminals), which form synapses onto one type of postsynap-
tic granule cell dendrites).
Figure 15.7 Summary of Microscopic Circuitry of the Cerebellar Cortex. Inputs arrive via mossy and climbing fibers, and outputs leave via Purkinje cell axons. Excitatory neurons include granule cells, and inputs from mossy and climbing fibers. Inhibitory neurons include stellate, basket, Golgi, and Purkinje cells.

To summarize (see Figure 15.7), mossy fibers excite granule cells, which excite the inhibitory Purkinje cells. Climbing fibers excite Purkinje cells directly. Purkinje cells have fanlike dendritic trees, the orientation of which you can imagine by holding up your open hand in a sagittal plane behind your head. Parallel fibers would then pass through your fingers, perpendicular to your palm. The third dimension is provided by basket cells, whose axons would pass from one finger to the next, perpendicular to the parallel fibers.

A simple way to remember the excitatory and inhibitory connections of the cerebellar cortex is to recall that all axons projecting upward are excitatory (mossy fibers, climbing fibers, granule cell parallel fibers), while all axons projecting downward are inhibitory (Purkinje cells, stellate cells, basket cells, Golgi cells). The outputs of the deep cerebellar nuclei, which are not part of the cerebellar cortex, are excitatory.

Cerebellar Output Pathways

As we have discussed, cerebellar pathways are organized around the three functional regions of the cerebellum: the lateral hemispheres, intermediate hemispheres, and vermis plus flocculonodular lobe (see Table 15.1, Figure 15.3A,C). Lesions of the lateral cerebellum therefore affect mainly distal limb coordination, while medial lesions affect mainly trunk control, posture, balance, and gait. Another important principle with cerebellar lesions is that deficits in coordination occur ipsilateral to the lesion. The reason is that the pathways from cerebellum to the lateral motor systems (see Table 15.1) and then to the periphery are "double crossed" (Figure 15.9E). The first crossing occurs as cerebellar outputs exit in the decussation of the superior cerebellar peduncle, and the second crossing occurs as the corticospinal and rubrospinal tracts descend to the spinal cord. Inputs to the cerebellum also follow this organization, so each cerebellar hemisphere receives information about the ipsilateral limbs. In contrast, midline lesions in the cerebellar vermis have effects on the midline motor systems (see Table 15.1; see also Table 6.3). Lesions of the cerebellar vermis do not typically cause unilateral deficits because the midline motor systems influence the proximal trunk muscles bilaterally.

Outputs from the cerebellum are summarized in Figure 15.9 and Table 15.2. Recall that all outputs from the cerebellum are carried by Purkinje cells to the deep cerebellar nuclei or vestibular nuclei (see Figure 15.5). The lateral cerebellar hemisphere, involved in motor planning, projects to the dentate nucleus (see Figures 15.4, 15.9A). The dentate nucleus projects via mossy fibers to excitatory or inhibitory inputs on granule cells.
Figure 15.9 Cerebellar Output Pathways. (A) Outputs from the lateral cerebellar hemisphere via the dentate nucleus. (B) Output from the intermediate cerebellar hemisphere via interposed nuclei influencing lateral motor systems. Note the "double crossing" of pathways between cerebellum and spinal cord. (C) Outputs from the cerebellar vermis and flocculonodular lobes via the fastigial nucleus influencing medial motor systems. The flocculonodular lobe and inferior vermis also have direct projections to the vestibular nuclei influencing balance and vestibuloocular control.

![Diagram showing cerebellar output pathways](image)

**TABLE 15.2 Main Cerebellar Output Pathways**

<table>
<thead>
<tr>
<th>REGION</th>
<th>DEEP NUCLEI</th>
<th>CEREBELLAR PEDUNCLE</th>
<th>MAIN OUTPUT TARGETS OR EQUIVALENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lateral hemispheres</td>
<td>Dentate nucleus</td>
<td>Superior cerebellar peduncle</td>
<td>Ventrolateral nucleus of thalamus (VL), paravocellular red nucleus</td>
</tr>
<tr>
<td>Intermediate hemispheres</td>
<td>Interposed nuclei</td>
<td>Superior cerebellar peduncle</td>
<td>VL, magnocellular red nucleus</td>
</tr>
<tr>
<td>Vermis</td>
<td>Fastigial nucleus</td>
<td>Uncinate fasciculus*</td>
<td>VL, tectum</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Justaexterniform body*</td>
<td>Reticular formation, vestibular nuclei</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Justaexterniform body*</td>
<td>Medial longitudinal fasciculus (eye movement pathways)</td>
</tr>
</tbody>
</table>

*The uncinate fasciculus travels with the superior cerebellar peduncle.

*The justaexterniform body travels with the inferior cerebellar peduncle.

The superior cerebellar peduncle (see Figure 14.4B), which decussates in the midbrain (see Figure 14.3B) to reach the contralateral ventral lateral nucleus (VL) of the thalamus (see Figure 15.9A). The fibers entering this nucleus are called the **thalamic fasciculus**, of which the more anterior parts include outputs from the basal ganglia, which terminate in different regions of the VL (VL, pars oralis) from cerebellar outputs (VL, pars caudalis) (see Figures 7.7, 16.6A, 16.9A). The VL, in turn, projects to the motor cortex, premotor cortex, supplementary motor area, and parietal lobe to influence motor planning in the corticospinal systems (see Figures 6.1, 6.9A). In addition, there is some evidence that outputs from the lateral cerebellum relay in the thalamus to reach the prefrontal association cortex, possibly playing a role in cognitive function. As the output fibers of the dentate nucleus penetrate the red nucleus, the VL, in the midbrain (Figure 14.3A), some terminate in the rostral paravocellular division of the red nucleus. Recall that the red nucleus has a large rostral parvocellular division that is involved in cerebellar circuitry and a smaller caudal magnocellular division that gives rise to the rubrospinal tract. As we will discuss in the next section, the parvocellular division of the red nucleus projects to the inferior olive (see Figure 15.9A).

The **intermediate hemisphere**, involved in the control of ongoing movements of the distal extremities, projects to the emboliform and globose (interposed) nuclei (see Figures 15.4, 15.9B). Like the dentate nucleus, the interposed nuclei project via the superior cerebellar peduncle to the contralateral thalamic VL, which in turn projects to the motor, supplementary motor, and premotor cortices to influence the lateral corticospinal tract. Inputs to the VL from the dentate and interposed nuclei (and from the basal ganglia) do not overlap. The interposed nuclei also project via the superior cerebellar peduncle to the contralateral magnocellular division of the red nucleus to influence the rubrospinal tract. The intermediate hemisphere thus influences the lateral motor systems (see Figure 15.9B).

The **cerebellar vermis** and **flocculonodular lobes** influence mainly proximal trunk movements and vestibulooocular control, respectively. The vermis influences proximal and trunk muscles through connections to the medial motor pathways (anterior corticopontine, reticulospinal, vestibulospinal, and tectospinal tracts; see Tables 15.1 and 6.3). The flocculonodular lobes and inferior vermis influence extronoculomotor movements mainly through connections...
Cerebellar Input Pathways

Inputs to the cerebellum (Table 15.3) arise from widespread areas in the nervous system. These inputs reach the cerebellum from (1) virtually all areas of the cerebral cortex; (2) multiple sensory modalities, including the vestibular, visual, auditory, and somatosensory systems; (3) brainstem nuclei; and (4) the spinal cord. Inputs to the cerebellum have a rough somatotopic organization, with the ipsilateral body represented in both the anterior and posterior lobes, as shown in Figure 15.10. Recall that cerebellar inputs are carried by mossy fibers, except for those from the inferior olivary nuclei, which are carried by climbing fibers. In addition, most inputs to the cerebellar cortex give rise to collaterals that synapse in the deep nuclei (see Figure 15.5).

A major source of input consists of corticopontine fibers from the frontalis, temporal, parietal, and occipital lobes that travel in the internal capsule and cerebral peduncles (see Figure 14.3A). The primary sensory and motor cortices and part of the visual cortex give rise to the corticopontine fibers. Let's briefly review the output of the cerebellum to the motor systems that influence proximal and distal movements of the body.

### TABLE 15.3 Main Cerebellar Input Pathways

<table>
<thead>
<tr>
<th>INPUT PATHWAY</th>
<th>MAIN ORIGIN(S)</th>
<th>CELLS PROJECTING TO CEREBELLUM</th>
<th>CEREBELLAR PEDUNCLE OR EQUIVALENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postcerebellar fibers</td>
<td>Cerebellum</td>
<td>Pontine nuclei</td>
<td>Middle cerebellar peduncle</td>
</tr>
<tr>
<td>Spinocerebellar pathways</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dorsal spinocerebellar tract</td>
<td>Leg proprioceptors</td>
<td>Nucleus dorsalis of Clarke</td>
<td>Inferior cerebellar peduncle</td>
</tr>
<tr>
<td></td>
<td>Arm proprioceptors</td>
<td>External cuneate nucleus</td>
<td>Inferior cerebellar peduncle</td>
</tr>
<tr>
<td></td>
<td>Leg interneurons</td>
<td>Spinal cord neurons</td>
<td>Superior cerebellar peduncle</td>
</tr>
<tr>
<td></td>
<td>Arm interneurons</td>
<td>Spinal cord neurons</td>
<td>Superior and inferior cerbel-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>la peduncles</td>
</tr>
<tr>
<td>Climbng fibers</td>
<td>Red nucleus, cortex,</td>
<td>Inferior olivary nucleus</td>
<td>Inferior cerebellar peduncle</td>
</tr>
<tr>
<td></td>
<td>hippocampus, spinal cord</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vestibular inputs</td>
<td>Vestibular system</td>
<td>Vestibular ganglia, vestibular nuclei</td>
<td>Justiexarestiform body</td>
</tr>
</tbody>
</table>

1. Afferent information about limb movements is conveyed to the cerebellum by the dorsal spinocerebellar tract for the lower extremities, and by the spinocerebellar tract for the upper extremities and neck. These spinocerebellar pathways provide feedback information to the cerebellum of two different kinds:

1. Information about activity of spinal cord interneurons, thought to reflect the amount of activity in descending pathways, is carried by the ventral spinocerebellar tract for the lower extremities, and by the rostral spinocerebellar tract for the upper extremity.

The dorsal spinocerebellar tract ascends in the dorsolateral funiculus, near the surface of the spinal cord, just lateral to the lateral corticospinal tract (see Figure 15.11; see also Figure 7.6). Large, myelinated axons of primary sensory neurons carrying proprioceptive, touch, and pain sensation from the lower extremities and trunk enter via the dorsal rami and ascend in the gracile fasciculus. Rather than continuing in the posterior columns, some of these fibers form synapses in the nucleus dorsalis of Clarke (see Figure 15.11; see also Figure 6.6). This is a long column of cells that runs in the dorsomedial spinal cord gray matter intermediate zone, from C8 to L2 or L3. Fibers arising from the nucleus dorsalis of Clarke ascend ipsilaterally in the dorsal spinocerebellar tract (see Figure 15.11). These fibers give rise to mossy fibers that travel to the ipsilateral cerebellar cortex via the inferior cerebellar peduncle. Unlike sensory inputs in the posterior column fibers, the spinocerebellar afferents do not reach conscious perception.
The upper-extremity equivalent of this pathway is the cuneocerebellar tract. Large-diameter fibers from the upper extremities enter the cuneate (nucleus), and ascend ipsilaterally to synapse in the external (or accessory, lateral) cuneate nucleus, located in the medulla, just lateral to the cuneate nucleus (see Figure 15.11; see also Figure 14.5B). The external cuneate nucleus is the upper-extremity analog of the nucleus dorsalis of Clarke. From the external cuneate nucleus, cuneocerebellar fibers ascend in the inferior cerebellar peduncle to the ipsilateral cerebellum. Note that for both the dorsal spinocerebellar tract and the cuneocerebellar tract, unsegmented information from the extremities reaches the ipsilateral cerebellum. These pathways provide rapid feedback to the cerebellum about ongoing movements, allowing fine adjustments to be made.

The ventral spinocerebellar tract arises from neurons along the outer edge of the central gray matter called spinal border cells, and from scattered neurons in the spinal cord intermediate zone (see Figure 7A). Axons from these cells cross over in the ventral commissure of the spinal cord to ascend in the ventral spinocerebellar tract, just ventral to the dorsal spinocerebellar tract and peripheral to the anteriorolateral systems (see Figure 7A). The majority of these fibers then join the superior cerebellar peduncle and cross over a second time, to reach the cerebellum ipsilateral to the side where the pathway began (see Figure 15.11). The rostral spinocerebellar tract is the least well characterized of these pathways, but it appears to be the upper-extremity equivalent of the ventral spinocerebellar tract, and it enters the cerebellum through both the inferior and superior cerebellar peduncles. Note that like the output circuits described in the preceding section, the spinocerebellar inputs are either ipsilateral or “double crossed,” explaining why cerebellar lesions cause ipsilateral limb ataxia.

The inferior olivary nuclear complex gives rise to olivocerebellar fibers that cross the medulla to enter the contralateral cerebellum (see Figure 14.5A). These fibers form the major portion of the inferior cerebellar peduncle and terminate as climbing fibers throughout the cerebellum (see Figure 15.7). The parvocellular red nucleus projects to the inferior olive via the central tegmental tract (see Figure 15.9A; see also Figures 14.5D-14.5F). Note that the parvocellular red nucleus receives inputs from the contralateral dentate nucleus. Thus, a complete loop is formed from lateral cerebellum to dentate nucleus to contralateral parvocellular red nucleus to inferior olive via the central tegmental tract and then crossing back via the inferior cerebellar peduncle to the original cerebellar hemisphere. The inferior olivary nuclear complex also receives inputs from the cerebral cortex, from other brainstem nuclei, and from the spinal cord. The lateral reticular nucleus is located just dorsal to the inferior olive (see Figure 14.5A,B) and receives similar input connections. The lateral reticular nucleus also projects to the cerebellum via the inferior cerebellar peduncle, but it gives rise to mossy fibers instead of climbing-fiber terminals.

Primary vestibular sensory neurons in Scarpa’s vestibular ganglia (see Figure 12.15) and secondary vestibular neurons in the vestibular nuclei project to the ipsilateral inferior cerebellar vermis and flocculonodular lobe via the juxtapostform body (see Figure 12.14). Connections between the vestibular system and cerebellum are important in the control of balance and equilibrium, as well as in vestibulo-ocular reflexes. The flocculus also receives visual inputs related to retinal slip (disparity of intended and perceived target position) that are important for the control of smooth pursuit eye movements.

Noradrenergic inputs from the locus ceruleus and serotonergic inputs from the raphe nuclei project diffusely throughout the cerebellum (see Figures 14.11, 14.12). These inputs are not conveyed by mossy-fiber or climbing-fiber terminals, and they are thought to play a neuromodulatory role.

REVIEW EXERCISES

For each of the four spinocerebellar pathways in Table 15.3, list the origin of input, the location of neurons projecting to the cerebellum, and peduncle.
Vascular Supply to the Cerebellum

Blood supply to the cerebellum is provided by three branches of the vertebral and basilar arteries (see Figure 15.2):

1. The posterior inferior cerebellar artery (PICA)
2. The anterior inferior cerebellar artery (AICA)
3. The superior cerebellar artery (SCA)

The PICA usually arises from the vertebral artery, the AICA from the lower basilar, and the SCA from the top of the basilar, just below the posterior cerebral artery (see Figure 15.2; see also Figure 14.17).

As these arteries wrap around the brainstem, they supply portions of the lateral medulla and pons in addition to the cerebellum. The posterior inferior cerebellar artery supplies the lateral medulla, most of the inferior half of the cerebellum, and the inferior vermis (see Figures 15.2, 15.12, 15.13A,B). Recall from Chapter 14 that a variable portion of the lateral medulla is also supplied by branches of the vertebral artery (see Figure 14.20D). The anterior inferior cerebellar artery supplies the lateral pons, the middle cerebellar peduncle, and a strip of the ventral (anterior) cerebellum between the territories of the PICA and the SCA, including the flocculonodular lobe (see Figures 15.12, 15.13B; see also Figure 14.20C). The superior cerebellar artery supplies the upper lateral pons, the superior cerebellar peduncle, most of the superior half of the cerebellar hemisphere, including the deep cerebellar nuclei, and the superior vermis (see Figures 15.12, 15.13C,D; see also Figure 14.20B).

Infarcts are more common in the PICA and SCA territories than in the AICA territory. Patients with cerebellar infarcts typically present with vertigo, nausea and vomiting, horizontal nystagmus, limb ataxia (see KCC 15.2), unsteady gait, and headache, which can be occipital, frontal, or in the upper cervical regions. In addition, as we saw in Chapter 14 (see KCC 14.3), many of the important clinical symptoms and signs of cerebellar artery infarcts often result from infarction of the lateral medulla or pons, rather than the cerebellum itself. These include trigeminal and spinocerebellar symptoms (e.g., Horner's syndrome, and other findings. Note that infarction of the lateral medulla or pons can cause ataxia because of involvement of the cerebellar peduncles, even if the cerebellum itself is spared.

Infarcts that spare the lateral brainstem and involve mainly the cerebellum itself are more common with SCA infarcts than with PICA or AICA infarcts. Therefore, infarcts causing unilateral (ipsilateral) ataxia with little or no brainstem signs are most commonly in the SCA territory. Infarcts in the PICA and AICA more often involve the lateral brainstem in addition to the cerebellum. In contrast, infarcts of the lateral pons or medulla that spare the cerebellum can also sometimes occur, more commonly with the PICA and AICA than with the SCA. Possible mechanisms for infarcts that spare the cerebellum include anastomotic connections sparing the cerebellum, or selective occlusion of branches to the lateral brainstem with sparing of cerebellar branches.

Large cerebellar infarcts in the PICA or SCA territories can cause swelling of the cerebellum. The resulting compression of the fourth ventricle can cause hydrocephalus (see KCC 5.7). In addition, compression in the tight space of the posterior fossa (see Figure 15.1) is a life-threatening emergency because the respiratory centers and other vital brainstem structures may be compromised. Large cerebellar infarcts, therefore, often require surgical decompression of the posterior fossa, including resection of portions of the infarcted cerebellum. Herniation into cerebellar white matter can also occur following an infarct and can cause brainstem compression. Once again, this highlights the importance of carefully evaluating patients who present with vertigo (see KCC 12.6). If vertigo is caused by a large PICA infarct sparing the brainstem, the seriousness of the condition may be overlooked until a few days after onset, when cerebellar swelling and posterior fossa compression develop.

Cerebellar hemorrhage, like spontaneous intraparenchymal hemorrhage in other brain regions, can occur in the setting of chronic hypertension, arteriovenous malformation, hemorrhagic conversion of an ischemic infarct, metastases, or other causes (see KCC 5.6). Patients usually present with headache, nausea, vomiting, ataxia, and nystagmus. If the hemorrhage is large, it can cause hydrocephalus (see KCC 5.7), accompanied by seventh and eighth cranial nerve palsies and impaired consciousness, and may eventually cause brainstem compression and death. Sometimes, cerebellar hemorrhage initially presents only with gastrointestinal symptoms of nausea and vomiting, a condition that has been termed "fetal gastroenteritis." Prompt identification and treatment of cerebellar hemorrhage is, therefore, crucial. Hydrocephalus can be treated with ventriculostomy (see KCC 5.7); however, this carries some risk of upward transient reversal of the posterior fossa herniation and edema expand. For large cerebellar hemorrhages, surgical evacuation of the hematoma, and decompression of the posterior fossa are often necessary. Patients with cerebellar hemorrhage who are treated promptly usually have a good functional outcome.
In this section we will discuss the clinical manifestations and localization of cerebellar lesions. First we will review basic definitions of ataxia and some simple localizing principles. Next we will discuss common symptoms and signs of cerebellar disorders and the expected findings on neuromonitoring examination. Causes of cerebellar disorders are discussed in KCC 15.1 and 15.3. Ataxia means literally "lack of order." This term refers to the disordered contractions of agonist and antagonist muscles, and the lack of normal coordination between movements at different joints that is seen in patients with cerebellar dysfunction. As shown in Figure 15.14A, even simple movements require coordination of agonists and antagonists around multiple joints in order to follow a normal smooth path. In ataxia, the movements have an irregular, wavering course that seems to consist of continuous overshooting, overcorrecting, and then overshooting again over the intended trajectory (Figure 15.14B). Ataxic movements have abnormal timing (dysrhythmia) and abnormal trajectories through space (dysmetria). Let's review a few principles of localization with cerebellar lesions.

**Truncal Ataxia versus Appendicular Ataxia**

Lesions confined to the cerebellar vermis affect primarily the medial motor systems (see Table 15.1). Patients with such lesions therefore often have a wide-based, unsteady "drunklike" gait with no other significant abnormalities on exam. This condition is referred to as **truncal ataxia**. In severe truncal ataxia, patients may even have difficulty sitting up without support.

In contrast, lesions of the intermediate and lateral portions of the cerebellar hemisphere affect the lateral motor systems. Therefore, these patients have ataxia on movement of the extremities like that shown in Figure 15.14B, referred to as **appendicular ataxia**. Often lesions extend to involve both the vermis and the cerebellar hemispheres, and truncal and appendicular ataxia frequently coexist in the same patient. Interestingly, a unilateral lesion in the lateral portion of the cerebellar hemisphere (see Figure 15.3) may produce no appreciable deficit. More severe and lasting deficits are seen with lesions of the intermediate vermian hemispheres, vermis, deep nuclei, or cerebellar peduncles.

** Ipsilateral Localization of Ataxia**

As we saw in the anatomical review earlier in this chapter, afferent and efferent cerebellar connections involved in the lateral motor systems either are ipsilateral or cross twice between the cerebellum and spinal cord (see Figures 15.9A, 15.11). Therefore, lesions of the cerebellar hemispheres cause ataxia in the extremities **ipsilaterally** to the side of the lesion. Similarly, in lesions of the cerebellar peduncles, the ataxia is ipsilateral to the lesion. In contrast, cerebellar lesions affecting the medial motor system cause truncal ataxia, which is a bilateral disorder. Nevertheless, patients with truncal ataxia often tend to fall or sway toward the side of the lesion.

**False Localization of Ataxia**

Ataxia is often caused by lesions outside the cerebellum that involve the cerebellar input or output pathways. **Lesions of the cerebellar peduncles or pons** can produce severe ataxia, even without involvement of the cerebellar hemispheres. **Hydrocephalus**, which may damage frontopontine pathways, and lesions of the prefrontal cortex can both result in gait abnormalities that resemble cerebellar truncal ataxia, as can **disorders of the spinal cord**.

**Ataxia-hemiparesis** is a syndrome often caused by lacunar infarcts (see KCC 10.14; Table 10.3), in which patients have a combination of unilateral upper motor neuron signs and ataxia, usually affecting the same side. In ataxia-hemiparesis, the ataxia and hemiparesis are both usually contralateral to the side of the lesion. Ataxia-hemiparesis is most often caused by lesions in the corona radiata, internal capsule, or pons that involve both corticospinal and corticopontine fibers. However, it can also be seen in lesions of the frontal lobes, parietal lobes, or sensorimotor cortex, or in midbrain lesions that involve fibers of the superior cerebellar peduncle or midnucleus (see KCC 14.3).

**Sensory ataxia** occurs when the posterior column–medial hemispheric pathway is disrupted, resulting in loss of joint position sense. Patients with sensory ataxia may have ataxic–appearing overshooting movements of the limbs, and a wide-based, unsteady gait resembling that of patients with cerebellar lesions. Unlike cerebellar patients, however, these patients have impaired joint position sense on exam. In addition, sensory ataxia can be improved significantly with visual feedback, and is worse with the eyes closed or in the dark. Sensory ataxia is usually caused by lesions of the peripheral nerves or posterior columns, which if one-sided, result in ipsilateral ataxia. However, it is also occasionally seen in lesions of the thalamus, thalamic radiations, or somatosensory cortex, which cause contralateral ataxia.

**Symptoms and Signs of Cerebellar Disorders**

Cerebellar disorders affect medial motor systems, lateral motor systems, eye movements, vestibular pathways, and other circuits, resulting in characteristic symptoms as well as specific findings on neuromonitoring examination.
Symptoms of Cerebellar Disorders. Patients with cerebellar lesions often complain of nausia, vomiting, vertigo, slurred speech, unsteadiness, or uncoordinated limb movements. Headache may occur in the occipital, frontal, or upper cervical areas and is usually on the side of the lesion. Lesions causing incipient tonsillar herniation (see KCC 5.4) can cause depressed consciousness, brainstem findings, hydrocephalus, or head tilt. Head tilt is also seen in cerebellar lesions extending to the anterior medullary velum (see Figures 12.2B, 15.1), which may affect the trochlear nerves.

Other Abnormalities Can Confound the Cerebellar Exam. When examining a patient with a suspected cerebellar disorder, it is essential to first look carefully for upper or lower motor neuron signs, sensory loss, or basal ganglia dysfunction. Abnormalities in these other systems will significantly affect cerebellar testing. Upper motor neuron findings make the exam more difficult, since both corticospinal and cerebellar lesions can cause slow, clumsy movements of the extremities. In addition, if there is severe upper or lower motor neuron weakness, cerebellar testing may not be possible. Some tests require little strength may be helpful, such as repeatedly tapping the tip of the index finger to the base of the thumb and looking for accuracy (see neuroexam.com Video 65). In cerebellar disorders, the tip of the index finger tends to hit a different spot on the thumb each time. Loss of joint position sense can cause sensory ataxia. However, the loss of position sense must be severe for significant ataxia to be present, and as mentioned above, already, sensory ataxia usually improves with visual feedback. Movement disorders (see KCC 16.1) such as parkinsonism, associated with basal ganglia dysfunction can cause slowness, clumsy movements, or gait unsteadiness, which can confound the cerebellar exam. Other movement disorders such as tremor or dyskinesias also make interpretation of cerebellar testing more difficult. We will discuss the various examination findings in patients with basal ganglia disorders, and how they differ from cerebellar disorders, in Chapter 16.

Testing for Appendicular Ataxia. Numerous tests can be used to detect appendicular ataxia. These were discussed in Chapter 3 and are demonstrated through video segments on neuroexam.com. Most abnormal findings can be described as a combination of dysmetria and dysdiadokinesia. Dysmetria is abnormal undershoot or overshoot (also known as past pointing) during movements toward a target. Dysdiadokinesia is abnormal rhythm and timing of movements. The best-known tests for ataxia are the finger-nose-finger test and the heel-shin test.

In the finger-nose-finger test (see neuroexam.com Video 64), the patient touches their nose with both hands, then the examiner touches their finger to the other hand, and then the patient touches their nose. The examiner can increase the sensitivity of this test by having the target finger at the limit of the patient’s reach, and by moving the target finger to a different position each time the patient touches their nose.

In the heel-shin test (see neuroexam.com Video 60) the patient raises their heel up and down the length of their shin in as straight a line as possible. This test should be done supine so that gravity does not contribute to the downward movement. Variations include tapping the heel repeatedly on the same spot just below the knee, or doing a test similar to the finger-nose-finger test, with the patient’s foot alternating touching their knee and the examiner’s finger.

Rapid tapping of the fingers together, of the hand on the thigh (see neuroexam.com Video 63), or of the foot on a string (see neuroexam.com Video 55) are good tests for dysmetria. In addition, testing the accuracy of tapping the tip of the index finger on the thumb base (see neuroexam.com Video 65) can be useful for identifying both dysmetria and dysdiadokinesia. Abnormalities of other rapid alternating movements, such as alternately tapping one hand with the palm and dorsum of the other hand (see neuroexam.com Video 62) have been called dysdiadochokinesia or adiadochokinesia.

An exam can be tested for overshoot, or loss of check, by having the patient raise both arms suddenly from their lap or lower them suddenly to the level of the examiner’s hand (see neuroexam.com Video 66). Alternatively, the examiner can apply pressure to the patient’s outstretched arms and then suddenly release it. Cerebellar lesions can be associated with an irregular large-amplitude postural tremor that occurs when the limb muscles are activated to hold a particular position—for example, both arms held outstretched. This characteristic postural tremor seen in disorders of the cerebellum pathways has been called a rubral tremor in the past, although more recently the involvement of the red nucleus has been questioned. In addition, the appendicular ataxia during movements toward a target that was described earlier (see Figure 15.4A) is sometimes referred to as an action or intention tremor. Tremors are discussed further in Chapter 16. Cerebellar disorders are also often associated with myoclonus, a sudden rapid-long movement disorder that is discussed in Chapter 16 as well (see KCC 16.1).

Testing for Truncal Ataxia. Patients with truncal ataxia have a wide-based, unsteady gait that resembles the gait of a drunk or of a toddler learning to walk (see also KCC 6.5, Table 6.6). This resemblance is not just coincidental: Alcohol impairs cerebellar function, and cerebellar pathways are not yet fully myelinated in infancy. Truncal ataxia can be demonstrated by having the patient perform a tandem gait, in which the heel touches the toe with each step, forcing the patient to assume a narrow stance (see neuroexam.com Video 66). Patients tend to fall or to deviate during their walking toward the side of the lesion. The Romberg test (see neuroexam.com Video 67) can also be helpful in identifying truncal ataxia and may help differentiate cerebellar lesions from lesions of the vestibular or proprioceptive systems (see Chapter 3). A peculiar tremor of the trunk or head, called titubation, can occur with mild cerebellar lesions.

Eye Movement Abnormalities. Patients with cerebellar lesions may exhibit ocular dysmetria, in which saccades overshoot or undershoot their target. Slow saccades are present in some degenerative conditions of the cerebellum. In addition, during attempted smooth pursuit eye movements there may be jerky saccadic intrusions, particularly when the floculonodular lobe is involved. Nystagmus is often present, usually of the gaze paretic type, meaning that when the patient looks toward a target in the periphery, slow phases occur toward the primary position and fast phases occur back toward the target. Unlike the nystagmus in peripheral vertigo, the nystagmus in cerebellar lesions may change directions depending on the direction of gaze (see Table 12.7). Vertical nystagmus may also be present in cerebellar disorders.

In normal individuals the vestibulo-ocular reflex (see Chapter 13) is often suppressed by visual inputs. For example, when normal individuals read a newspaper while riding a train as it pulls into the station, their eyes do not jump off the page even though their inner ears detect a large deceleration. This normal suppression of the vestibulo-ocular reflex (VOR) can be impaired in cerebellar lesions, particularly if the floculonodular lobe is involved. A good way to test for such impairment is to have the patient fixate on their thumbs, held together at arms’ length, and then to ask the patient to rotate their upper body while attempting to maintain fixation on their thumbs. Normal patients exhibit no nystagmus during this test, but nystagmus occurs in patients with impaired suppression of the VOR. The
same test can be done with adults in a swivel chair, or with pediatric patients by picking them up and turning them from side to side while they fixate on the examiner’s face.

Paraneoplastic cerebellar disorders, encephalitis, and some other conditions can be associated with unusual eye movements called opsonocytosis or ocular flutter, in which the eyes show brief bursts of oscillating movements during fixation.

**Speech Abnormalities.** Speech can have an atactic quality in cerebellar disorders, with irregular fluctuations in both rate and volume. This is sometimes called scanning or explosive speech. Instead of atactic speech, cerebellar dysarthria can also cause speech to be slurred and difficult to understand. Alcohol toxicity once again provides a good example of this phenomenon.

**Other Findings.** Muscle tone may be somewhat decreased in cerebellar disease, and reflexes can have a "penciled" quality. These findings are often not emphasized in the setting of other, more dramatic abnormalities caused by cerebellar lesions. Recent evidence suggests the possibility of cognitive disturbances in patients with cerebellar lesions. This is currently under investigation.

### TABLE 15.4A Differential Diagnosis of Ataxia in Adults

<table>
<thead>
<tr>
<th>ACUTE OR RECURRENT ATAXIA</th>
<th>CHRONIC OR PROGRESSIVE ATAXIA</th>
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<tr>
<td>Toxic ingestion&lt;br&gt;• Ribavirin; anticonvulsants; other medications&lt;br&gt;• Ischemic stroke&lt;br&gt;• Hemorrhagic stroke&lt;br&gt;• Basilar migraine&lt;br&gt;• Benign paroxysmal vertigo&lt;br&gt;• Conversion disorder&lt;br&gt;• Postconcussional syndrome&lt;br&gt;• Traumatic hematoma&lt;br&gt;• Multiple sclerosis&lt;br&gt;• Infectious or postinfectious cerebellitis&lt;br&gt;• Brainstem encephalitis&lt;br&gt;• Miller Fisher Guillaumin-Barré variant&lt;br&gt;• Wernicke’s encephalopathy&lt;br&gt;• Torsoplastosis&lt;br&gt;• Brain abscess&lt;br&gt;• Brain tumor (usually chronic)&lt;br&gt;• Hereditary episodic ataxias&lt;br&gt;• Metabolic disorders&lt;br&gt;• Hartnup disease; maple syrup urine disease; pyruvate dehydrogenase deficiency&lt;br&gt;• Paraneoplastic syndrome (especially in breast or ovarian cancer)</td>
<td>Cerebellar or other mass lesions&lt;br&gt;• Lung carcinoma; breast carcinoma; melanoma; other tumors&lt;br&gt;• Multiple sclerosis&lt;br&gt;• Chronic toxic exposure&lt;br&gt;• Alcohol/nutritional deprivation; phenytoin; mercury; thallium; toluene (glue; spray paint)&lt;br&gt;• Degenerative disorders&lt;br&gt;• Olivopontocerebellar atrophy; Machado-Joseph disease (SCA-3); dentatorubro-pallidolysian atrophy (DRPLA); other spinocerebellar ataxias&lt;br&gt;• Progressive multifocal leukoencephalopathy (PML)&lt;br&gt;• Toxoencephalitis&lt;br&gt;• Creutzfeldt-Jakob disease&lt;br&gt;• Aneurysma renale&lt;br&gt;• Paraneoplastic syndrome (especially in breast or ovarian cancer)&lt;br&gt;• Wilson’s disease&lt;br&gt;• Vitamin E deficiency&lt;br&gt;• Adult forms of disorders listed in Table 15.4B</td>
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### TABLE 15.4B Differential Diagnosis of Ataxia in Infants and Children

<table>
<thead>
<tr>
<th>ACUTE OR RECURRENT ATAXIA</th>
<th>CHRONIC OR PROGRESSIVE ATAXIA</th>
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<td>Cerebellar or other mass lesions&lt;br&gt;• Lung carcinoma; breast carcinoma; melanoma; other tumors&lt;br&gt;• Multiple sclerosis&lt;br&gt;• Chronic toxic exposure&lt;br&gt;• Alcohol/nutritional deprivation; phenytoin; mercury; thallium; toluene (glue; spray paint)&lt;br&gt;• Degenerative disorders&lt;br&gt;• Olivopontocerebellar atrophy; Machado-Joseph disease (SCA-3); dentatorubro-pallidolysian atrophy (DRPLA); other spinocerebellar ataxias&lt;br&gt;• Progressive multifocal leukoencephalopathy (PML)&lt;br&gt;• Toxoencephalitis&lt;br&gt;• Creutzfeldt-Jakob disease&lt;br&gt;• Aneurysma renale&lt;br&gt;• Paraneoplastic syndrome (especially in breast or ovarian cancer)&lt;br&gt;• Wilson’s disease&lt;br&gt;• Vitamin E deficiency&lt;br&gt;• Adult forms of disorders listed in Table 15.4B</td>
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**KEY CLINICAL CONCEPT**

Ataxia can be caused by a wide variety of disorders. The differential diagnosis depends on the age of the patient and on the time course of evolution of the ataxia. In adults (Table 15.4A), the most common causes of acute ataxia are toxic ingestion and ischemic or hemorrhagic stroke. Chronic ataxia in adults is often caused by brain metastases, chronic toxic exposure (especially to alcohol), multiple sclerosis, or degenerative disorders of the cerebellum and cerebellar pathways. In the pediatric population (Table 15.4B), acute ataxia is most often caused by accidental drug ingestion, varicella-associated cerebellitis, or migraine. Chronic progressive ataxia in children can be caused by cerebellar astrocytoma, medulloblastomas, Friedrich’s ataxia, ataxia-telangiectasia, or a variety of other conditions (see Table 15.4C).

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CASE 15.1 SUDDEN ONSET OF UNILATERAL ATAXIA

MINICASE
A 70-year-old semiretired janitor with a history of hypertension went to work one morning and at 7:00 AM was noted by his co-workers to be slurred and ataxic. He was taken to the emergency room, where his exam was notable for mildly slurred speech with slowed tongue movements, dysmetria on finger-to-nose testing on the left, and dysdiadochokinesis. Upon attempting to stand, he fell to the left, even when he kept his eyes open. The remainder of the exam was unremarkable.

LOCALIZATION AND DIFFERENTIAL DIAGNOSIS
1. On the basis of the symptoms and signs shown in bold above, where is the lesion?
2. What is the most likely diagnosis, and what are some other possibilities?

Discussion
The key symptoms and signs in this case are:
- Left arm and leg ataxia
- Unsteadiness, falling to the left
- Slurred speech
- Nausea and vomiting

1. This patient had marked appendicular ataxia of the left arm and leg, as well as probable truncal ataxia, causing him to fall to the left side. One possible explanation is an ipsilateral cerebellar lesion involving the left cerebellar hemisphere, extending to the vermis. Another possibility is a lesion of one of the left cerebellar peduncles, which would cause left appendicular ataxia and truncal ataxia. Nausea and vomiting (caused by involvement of cerebellar, vestibular, and brainstem circuits) and slurred speech are also common in cerebellar lesions (see KCC 15.2). Lesions in other locations that cause ataxia are also possible (see KCC 15.2) but would most likely have other associated signs, such as hemiparesis or brainstem findings. The most likely clinical localization is left cerebellar hemisphere and vermis, or left superior, middle, or inferior cerebellar peduncle.

2. Given the patient's age, history of hypertension, and the sudden onset of symptoms, the most likely diagnosis is an infarct of the left cerebellum. The cerebellar arteries, superior cerebellar infarct would be most likely to cause pronounced ipsilateral ataxia without other brainstem findings (see KCC 15.1). Another possibility is a cerebellar hemorrhage involving mainly the left cerebellar hemisphere. Less likely possibilities include a left cerebellar abscess or one of the other diagnoses listed in Table 15.4. An acute lesion confined to a cerebellar peduncle is unlikely, although a lesion extending from the left cerebellar hemisphere to one of the left cerebellar peduncles is possible.

Clinical Course and Neuroimaging
The patient was admitted, and a brain MRI (Figure 15.15) revealed an infarct in the left superior cerebellar artery territory, involving the left superior cerebellar peduncle and the left superior cerebellar hemisphere (compare to Figures 15.12 and 15.13C-D). He was treated with intravenous heparin while an embolic workup was pursued. This workup included a transesophageal echocardiogram, 24-hour Holter monitor, transcranial Doppler studies, and MRA, none of which revealed an obvious embolic source. His ataxia gradually improved, and 1 week later he had normal speech, with minimal left ataxia, and was ambulating with assistance from a physical therapist. He was entered into a randomized trial of aspirin versus Coumadin therapy to prevent recurrent stroke in patients with stroke of unknown cause.

Related Cases. Figure 15.16A shows an MRI from a different patient, who had bilateral superior cerebellar artery infarcts. This coronal image nicely outlines the SCA territories, with sparing of the PICA territories, inferiorly. The precise SCA and PICA boundaries are variable, but it is possible that the right PICA was involved as well (compare to Figure 15.12). This patient had severe vertebrobasilar disease and ultimately died. Note that infarcts in the PICA territory were present as well (see Figure 15.16A), suggesting that these strokes were caused by disease of the basilar artery (see KCC 14.3).

Figure 15.16B shows an axial MRI image from a patient with bilateral posterior inferior cerebellar artery (PICA) infarcts. Note the sparing of the AICA territories (compare to Figure 15.13B). Recall that the posterior fossa is a small, tight compartment and that large infarcts of the cerebellum present a high risk for brainstem compression and herniation. Therefore, surgical decompression is sometimes required.

CASE 15.2 WALKING LIKE A DRUNKARD

MINICASE
A 76-year-old man with a history of cigarette smoking developed progressive difficulty walking over the course of 1 month. He noticed that when he stood up he felt "woozy," and he described his gait as feeling like he was drunk, saying "my legs go one way, and I go the other." He occasionally had episodes in which he lost his balance, with staggering and unsteadiness. He also had frequent mild headaches that occurred at any time of the day and night and seemed to be getting worse. Exam was unremarkable except for a wide-based, unsteady gait, tending to fall to the left, especially with tandem walking. Of note, there was no ataxia on finger-to-nose or heel-to-toe testing, and rapid alternating movements were normal. There was no history of alcohol intake.

LOCALIZATION AND DIFFERENTIAL DIAGNOSIS
1. On the basis of the symptoms and signs shown in bold above, where is the lesion?
2. What is the most likely diagnosis, and what are some other possibilities?

Discussion
The key symptoms and signs in this case are:
- Unsteady gait, wide-based, falling to the left, especially with tandem walking
- Headache

1. The patient had truncal ataxia, with no significant appendicular ataxia. This symptom may be caused by a lesion of the cerebellum. Other possibilities of this gait disorder include hydrocephalus or a lesion of the frontal lobes or spinal cord (see KCC 15.2; see also KCC 6.5), although additional abnormalities on exam are often (but not always) present with these disorders. The presence of headache suggests that the lesion is intracranial (see KCC 5.3).

2. The most likely clinical localization is cerebellar vermis.

2. Given the history of cigarette smoking and the gradual onset of symptoms, and the patient's history of cancer, all of which predispose to the development of cerebellar changes, the patient should be closely monitored. Other important causes of chronic ataxia in adults are listed in Table 15.4A. In addition, as already mentioned, the patient's gait abnormalities could possibly be caused by hydrocephalus or by lesions of the frontal lobe or spinal cord.
**CASE 15.1 SUDDEN ONSET OF UNILATERAL ATAXIA**

Figure 15.15  Left Superior Cerebellar Artery (SCA) Infarct  
(A) Axial, diffusion-weighted MRI at the level of the superior cerebellum and rostral pons. A bright region of decreased diffusion coefficient, consistent with infarction, is visible in the left superior cerebellar peduncle and left superior cerebellum. (B) Axial, T2-weighted MRI at the level of the mid to upper pons and cerebellum. A T2-bright region, consistent with infarction, is seen in the left superior cerebellar hemisphere.

![Image of MRI scans showing cerebellar infarct](image-url)
Clinical Course and Neuroimaging

A head CT with intravenous contrast (Figure 15.17) revealed an enhancing, cystic lesion in the cerebellum vermis. Although the patient often fell to the left on exam, the lesion did not have any obvious asymmetries. This case demonstrates that lesions of the cerebellar vermis can cause truncal ataxia manifesting primarily as a gait abnormality with little or no appendicular ataxia (see KCC 15.2).

On admission, a chest X-ray revealed a left apical 2 to 3 cm opacity, and prominence of the left pulmonary hilum. A CT-guided needle biopsy of the lung lesion showed adenocarcinoma. An MRI of the brain again demonstrated the vermi lesion, but it also showed a small area of enhancement in the left parietal lobe. The patient initially refused surgery and was treated with radiation therapy and steroids as an outpatient. As a result, the left parietal lesion disappeared, the vermi lesion decreased in size, and the patient’s gait improved. Four months later, however, he was readmitted with recurrent gait difficulty, and imaging showed that the vermi lesion had increased in size. He consented to surgery to decompress the posterior fossa, and the vermi lesion was resected, with pathology showing adenocarcinoma. Postoperatively, he had some dysmetria, which gradually improved. Unfortunately, metastatic carcinoma is not curable, and although further follow-up information is not available, it is presumably eventually died of his illness.

CASE 15.3 A BOY WITH HEADACHES, NAUSEA, SLURRED SPEECH, AND ATAXIA

CHIEF COMPLAINT

A 13-year-old boy was brought to the pediatrician’s office because of 2 months of progressive left occipital headaches, nausea, slurred speech, and unsteadiness.

HISTORY

The patient was well until 2 months previously, when he began having headaches, which were initially attributed to sinus infection. The headaches gradually worsened, with headache mainly in the left occipital area, and sometimes accompanied by nausea and vomiting, but no visual changes. The headaches were worse at night and in the early morning hours. His teachers noticed that over the past few months he had had some difficulty concentrating and learning new material at school. During the week prior to presentation his mother noted increasingly gait instability and mildly slurred speech and decided to bring him to the pediatrician.

PHYSICAL EXAMINATION

Vital signs: T = 98°F, P = 90, BP = 130/88, R = 16.

Neck: Supple.

Lungs: Clear.

Heart: Regular rate with no murmurs.

Abdomen: Soft, nontender.

Extremities: Normal.

Neurologic exam:

MENTAL STATUS: Alert and oriented x3. Speech fluent, with normal repetition and comprehension.

OCULAR MOVEMENTS: Pupils equal round and reactive to light. Visual fields full. Fundus had blurred disc margins (mild papilledema) bilaterally. Exotropia was noted, although no full-suppression was seen. Vertical nystagmus on gaze to left. Upgaze was normal, but there was horizontal nystagmus on lateral gaze bilaterally, and vertical nystagmus on upgaze worse than downgaze. In addition, the vestibulo-ocular reflex was normal, but the vertical nystagmus on upgaze was not fully suppressed in fixation. Facial sensation and corneal reflexes intact. Face symmetrical. Hearing intact to whisper bilaterally.


MOTOR: No drift. Normal tone. 5/5 power throughout.

REFLEXES:

CASE 15.3 (CONTINUED)

COGNITION: Marked dysmetria on finger-to-nose testing, worse on the left, with approximately 2 inches of error. There was also dysdiadochokinesia, with an inability to alternate movements, worse on the left side. Heel-to-shin movements were ataxic on the left, but normal on the right. Gait: Wide-based, with feet approximately 2 feet apart, and unsteady, staggering to the left. Unable to perform tandem gait. On Romberg test with feet 4 inches apart there was no worsening of unsteadiness (unable to stand with feet together even with eyes open).

SENSATIONS: Intact light touch, pinprick, vibration, and joint position sense. Intact graphesthesia and stereognosis.

LOCALIZATION AND DIFFERENTIAL DIAGNOSIS

1. On the basis of the symptoms and signs shown in bold above, where is the lesion?
2. What is the most likely diagnosis, and what are some other possibilities?

Discussion

1. The key symptoms and signs in this case are:

   - Left greater than right arm and leg ataxia
   - Unsteady gait, wide-based, staggering to the left
   - Slurred speech, with an irregular rate
   - Bilateral horizontal nystagmus on lateral gaze, and vertical nystagmus on upgaze worse than downgaze
   - Vestibulo-ocular reflex not fully suppressed by visual fixation
   - Left occipital headache
   - Nausea and vomiting
   - Difficulty concentrating
   - Bilateral papilledema

   This patient had multiple symptoms and signs suggesting diffuse cerebellar dysfunction. The left-sided appendicular ataxia is consistent with a lesion in the left cerebellar hemisphere, while the truncal ataxia suggests involvement of the vermi. The patient also had ataxic speech and typical eye movement abnormalities seen in cerebellar lesions, including impeded suppression of the vestibulo-ocular reflex (see KCC 15.2). The left occipital headache, nausea, and vomiting also fit with a left cerebellar lesion. However, when seen together with papilledema and difficulty concentrating, these symptoms strongly suggest elevated intracranial pressure (see KCC 5.3). Elevated intracranial pressure in cerebellar lesions is commonly due to compression of the fourth ventricle causing hydrocephalus (see KCC 5.7).

   The most likely clinical diagnosis is a large left cerebellar lesion with associated meningeal irritation.

2. The slowly progressive course in this child suggests a tumor of the posterior fossa, such as cerebellar astrocytoma or medulloblastoma (see KCC 5.8).

   Given this patient's age, an astrocytoma would be somewhat more likely since medulloblastoma occurs in the first decade about 90% of the time, while it is not uncommon for cerebellar astrocytoma to occur after age 10. Other less likely possibilities are listed in Table 15.1B.

Clinical Course and Neuroimaging

A brain MRI (Figure 15.18) showed an enhancing mass in the cerebellum with a large, fluid-filled cyst occupying almost the entire left cerebellum. A cyst with a mural nodule of this kind is typical of cerebellar astrocytoma (see KCC 5.6). The fourth ventricle was compressed (see Figure 15.18A), and hydrocephalus was present, with dilution of the lateral and third ventricles (see KCC 5.6).
Figure 15.18B. The patient was admitted to the hospital and started on steroids to reduce swelling. Surgery was performed 2 days after admission. A midline incision was made over the occipital bone. A bone flap was temporarily removed to gain access to the posterior fossa, and the dura over the cerebellum opened, revealing tumor and cyst in the vermis extending into the left cerebellum more than the right. All visible tumor was carefully removed, and the cyst was drained. Pathology was consistent with juvenile pilocytic astrocytoma. This is a histologically benign lesion that, unlike medulloblastoma (see Case 5.7), can often be cured by resection alone (see KCC5.8). The patient did very well postoperatively, but he did have some residual left greater than right ataxia.

CASE 15.4 NAUSEA, PROGRESSIVE UNILATERAL ATAXIA, AND RIGHT FACE NUMBNESS

MINICASE
A 72-year-old right-handed woman came to see an internist because of several months of worsening nausea and vomiting. Gastroenterology evaluation had revealed a hiatal hernia, and she was being treated with antacids with little benefit. On discussion of her overall symptoms, it became clear that about 2 months previously she noticed her handwriting was deteriorating, becoming less precise. Later, she noted some difficulty opening bottles with her right hand, as if she "didn't have good control," and difficulty putting on her earrings. She also was slightly unsteady, slipping more frequently than usual on the ice. Most recently, she had noticed that the right side of her face felt cool. She had lost 3 pounds over the past 2 months and had one episode of hemoptysis (blood-tinged sputum). She did not complain of headaches. On examination, she had nystagmus on horizontal and vertical end gaze, as well as decreased temperature sensation in the right face. She also had mild left facial weakness and heeltos-nose and heel-toshink testing on the right. On attempted tandem gait she fell to the right. The remainder of the exam was normal.

LOCALIZATION AND DIFFERENTIAL DIAGNOSIS
1. On the basis of the symptoms and signs shown in bold above, what is the lesion?
2. Given the history of smoking and recent hemoptysis, is what the most likely diagnosis?

Discussion
The key symptoms and signs in this case are:
- Nausea and vomiting
- Right arm and leg ataxia
- Mild unsteadiness, and inability to perform tandem gait, falling to the right
- Nystagmus on horizontal and vertical end gaze
- Right face cool paresthesias and decreased temperature sensation

1. This patient has appendicular ataxia affecting the right arm and leg, as well as truncal ataxia with an unsteady tandem gait, falling to the right. These findings strongly suggest a right cerebellar lesion (see KCC15.2). Nystagmus is also common in cerebellar disorders. Loss of temperature sensation in the right face suggests a lesion affecting the right spinocerebellar tracts (see Figure 12.6; Table 12.6). The right middle and inferior cerebellar peduncles also pass by this region (see Figure 14.4C, 14.5A), which could explain the right-sided ataxia. Nausea and vomiting can have many causes, both neurologic and systemic. Lesions involving the cerebellum and its connections to the vestibular system, the vestibular system itself, or the chemo- tactic trigger zone (see Chapter 14) are particularly likely to cause nausea. Elevated intracranial pressure can also cause nausea and vomiting (see KCC5.3), although there is no evidence of elevated intracranial pressure on the basis of history or physical examination in this patient.

CASE 15.2 WALKING LIKE A DRUNKARD

Figure 15.17 Lung Metastasis in the Cerebellar Vermis: Axial head CT scan with intravenous contrast. An enhancing, cystic, lung carcinoma metastasis is visible in the midline cerebellar vermis.

Enhancement in the basilar artery
Temperature lobe
Petros temporal bone
Metastatic air cells
Fourth ventricle
Enhancing cerebellar mass
Cerebellar hemispheres

The most likely clinical localization is right middle cerebellar or inferior peduncle and right spinocerebellar tract. Other less likely possibilities in this patient include primary neoplasm, infection, or vascular malformation.

Clinical Course and Neuroimaging
The internist ordered a brain MRI scan with gadolinium (Figure 15.19). An enhancing lesion was found in the right middle cerebellar peduncle. This case illustrates that ataxia is often caused by lesions outside the cerebellum proper, in the cerebellar peduncles, brainstem, or other locations in the cerebellar circuitry (see also the next section). This patient’s clinical findings resemble, in some ways, that of the patient we discussed in Chapter 14 with a lateral pontine infarct in the AICA territory (see Case 14.4).

A second very small (5 mm) lesion was found on the lateral surface of the right cerebellum (not shown). On chest X-ray, a right peribronchial lesion was seen. A CT-guided needle biopsy of the peribronchial lesion revealed adenocarcinoma of the lung. Abdominal CT demonstrated another lesion in the adrenal area extending into the cervix. Cervical biopsy confirmed metastatic lung adenocarcinoma in this location as well. Because of the presence of multiple brain metastases, and the location of the major lesion extending into the brainstem (see Figure 15.19), resective neurosurgery was not per-
Case 15.3 A Boy with Headaches, Nausea, Slurred Speech, and Ataxia

Figure 15.18 Cerebellar Astrocytoma in the Vermis and Left Cerebellar Hemisphere. Axial T1-weighted MRI images with intravenous gadolinium contrast enhancement, with images A, B progressing from inferior to superior. (A) Cystic lesion in the vermis and left cerebellar hemisphere, with enhancing mural nodule, compatible with cerebellar astrocytoma. Fourth ventricle is compressed. (B) Dilation of lateral and third ventricles with effacement of cortical sulci due to noncommunicating hydrocephalus.

Case 15.4 Nausea, Progressive Unilateral Ataxia, and Right Face Numbness

Figure 15.19 Metastasis of Lung Adenocarcinoma to the Right Middle Cerebellar Peduncle. Axial T1-weighted MRI images with intravenous gadolinium contrast. (A) Axial image demonstrating an enhancing lung adenocarcinoma metastasis in the right middle cerebellar peduncle. (B) Coronal view of the same region.
formed. The patient was treated with radiation therapy to the brain and chest and with steroids. She initially worsened with the radiation therapy, but then improved for a while before ultimately requiring admission to a specialized hospice facility for patients with terminal cancer.

**Additional Cases**

Related cases can be found in other chapters for the following topics: brainstem lesions associated with ataxia (Cases 14.4, 14.7, 14.9); ataxia in childhood (Case 5.7); and ataxic-appearing gait (Cases 5.9, 7.6). Other relevant cases can be found using the Case Index.

**Brief Anatomical Study Guide**

1. The cerebellum is located in the posterior fossa (see Figure 15.1). It consists of the midline vermis, the intermediate part of the cerebellar hemisphere and the lateral part of the cerebellar hemisphere (see Figure 15.3A). The cerebellum is attached to the brainstem by the superior, middle, and inferior cerebellar peduncles, which contain the input and output fibers of the cerebellum (see Figure 15.3B, C).

2. All outputs of the cerebellum are carried by the deep cerebellar nuclei and the vestibular nuclei (see Figures 15.4, 15.5). The cerebellar cortex and deep nuclei can be divided into three functional zones (see Table 15.1):
   A. The vermis (via fastigial nuclei) and flocculonodular lobes (via vestibular nuclei) are important in the control of proximal and trunk muscles and in vestibulo-ocular control, respectively.
   B. The intermediate part of the cerebellar hemisphere (via interposed nuclei) is involved in the control of more distal appendicular muscles mainly in the arms and legs.
   C. The largest part of the cerebellum is the lateral part of the cerebellar hemisphere (via dentate nuclei), which is involved in planning the motor program for the extremities.

3. The microscopic circuitry of the cerebellum involves excitatory inputs carried by mossy fibers and climbing fibers. These inputs synapse directly or indirectly onto Purkinje cells, which carry the outputs to the deep cerebellar and vestibular nuclei (see Figures 15.2, 15.3E). Important local cerebellar neurons include granule cells and the inhibitory Golgi, basket, and stellate cells.

4. Cerebellar input and output pathways are fairly complex; they are summarized in Figures 15.9, 15.10, and 15.11, and in Tables 15.2 and 15.3. The most clinically important points are that these pathways again follow a medial-lateral organization and that all pathways to the lateral motor systems are either ipsilateral or double crossed so that cerebellar lesions cause ipsilateral deficits.

5. Ataxia is a characteristic irregular movement abnormality seen in cerebellar disorders (see Figure 15.4). On the basis of the anatomical organization of cerebellar pathways, the following principles of localizing cerebellar lesions emerge:
   A. Ataxia is ipsilateral to the side of the cerebellar lesion.
   B. Midline lesions of the cerebellar vermis or flocculonodular lobes cause mainly unsteady gait (truncal ataxia) and eye movement abnormalities.

**References**

**General**


**Cerebellar Vascular Disorders**


**Other Cerebellar Disorders**


CHAPTER 16

Basal Ganglia

A 35-year-old man and his wife came to see a psychiatrist because of marital problems. The wife reported that during recent months her husband had become increasingly argumentative and had also developed occasional irregular jerking movements of the head, trunk, and limbs. The husband denied having any involuntary movements. His father and several other paternal relatives had developed a similar syndrome, caused by a devastating neurodegenerative disease that destroys the basal ganglia. In this chapter, we will learn about the anatomy, circuitry, and functional neurochemistry of the basal ganglia and will see cases in which damage to the basal ganglia produces movement disorders and other deficits, including behavioral and cognitive abnormalities.
ANATOMICAL AND CLINICAL REVIEW

Like the cerebellum, the basal ganglia participate in complex networks that influence the descending motor systems (see Figures 2.17, 6.6). Also like the cerebellum, the basal ganglia do not themselves project directly to the periphery. However, the movement abnormalities seen with basal ganglia disorders differ markedly from those seen with cerebellar lesions. Patients with basal ganglia lesions have either hyperkinetic or hypokinetic movement disorders. Hyperkinetic movement disorders are typified by Huntington’s disease, in which uncontrolled involuntary movements produce a random pattern of jerks and twists. Hypokinetic movement disorders are typified by Parkinson’s disease, which is characterized by rigidity, slowness, and marked difficulty initiating movements. Often there will be a mixture of these two kinds of movement disorders in any given patient.

In the sections that follow we will review the basic three-dimensional anatomy of the basal ganglia and then discuss their network connections in an attempt to understand the mechanisms underlying hyperkinetic and hypokinetic movement disorders. We will also discuss some of the other functions of the basal ganglia including emotional control, cognition, and eye movements.

Basic Three-Dimensional Anatomy of the Basal Ganglia

The basal ganglia are a collection of gray matter nuclei located deep within the white matter of the cerebral hemispheres. The main components of the basal ganglia are the caudate nucleus, putamen, globus pallidus, subthalamic nucleus, and substantia nigra (Table 16.1, Figure 16.1; see also Figure 16.4). Other nuclei, such as the nucleus accumbens and ventral pallidum, which participate in limbic and basal ganglia circuits, are usually included as well. Some authors also include the amygdala; however, this nucleus functions primarily as part of the limbic system (see Chapter 18).

The caudate and putamen are histologically and embryologically closely related and can be thought of as a single large nucleus called the neostriatum or simply striatum. The striatum receives all inputs to the basal ganglia. The caudate and putamen are separated by penetrating fibers of the internal capsule but remain joined in some places by cellular bridges (see Figure 16.1A). The cellular bridges appear as stripes, or striations, connecting the caudate and putamen in histological sections, giving rise to the name “striatum.” The caudate nucleus is one of the C-shaped structures that we discussed in Chapter 5: like the corpus callosum and the fornix, it has a centreline relationship with the lateral ventricle, as we will discuss shortly. The caudate (meaning “possessing a tail”), is divided into three parts, the head, body, and tail, which do not have distinct boundaries from each other (see Figure 16.1A). The amygdala lies just anterior to the tip of the caudate tail, in the temporal lobe.

The putamen is a large nucleus forming the lateral portion of the basal ganglia (see Figure 16.1). Anteriorly and ventrally the putamen fuses with the head of the caudate. This region, called the ventral striatum, is important in limbic circuitry and is often considered part of the striatum because of its similar embryological development and input and output connections. Most of the ventral striatum consists of the nucleus accumbens.

Just medial to the putamen lies the globus pallidus (or pallidum), meaning “pale globe,” so named because of the many myelinated fibers traversing this region. The globus pallidus has an internal segment and an external segment (see Figure 16.1B). The putamen and globus pallidus together are called the lenticular, or lentiform, nucleus, meaning “lentil or lens shaped.” In fact, as we will see in the sections that follow, these nuclei more closely resemble an ice cream cone lying on its side, with the putamen representing the ice cream and the globus pallidus the cone.

To better appreciate the three-dimensional nature of the basal ganglia and related structures, let’s review these structures through artistic renderings (Figure 16.2) and stained brain sections (Figures 16.3, 16.4). Moving from lateral to medial in the horizontal brain sections shown in Figure 16.3, we can identify the following structures in sequence:

- Insula
- Extreme capsule
- Caudatus
- External capsule
- Putamen
- External medullary lamina
- External segment of the globus pallidus
- Internal medullary lamina
- Internal segment of the globus pallidus
- Internal capsule

As we discussed in Chapter 6, the internal capsule is a V-shaped collection of fibers going to and from the cortex (see Figure 16.3). The anterior limb of the internal capsule passes between the lentiform nucleus and the head of the caudate. The posterior limb of the internal capsule passes between the lentiform nucleus and the thalamus. Recall that the corticobulbar and corticospinal tracts lie in the posterior limb of the internal capsule (see Table 16.1).

*The exact functions of the claustrum remain unknown, although it may play a role in visual attention.*
Figure 16.2 Basal Ganglia and Thalamus in Relation to the Internal Capsule and Lateral Ventricle

(A) View from the lateral aspect, showing relation of internal capsule to basal ganglia and thalamus (see also Figure 16.3). The anterior limb of the internal capsule passes between the lentiform nucleus (putamen and globus pallidus) and the caudate, while the posterior limb of the internal capsule passes between the lentiform nucleus and the thalamus. (B) View after removal of the putamen, revealing the globus pallidus more medially. (C) View after removal of the globus pallidus, showing the entire internal capsule. (D) View after removal of the internal capsule, showing relations of the caudate to the lateral ventricle and of the thalamus to both the lateral ventricle and the third ventricle.
Figure 6.9. Note that the caudate and thalamus are always medial to the internal capsule, while the lentiform nucleus (putamen and globe pallidus) is always lateral to the internal capsule.

These relationships are again reviewed in Figure 16.2, which shows a left lateral view of these structures. In Figure 16.2A the putamen is visible most laterally, concealing the globus pallidus. The caudate and thalamus lie behind the internal capsule. In Figure 16.2B, the putamen has been removed to reveal the globus pallidus. The external and internal segments of the globus pallidus have been removed in Figure 16.2C to fully expose the internal capsule. Finally, in Figure 16.2D, the internal capsule has been removed to reveal the caudate and thalamus. Note the relationship between these structures and the ventricular system. The head and body of the caudate form a bulge on the lateral wall of the lateral ventricle, while the tail of the caudate runs along the roof of the temporal horn (see Figures 16.2D, 16.3, 16.4). The thalamus forms the lateral walls of the third ventricle (see Figures 16.2D, 16.3, 16.4D) and lies along the floor of the body of the lateral ventricle.

Coronal sections (see Figure 16.4) provide additional perspective. In Figure 16.4A (the most anterior section), the head of the caudate, the putamen, and the nucleus accumbens can be seen. The internal capsule seen at this level is part of the anterior limb, since it is separating caudate from lentiform nucleus, with no thalamus visible. Note that this section includes the putamen but not the globus pallidus. We can understand this if we imagine that the lentiform nucleus is an ice cream cone lying on its side with the cone pointing medially. The most anterior coronal sections would thus cut through ice cream (putamen) without cone (globus pallidus).

The globus pallidus first appears in the next coronal section (see Figure 16.4B) moving toward the back. The external segment of the globus pallidus can be seen at this level. The head of the caudate nucleus is visible as a bulge along the lateral wall of the lateral ventricle. Moving posteriorly, in the next section (see Figure 16.4C) the internal segment of the globus pallidus (tip of the ice cream cone) can be seen, along with all of the structures listed above that were identified in Figure 16.3. The head of the caudate can still be seen bulging into the lateral ventricle. Since the thalamus is not yet visible, we are still in the anterior limb of the internal capsule.

In the most posterior section (see Figure 16.4D) we have begun to lose the globus pallidus again, and in more posterior sections (not shown), only the putamen (ice cream) is visible.

In Figure 16.4D the thalamus can be seen, meaning that we are at the level of the posterior limb of the internal capsule, separating thalamus from lentiform nucleus. Both the body and the tail of the caudate can be seen in this section, adjacent to the body and temporal horn of the lateral ventricle, respectively. In addition, by following the internal capsule downward, we see the beginnings of the cerebral peduncles of the midbrain. The substantia nigra is visible, just dorsal to the cerebral peduncles (see also Figure 14.3A,B). The substantia nigra has a ventral portion called the substantia nigra pars reticulata, which contains cells very similar to those of the internal segment of the globus pallidus. The internal segment of the globus pallidus and the substantia nigra pars reticulata are separated from each other by the internal capsule, much in the same way as it separates the caudate and putamen.

The median portion of the substantia nigra pars compacta contains the darkly pigmented dopaminergic neurons that give this nucleus its name. Degeneration of these dopaminergic neurons is an important pathogenetic mechanism in Parkinson’s disease. Under the thalamus lies the spindle- or cigar-shaped subthalamic nucleus (see Figure 16.4D). Unlike the thalamus, the subthalamic nucleus is derived embryologically from the midbrain rather than the forebrain. As discussed...
Figure 16.4 Coronal Brain Sections through Basal Ganglia and Thalamus. Myelin is stained dark. The spatial relationships between the basal ganglia, thalamus, internal capsule, ventricles, and other structures can be seen. (A-D) progressing from anterior to posterior. (From Martin J. L. 1996. Neuroanatomy: Text and Atlas. 2nd Ed. McGraw-Hill, New York.)
in Chapter 10, the blood supply to the striatum and globus pallidus is mainly from the lentiformic branches of the middle cerebral artery, although the medial globus pallidus is often supplied by the anterior choroidal artery (branch of internal carotid artery), and the caudate head and anterior portions of the lentiform nucleus are often supplied by the recurrent artery of Heubner (branch of anterior cerebral artery) (see Figures 10.7-10.9).

At this point you may find it worthwhile to review the basic anatomy of the basal ganglia one more time, as depicted in Figures 16.1-16.3, before proceeding to the network connections of these structures.

**Input, Output, and Intrinsic Connections of the Basal Ganglia**

Virtually all inputs to the basal ganglia arrive via the striatum (caudate, putamen, and nucleus accumbens). Outputs leave the basal ganglia via the internal segment of the globus pallidus and the closely related substantia nigra pars reticulata. Inputs and outputs through the basal ganglia are thus easily visualized as a funnel, with the spout pointing medially (see Figure 16.4D). Within the basal ganglia there are a variety of complex excitatory and inhibitory connections utilizing several different neurotransmitters. In addition, there appear to be several parallel pathways in the basal ganglia for different functions, including:

- General motor control
- Eye movements
- Cognitive functions
- Emotional functions

In this section we will review the main pathways involved in motor control and discuss a model to explain hyperkinetic and hypokinetic movement disorders. In the next section (see also Table 16.2) we will briefly discuss some of the circuits involved in other basal ganglia functions.

**Inputs to the Basal Ganglia**

The main input to the basal ganglia comes from massive projections from the entire cerebral cortex to the striatum (Figure 16.5). The putamen is the most important input nucleus of the striatum for motor control pathways. Most cortical inputs to the striatum are excitatory and use glutamate as the neurotransmitter. Another important input to the striatum is the substantia nigra pars compacta. This dopaminergic nigrostriatal pathway is excitatory to some cells and inhibitory to others in the striatum (see Figures 16.5, 16.7). Inputs to the pars compacta are still under investigation. However, one important source of input may arise from a subpopulation of striatal neurons located in patches called striosomes. The striatum also receives excitatory (glutamatergic) inputs from extranigral nuclei lying within the internal medullary lamina of the thalamus, especially the centromedian and parafascicular nuclei. The internal medullary lamina of the thalamus should be distinguished from the internal medullary lamina of the globus pallidus (see Figure 16.5). Finally, there are serotoninergic inputs to the basal ganglia that arise from the raphe nuclei of the brainstem.

**Outputs from the Basal Ganglia**

Basal ganglia outputs arise from the internal segment of the globus pallidus and from the substantia nigra pars reticulata (Figure 16.6). For motor control, the substantia nigra pars reticulata appears to convey information for the head and neck, while the internal segment of the globus pallidus conveys information for the rest of the body. These output pathways are inhibitory and use the neurotransmitter gamma-aminobutyric acid (GABA). The main output pathways are to the ventral lateral (VL) and ventral anterior (VA) nuclei of the thalamus via the thalamic fasciculus. The more anterior parts of the thalamic fasciculus carry outputs from the basal ganglia to the anterior portion of VL, while the more posterior parts of the thalamic fasciculus carry cerebellar outputs to the posterior VL (mnemonic: CAudate part of VL receives inputs from Cerebellum) (see Chapter 15). Thalamic neurons convey information from the basal ganglia to the entire frontal lobe. However, information for motor control travels mainly to the prefrontal cortex, supplementary motor area, and primary motor cortex (see Figure 16.8).

Basal ganglia outputs also travel to other thalamic nuclei. These include intralaminar nuclei (centromedian and parafascicular), which project back to the striatum, and the mediodorsal nucleus, which is involved primarily in limbic pathways. In addition, the internal segment of the globus pallidus and the substantia nigra pars reticulata project to the pontomedullary reticular formation, thereby influencing the descending reticulospinal tract. The substantia nigra pars reticulata also projects to the superior colliculus, to influence tectobulbar pathways. In this way the basal ganglia influence both the lateral motor systems (e.g., the lateral corticospinal tract) and the medial motor systems (e.g., the reticulospinal and tectospinal tracts) (see Table 16.3).

**Intrinsic Basal Ganglia Connections**

An understanding of the excitatory and inhibitory connections in these pathways provides some insight into the mechanisms of hyperkinetic and hypokinetic movement disorders. There are two predominant pathways from input to output nuclei through the basal ganglia. One is the direct pathway, which includes the striatum, the substantia nigra pars compacta, and the ventral striatum. The other is the indirect pathway, which involves the substantia nigra pars reticulata, the globus pallidus, and the thalamus. The direct pathway is excitatory, while the indirect pathway is inhibitory. The balance between these two pathways determines whether movement is facilitated or inhibited, leading to the hyperkinetic or hypokinetic movement disorders.
basal ganglia (Figure 16.7). The direct pathway travels from the striatum directly to the internal segment of the globus pallidus or the substantia nigra pars reticulata. The indirect pathway takes a detour from the striatum, first to the external segment of the globus pallidus and then to the subthalamic nucleus, before finally reaching the internal segment of the globus pallidus or the substantia nigra pars reticulata. For simplicity, only the pathways through the putamen and internal segment of the globus pallidus are shown in Figure 16.7, although similar pathways also involve the caudate and the substantia nigra pars reticulata.

Figure 16.7B shows that the net effect of excitatory input from the cortex through the direct pathway will be excitation of the thalamus, which in turn will facilitate movements through its connections with the motor and premotor cortex. On the other hand, the net effect of excitation of the indirect pathway will be inhibition of the thalamus, resulting in inhibition of movements through connections back to the cortex (mesencephalic Indirect Inhibition).

Hyperkinetic and Hypokinetic Movement Disorders

Several aspects of hyperkinetic and hypokinetic movement disorders can be understood from the scheme in Figure 16.7. In Parkinson’s disease (see KCC 16.2), dopamine-containing neurons in the substantia nigra pars compacta degenerate. Dopamine appears to have excitatory effects on striatal neurons of the direct pathway, but inhibitory effects on striatal neurons of the indirect pathway (Figure 16.7), which normally has a net excitatory effect on the thalamus. Therefore, the loss of dopamine will result in net inhibition of the thalamus, through both the direct and the indirect pathways, which may account for the paucity of movement seen in Parkinson’s disease. Drugs that bolster dopaminergic transmission can improve the symptoms of Parkinson’s disease.

In addition, anticholinergic drugs can be beneficial. There are large interneurons in the stratum called aspin neurons, some of which contain the neurotransmitter acetylcholine. Some evidence suggests that these cholinergic interneurons preferentially form excitatory synapses onto striatal neurons of the indirect pathway. Removal of cholinergic excitation of the indirect pathway produces a net decrease in inhibition of the thalamus, which may account for the beneficial effects of anticholinergic agents in parkinsonism (see Figure 16.7). Note that this model does not account for the tremor commonly seen in Parkinson’s disease, and the model therefore continues to evolve.

In hemiballismus (KCC 16.1) there are unilateral wild flinging movements of the extremities contralaterally to a lesion in the basal ganglia, typically involving the subthalamic nucleus. Figure 16.7 shows how damage to the subthalamic nucleus could decrease excitation of the internal segment of the globus pallidus, resulting in loss of inhibition of the thalamus, causing a hyperkinetic movement disorder. In Huntington’s disease, striatal neurons in the caudate and putamen degenerate. There is some evidence that, at least initially, the enkephalin-containing striatal neurons of the indirect pathway are more severely affected. This would cause removal of inhibition from the external segment of the globus pallidus, allowing it to inhibit the subthalamic nucleus (see Figure 16.7). Inhibition of the subthalamic nucleus produces an action similar to a lesion of the subthalamic nucleus, and may account for the hyperkinetic movement disorder seen in Huntington’s disease. In more advanced stages of Huntington’s disease, both the direct and the indirect pathways degenerate, and a rigid hypokinetic parkinsonian state results.
Parallel Basal Ganglia Pathways for Movement, Eye Movement, Cognition, and Emotion

The basal ganglia contain multiple parallel channels of information processing for different functions. Four channels have been well described (Table 16.2), although others probably exist as well. Each channel passes through slightly different pathways and projects to different regions of the frontal lobes (Figure 16.8). In another classification scheme, the first three channels are lumped together as dorsal striatal pathways, while the limbic channel is distinguished because it involves ventral striatal pathways. We will see in KCC 16.1–16.3, that basal ganglia disorders can affect all four of these parallel channels, not just the motor system.

The motor channel is the best known and forms the basis for most of the discussion in the previous section. Cortical inputs travel mainly to the putamen, and outputs arise from the internal segment of the globus pallidus and the substantia nigra pars reticulata to reach the VI and VA of the thalamus (see Table 16.2). From the thalamus the motor channel continues to the supplementary motor area, premotor cortex, and primary motor cortex (see Figure 16.8).

A separate oculomotor channel subserves basal ganglia regulation of eye movements. The input for this pathway is predominantly from the body of the caudate nucleus. Output is to the frontal eye fields and supplementary eye fields of the frontal lobes, areas important for the higher control of eye movements, as discussed in Chapter 13. The prefrontal channel is probably important in cognitive processes involving the frontal lobes (see Chapter 19). Input is primarily from the head of the caudate, and output reaches the prefrontal cortex (see Table 16.2; Figure 16.8). Finally, the limbic channel is an important ventral pathway through the basal ganglia that is involved in limbic regulation of emotions and motiva-

<table>
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<th>TABLE 16.2 Four Parallel Channels through the Basal Ganglia</th>
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<td>SOURCES OF</td>
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<tr>
<td>MOTOR CHANNEL</td>
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<tr>
<td>Somatosensory cortex; primary motor cortex; premotor cortex</td>
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<tr>
<td>OCULOMOTOR CHANNEL</td>
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<td>Posterior parietal cortex; prefrontal cortex</td>
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<tr>
<td>PREFRONTAL CHANNEL</td>
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<td>Posterior parietal cortex; premotor cortex</td>
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<tr>
<td>LIMBIC CHANNEL</td>
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<td>Temporal cortex; hippocampus; amygdala</td>
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*GPI, globus pallidus, internal segment; SNr, substantia nigra pars reticulata.
*MD, mediodorsal nucleus; VA, ventral anterior nucleus; VL, ventral lateral nucleus.

Figure 16.8 Frontal Lobe Outputs of the Four Parallel Channels through the Basal Ganglia
See Table 16.2. Thalamic origins of the outputs are indicated. Thalamic nuclei: VI, ventral lateral; VA, ventral anterior; MD, mediodorsal.

**REVIEW EXERCISE**

Name the four main channels through the basal ganglia. For each channel give the input nuclei in the striatum and the output targets in the cortex.
may be affected in the pathophysiology of schizophrenia and other psychiatric disorders.

**Ansa Lenticularis, Lenticular Fasciculus, and the Fields of Forel**

The output pathways of the globus pallidus and related structures have been dubbed with several more esoteric-sounding names. We will review these nomenclature briefly here, since it occasionally crops up in neuroanatomical discussions. The structures in question are summarized in Figure 16.9.

The internal segment of the globus pallidus sends outputs to the thalamus through two different pathways. One pathway is the ansa lenticularis (meaning "lenticular loop"), named for the looping course it takes ventrally under the internal capsule before passing dorsally to reach the thalamus (Figure 16.9). The ansa lenticularis actually consists of several loops around the anterior medial edge of the internal capsule, and it then turns back toward the thalamus. Recall that the globus pallidus is lateral to the internal capsule, while the thalamus is medial to the posterior limb of the internal capsule (see Figures 16.3, 16.4D).

The other pathway is the thalamic fasciculus (see Figure 16.9). Instead of taking a looping course, fibers of the lenticular fasciculus penetrate straight through the internal capsule. They then pass dorsal to the subthalamic nucleus and ventral to the zona incerta before turning superiorly and laterally to enter the thalamus. The zona incerta (see Figures 16.4D, 16.9) is the inferior extension of the reticular nucleus of the thalamus (see Figure 7E), which should not be confused with the reticular formation of the brainstem. The fibers of the ansa lenticularis and lenticular fasciculus join together to form the thalamic fasciculus, which enters the thalamus. The thalamic fasciculus also contains fibers ascending to the thalamus from the deep cerebellar nuclei. At this point it is helpful to review the course of the ansa lenticularis, lenticular fasciculus, and thalamic fasciculus as summarized in Figure 16.9.

Another nomenclature for these regions was contributed by the Swiss neurologist and psychiatrist August H. Forel. His terminology describes the Hahnfelder (meaning "fused" or "cleft") fields of the subthalamic tegmentum, currently abbreviated as the H fields of Forel (see Figure 16.9). The H1 field of Forel is the thalamic fasciculus, and the H2 field of Forel is the lenticular fasciculus, where it lies dorsal to the subthalamic nuclei. The prerubral field, or H field of Forel, is the region where the ansa lenticularis and lenticular fasciculus join together.

We will add one more name to the list of tracts discussed so far. In addition to the ansa lenticularis, lenticular fasciculus, and thalamic fasciculus, there is the subthalamic fasciculus (see Figure 16.9). The subthalamic fasciculus carries fibers of the indirect pathway from the external segment of the globus pallidus to the subthalamic nucleus, and from the subthalamic nuclei to the internal segment of the globus pallidus.

**KEY CLINICAL CONCEPT**

**MOBMENT DISORDERS**

Abnormal movements can be caused by dysfunction anywhere in the complex hierarchical motor network, including upper motor neurons, lower motor neurons, cerebellar circuitry, basal ganglia circuitry, motor association cortex, and even sensory systems. However, when clinicians discuss movement disorders, they are often referring to abnormal movements resulting from basal ganglia pathology. Basal ganglia disorders tend to look different from disorders in other parts of the motor system, and there are several well-recognized syndromes caused by lesions of the basal ganglia.

Lesions in other systems are often referred to by other names, rather than being called movement disorders. For example, slow, clumsy, stiff movements and hyperreflexia resulting from corticospinal, upper motor neuron lesions are called spasticity (see KCC 6.1). Irregular, uncoordinated movements caused by lesions of cerebellar circuitry are called ataxia or a variety of other names (see KCC 15.2). On the other hand, abnormal movements caused by basal ganglia dysfunction may be referred to as dyskinesia, meaning simply "abnormal movement."

As in the cerebellar exam (see KCC 15.2), when examining a patient with abnormal movements thought to be of basal ganglia origin, it is essential to first look carefully for abnormalities in other systems that can also cause abnormal movements, including upper or lower motor neuron signs, sensory loss, or ataxia (see neuroexam.com/Videoe 48-78). In addition, abnormal movements are occasionally caused by psychological conditions such as conversion disorder (see Chapter 3).

There is also a historical basis for focusing on the basal ganglia when discussing movement disorders. In the beginning of the twentieth century, it was believed that two independent "pyramidal" and "extrapyramidal" motor systems converged on lower motor neurons. The pyramidal system was similar to current corticospinal or upper motor neuron pathways. However, the extrapyramidal system was mistakenly thought to constitute an independent pathway from the striatum descending through polymodal connections to the spinal cord. As we have discussed in this chapter, the basal ganglia are in fact part of a network of complex loops that exert a major influence on descending motor systems through projections to the motor and premotor cortex. Nevertheless, movement disorders resulting from basal ganglia dysfunction are still often referred to as extrapyramidal syndromes.

Some of the abnormal movements seen in movement disorders are slow, and some are fast. Some occur at rest, and others are accentuated by...
movement or occur only during movement. One common, even if simplified, way of discussing abnormal movements is on a spectrum from slow to fast (Table 16.3). Some movement disorders, such as tremor, can be either slow or fast; Movement disorders can be focal or generalized, unilateral or bilateral. In unilateral movement disorders caused by focal basal ganglia lesions such as infarct, hemorrhage, abscess, tumor, or degeneration, the movement disorder is contralateral to the basal ganglia lesion.

During sleep, most obvious movement abnormalities cease, with rare exceptions, such as palatal myoclonus and tic disorders. Nevertheless, certain aspects of movement disorders often persist in sleep, causing a marked disruption in the normal stages of sleep, and insomnia in some patients. Gait is frequently abnormal in movement disorders, as discussed in KCC 6.5. We will now define several different types of abnormal movements and briefly discuss their differential diagnosis. Localization will also be discussed when possible; however, note that for many movement disorders, the precise localization is still under investigation. In the sections that follow (see KCC 16.2, 16.3), we will then review a few specific syndromes in greater detail. In addition, we will see how basal ganglia dysfunction affects not only general body movements, but also eye movements, cognition, and emotional regulation (see Table 16.2).

<table>
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<th>Bradykinesia, Hypokinesia, Akinesia</th>
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| Bradykinesia means "slow movements": hypokinesia "decreased amount of movement"; and akinesia "absence of movement." These terms are traditionally reserved for localizations at levels higher than the upper motor neurons. In other words, these terms are not used for corticobulbar, lower motor neuron, or muscular disorders. Bradykinetic movement disorders can be caused by increased inhibitory basal ganglia outflow to the thalamus. Reviewing the connections in Figure 16.7 should make it clear that lesions in several regions of the basal ganglia can indirectly cause an increase in inhibitory output from the internal globus pallidus and substantia nigra pars reticulata to the thalamus. Examples include loss of function of the dopaminergic nigrostriatal system, loss of inhibitory pathways from the striatum to the substantia nigra and internal pallidum, or loss of inhibitory neurons projecting from the external pallidum to the subthalamic nucleus. Bradykinesia and hypokinesia resulting from basal ganglia dysfunction are an important feature of Parkinson's disease and related disorders (see KCC 16.2). In addition, decreased spontaneous movements without coma can be seen in diffuse lesions of the frontal lobes (see KCC 19.12), subcortical white matter, thalamic, or brainstem reticular formation (see KCC 14.2). These disorders have been given a variety of names, including abulia and akinetic mutism. Deep brain stimulation and advanced medications can also cause marked psychomotor retardation, which in the extreme is called catalepsy.

<table>
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<th>Rigidity</th>
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| Rigidity is often present in disorders that cause bradykinesia or dystonia. There are numerous different types of rigidity, for different conditions. In rigidity, which results from upper motor neuron lesions, rigidity is velocity dependent. Resistive tone initially increases as the muscles of the limb are stretched, but it may then decrease, giving rise to the term "clasp-knife rigidity."
are visible on ophthalmological slit-lamp examination, and serum carboxylase
may concentrations of less than 20 milligrams per deciliter. In equivocal cases,
liver biopsy may be necessary for diagnosis. Treatment with copper-chelating
agents such as penicillamine or delayed (tardive) side effects in patients
taking antipsychotic or anti-emetic medications. There are numerous
erother causes of chorea, including perinatal anoxia, hyperthyroidism, hy-
perparathyroidism, electrolyte and glucose abnormalities, phenytoin and
other drugs or toxins, neuroanoxiccytopathy, Wilson’s disease, Lesch-Nyan
syndrome, amino acid disorders, and lysosomal storage disorders. Hemi-
chorea can occur contralateral to infarct, hemorrhage, tumor, abscess, or
other focal lesions of the basal ganglia.

**Ballsimus**

Movements of the proximal limb muscles with a larger-amplitude, more
rotary or flinging quality than chorea are referred to as **ballsimus**.
The most common type is **hemiballsimus**, in which there are unilateral
flinging movements of the extremities contralateral to a lesion in the basal
ganglia. The classic cause is a lacunar infarct of the subthalamic nucleus,
which leads to decreased pallidal inhibition of the thalamus (see Figure
16.7). However, lacunae in other regions of the basal ganglia, especially the
striatum, can also cause contralateral hemiballsimus. Hemiballsimus usually
gives way over days or weeks to subtler choreatropic movements. How-
ever, the movements are often initially quite disabling, and they can be im-
proved with dopaminergic antagonists such as haloperidol. Additional
causes of hemiballsimus include other unilateral lesions of the basal ganglia,
such as hemorrhage, tumor, infection, or inflammation.

**Tics**

A sudden brief action that is preceded by an urge to perform it and is fol-
lowed by a sense of relief is called a tic. **Motor tics** usually involve the face
or neck, and less often, the extremities. **Vocal tics** can be brief grunts, cough-
ing sounds, howling or barking-like noises, or even more elaborate vocaliza-
tions that sometimes include obscene words (coprolalia). Tic disorders make up
a spectrum ranging from transient single motor or vocal tics of childhood
to **Tourette’s syndrome** (also known as Gilles de la Tourette’s syndrome),
which is characterized by persistent motor and vocal tics.

Tourette’s syndrome is four times more common in boys than girls, and it
appears to have an autosomal dominant inheritance pattern with incom-
plete penetrance. Onset is usually in late childhood, and there is often some
spontaneous improvement during adolescence. There is an increased inci-
dence of attention-deficit hyperactivity disorder and obsessive-compulsive
disorder in patients with Tourette’s syndrome, as well as in family members.

Diagnosis is based on clinical presentation, since MRI and other tests are
usually unrevealing. The most important aspect of treatment is counseling
and education of the patient, family, and other contacts about the nature of
the disorder, to reduce stigmatization. Symptoms tend to wax and wane,
and during severe periods treatment with dopaminergic agonists such as
haloperidol or pimozide may be beneficial. Alternative pharmacological
agents, such as clonidine (a central α2-receptor antagonist) are increas-
ingly being tried first, despite modest efficacy, because of the long-term side ef-
ects of dopaminergic agonists.

**SLE**

Like other rheumatic fever syndromes, there are other idiopathic tic disorders,
which involve either motor or vocal tics, but not both. Finally, tics can some-
times occur as a consequence of lesions such as encephalitis, infarcts, hemor-
Myoclonus

Generally considered the fastest of all movement disorders (see Table 16.3), myoclonus is a sudden rapid muscular jerk that can be focal, unilateral, or bilateral. Myoclonus can have numerous causes with many possible localizations, including the cerebellum, basal ganglia, cerebral cortex, and even the spinal cord. Axonal injury, encephalitis, and toxic or metabolic encephalopathies are common causes of myoclonus seen in severely ill patients. Myoclonus can result from epileptic cortical activity in disorders such as juvenile myoclonic epilepsy and the progressive myoclonic epilepsies. Myoclonus can occur as a paraneoplastic disorder, especially with small cell lung carcinoma, ovarian or breast carcinoma, and neuroblastoma. It is also often prominent in the neurodegenerative condition cortical basal ganglionic degeneration, in prion-related illnesses such as Creutzfeldt-Jakob disease (see KCC 5.9), in lysosomal storage disorders, and late in the course of diffuse Lewy body disease or Alzheimer’s disease.

Palatal myoclonus is famous for its notable persistence during sleep, as well as its rhythmicity, which distinguishes it from most other forms of myoclonus. Movements of the palate occur at 1 to 2 hertz and can sometimes extend to the face and even proximal upper extremities. Some patients complain of hearing “clucking sounds” arising from their palate. Palatal myoclonus is typically caused by lesions of the central tegmental tract (see Figure 15.9A), most commonly with brainstem infarcts.

Asterixis (meaning “lack of fixed position”) or flapping tremor, is another form of rapid movement that is often seen in toxic or metabolic encephalopathies, particularly in hepatic failure, in which case it is called a “liver flap.” An examiner can bring out the movements by asking the patient to hold both arms straight in front of their chest with their palms facing forward and wrists extended, as if they are “stopping traffic.” In asterixis, intermittent flexion movements are seen at the wrists bilaterally, as the patient attempts to hold this pose. Unlike myoclonus, the movements in asterixis are not muscle contractions, but are actually caused by brief interruptions in contraction of the wrist extensors, which have been recorded on EMG as brief silent periods, prompting the term “negative myoclonus.”

Tremor

Rhythmic or semirhythmic oscillating movements are called tremor. Tremor differs from myoclonus and asterixis in that both agnostic and antagonist muscles are activated, resulting in bidirectional movements. Tremor can have many causes, and it can be slow or fast. The specific characteristics of a tremor can help define its localization and etiology (Table 16.4).

Tremors are most simply classified as resting tremor, postural tremor, and intention (ataxic) tremor. Resting tremor is most prominent when the limbs are relaxed. It is usually easiest to observe while the patient's hands are resting on their lap and are distracted—for example, while discussing unrelated aspects of their past medical history. The tremor decreases or stops when the patient moves their limbs. Resting tremor is an important feature of Parkinson's disease and is sometimes called parkinsonian tremor. The tremor is often asymmetrical and involves mainly the hands and arms, but it can also involve the lower extremities and mouth. Since patients may appear to be rolling something between their thumb and other fingers, the term pill-rolling tremor is sometimes used. Resting tremor typically has a frequency of 3 to 5 hertz.

In contrast, postural tremor is most prominent when the patient's limbs are actively held in a position—for example, with both arms parallel to the floor and disappears at rest. Essential tremor is the most typical example, and it is arguably the most common of all movement disorders. It is sometimes also called familial, benign, or senile tremor, although none of these names strictly apply. Essential tremor most commonly involves the hands or arms, but it can also affect the jaw, tongue, lips, head, vocal cords, and less often, the legs or trunk. It is usually bilateral, but it may be asymmetrical. The tremor can be mild, or it can cause significant functional impairment. Patients often complain about difficulty holding a glass of water without spilling, and they may have problems with handwriting. The tremor increases with stress and can often be improved by beta-adrenergic antagonists such as propranolol. A drink of alcohol frequently decreases the tremor temporarily. Essential tremor often occurs in families, with autosomal dominant inheritance; however, sporadic cases occur as well. Onset can occur anytime from early adulthood to advanced age, and the tremor tends to progress only very slightly over time. No treatment is needed for mild cases, and more severe cases often show symptomatic improvement with beta-blockers or primidone. In very severe cases, ventrolateral thalamotomy or thalamic stimulation (see KCC 16.4) may be beneficial.

Intention tremor is also called ataxic tremor because it is usually a feature of appendicular ataxia associated with cerebellar disorders, as discussed in Chapter 15 (see KCC 15.2). Intention tremor occurs as the patient attempts to move their limb toward a target and has irregular, oscillating movements in multiple planes throughout the trajectory. Intention, or ataxic, tremor has a frequency of 2 to 4 hertz.

A variety of other terms for tremor are sometimes used, and they can cause confusion. Action tremor can mean either a postural or an intention tremor. Static tremor can mean either a resting or a postural tremor. Intention tremor is sometimes also referred to as kinetic tremor. When tremor increases toward the end of a movement, as is common in intention tremor, it is called terminal tremor. In addition, terminal tremor can result from the emergence of a postural tremor as the limb approaches its final position.

Before leaving the topic of tremors, let's briefly discuss the other examples listed in Table 16.4. In addition to ataxic (intention) tremor, cerebellar lesions can cause other kinds of tremors that occur at rest or while holding a posture. Despite its name, so-called rubral tremor is most likely caused by a lesion rostral to the red nucleus, but rather of the nearby superior cerebellar peduncle or other cerebellar circuitry. Rubral tremor has a frequency of 2 to 4 hertz and is usually of low amplitude at rest, but it becomes more violent as soon as the limbs are abducted slightly or attempts are made to hold a posture and perform a movement. This tremor is usually caused by multiple sclerosis or brainstem infarcts, and it can resemble the tremor seen in Wilson's disease. Other tremors seen in cerebellar disorders include trunk and head tremor associated with lesions of the vermis, and palatal myoclonus, which some authorities classify as a tremor rather than true myoclonus.

Postural tremor can be caused by a variety of drugs, medications, metabolic derangements, alcohol withdrawal, intense fear, anxiety, and other conditions. In some cases the tremor is thought to be caused by an enhancement of the normal physiological tremor, present in all individuals but not usually visible without special equipment. Physiological tremor has a frequency of 4 to 13 hertz, slightly higher than essential tremor, and is enhanced with

**TABLE 16.4 Classification of Tremors**

<table>
<thead>
<tr>
<th>Tremor Type</th>
<th>Cause</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resting tremor</td>
<td>Parkinsonian tremor</td>
<td>Constant, bilateral</td>
</tr>
<tr>
<td>Cerebellar disorders</td>
<td>Essential tremor</td>
<td>Bilateral, asymmetric</td>
</tr>
<tr>
<td>(*)</td>
<td>Toxic/metabolic causes</td>
<td>Variable</td>
</tr>
<tr>
<td>Neurovascular disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebellar disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(*rubral) tremor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trunk and head tremor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parkinsonian tremor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intention tremor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebellar appendicular ataxia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All causes of postural tremor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Especially near end of movement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other disorders resembling tremor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebellum</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myoclonus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flapping tremor (ataxic)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dys tonic tremor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pseudotremors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motor seizures</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**KEY CLINICAL CONCEPT**

PARKINSON'S DISEASE AND RELATED DISORDERS

**Table 16.5** Differential Diagnoses of Parkinsonism

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parkinson's disease</td>
<td>Most common, progressive, bilateral, causes rigidity and tremor</td>
</tr>
<tr>
<td>Drug-induced parkinsonism (dopamine agonists)</td>
<td>Causes similar symptoms to Parkinson's disease</td>
</tr>
<tr>
<td>Multi-system atrophy</td>
<td>Causes some of the symptoms of Parkinson's disease</td>
</tr>
<tr>
<td>Striatal degeneration</td>
<td>Causes some of the symptoms of Parkinson's disease</td>
</tr>
<tr>
<td>Shy-Drager syndrome</td>
<td>Causes some of the symptoms of Parkinson's disease</td>
</tr>
<tr>
<td>Orthostatic cerebellar atrophy</td>
<td>Causes some of the symptoms of Parkinson's disease</td>
</tr>
<tr>
<td>Progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome)</td>
<td>Causes some of the symptoms of Parkinson's disease</td>
</tr>
<tr>
<td>Dementia with Lewy bodies</td>
<td>Causes some of the symptoms of Parkinson's disease</td>
</tr>
<tr>
<td>Cortical basal ganglionic degeneration</td>
<td>Causes some of the symptoms of Parkinson's disease</td>
</tr>
<tr>
<td>Multiple system atrophy</td>
<td>Causes some of the symptoms of Parkinson's disease</td>
</tr>
<tr>
<td>Parkinson's disease</td>
<td>Causes some of the symptoms of Parkinson's disease</td>
</tr>
<tr>
<td>Wilson's disease</td>
<td>Causes some of the symptoms of Parkinson's disease</td>
</tr>
<tr>
<td>Multiple system atrophy</td>
<td>Causes some of the symptoms of Parkinson's disease</td>
</tr>
<tr>
<td>Wilson's disease</td>
<td>Causes some of the symptoms of Parkinson's disease</td>
</tr>
<tr>
<td>Myoclonus</td>
<td>Causes some of the symptoms of Parkinson's disease</td>
</tr>
<tr>
<td>Myasthenia</td>
<td>Causes some of the symptoms of Parkinson's disease</td>
</tr>
<tr>
<td>Other metabolic and neurodegenerative disorders</td>
<td>Causes some of the symptoms of Parkinson's disease</td>
</tr>
</tbody>
</table>

**Idiopathic Parkinson’s Disease**

Parkinson's disease is a sporadic disorder of unknown etiology that occurs worldwide. The usual age of onset is between 40 and 70 years. About 1% of individuals over age 65 are affected. There is generally a familial tendency, except in rare cases of familial Parkinson's. Pathologically, there is loss of pigmented dopaminergic neurons in the substantia nigra pars compacta, causing the substantia nigra to appear pale to the eye on cross-section (Figure 16.10A). Remaining dopaminergic neurons often contain characteristic cytoplasmic inclusions called Lewy bodies, which are eosinophilic, contain ubiquitin and α-synuclein, and have a fossil halo (see Figure 16.10B). There is also loss of pigmented neurons in other regions of the nervous system.

Diagnosis is based on clinical features. Initially patients may have only some subtle difficulty using one limb, slowing of movements, or an asymmetrical resting tremor. Eventually patients with idiopathic Parkinson’s disease usually have the classic triad of resting tremor, bradykinesia, and cogwheel rigidity, accompanied by postural instability that causes an 'unsteady gait.' The disorder initially unilateral but later becomes bilateral although the severity often remains asymmetrical. It usually worsens with time and eventually involves the entire body. It is a progressive disorder and can result in death. Depression and dementia are common, especially in advanced Parkinson’s disease. Other associated features in Parkinson's disease of uncertain etiology include autoimmunity and hyperactivity.

**Figure 16.10** Pathologic Changes of Parkinson's Disease

(A) Section through the midbrain from a patient who died with Parkinson's disease. Arrows indicate the substance nigra pars compacta. (B) Microscopic section through the substantia nigra from a different patient with Parkinson's disease showing a typical Lewy body. The Lewy body has a characteristic dense (pink) center with a lighter halo and is located in the cytoplasm of a darkly pigmented dopaminergic neuron. (A from Nobile J. 1999. The Human Brain, 4th Ed. Mosby, St. Louis; courtesy of Naomi Rance, The University of Arizona College of Medicine. B courtesy of Jean Paul V. Vonsattel, Massachusetts General Hospital, Harvard School of Medicine.)

Some of the clinical features of Parkinson's disease are worth discussing in greater detail. The resting "pill rolling" tremor has already been discussed in KCC 16.1, as has the rigidity, which is often of the cogwheel type. There are numerous manifestations of bradykinesia and hypokinesia in Parkinson's disease. There is a characteristic decrease in spontaneous blink rate and in facial expression called masked facies or hypomimia. The voice becomes hypophonic, and speech has a hurried, muttering quality. Saccades are slow, and smooth pursuit eye movements are often broken up into a series of catch-up saccades. Writing becomes small, a symptom termed micrographia. The posture is stooped, and some patients may have some dystonia. Postural instability, the diminished ability to make reflex postural adjustments that maintain balance, can be disabling and results in a characteristic parkinsonian gait (see Table 6.6). If pulled backward slightly, patients may exhibit retropulsion, in which they take several backward steps to regain balance, or they may fall. They cannot rise from a chair without using their hands, and they have difficulty initiating gait. Once they have started, they tend to walk with small shuffling steps, termed a festinating gait. They sometimes appear to continue falling and shuffling forward, referred to as anteropulsion. Arm swing is diminished, and they often exhibit en bloc turning, in which turns are executed without the normal twist of the torso. Inability to suppress blinking when the center of the brow ridge (glabella) is tapped repeatedly (Myerson's sign) is a nonspecific finding that can be seen in other neurodegenerative conditions as well. Instability is not an early feature of Parkinson's disease, but estimates of dementia later in the course vary from 15 to 40% or higher. Some of these cases are likely due to the coincidence of Alzheimer's disease and Parkinson's disease, and others may represent diffuse Lewy body disease (discussed shortly), but additional cases may not be explained by either of these causes. Patients with advanced Parkinson’s disease often have parkinsonism, in which responses to questions are slowed but may be accurate if enough time is allowed. Depression and anxiety are common, especially in advanced Parkinson’s disease. Other associated features in Parkinson's disease of uncertain etiology include autoimmunity and hyperactivity.

The most effective drug for treatment of Parkinson's disease is levodopa. Most formulations also contain carbidopa, a decarboxylase inhibitor that cannot cross the blood-brain barrier. Carbidopa inhibits the breakdown of levodopa to dopamine in peripheral tissues, making more levodopa available.
able for conversion to dopamine in the central nervous system where it is needed. The most common peripheral side effects of dopamine are gastrointestinal disturbances and orthostatic hypotension, and these are substantially reduced by carbidopa. Higher doses of levodopa can sometimes precipitate psychotic symptoms such as psychosis. As Parkinson’s disease progresses, patients have other problems with levodopa therapy. Trouble in wearing off can occur toward the end of the time between doses during which the patient may experience freezing, being unable to move. The opposite problem—levodopa-induced dyskinesias—also becomes increasingly troublesome. With advanced Parkinson’s disease, patients may increasingly experience on-off phenomena, in which they fluctuate between dyskinesias and immobility, with very little time during which they are functional. On-off phenomena may be helped somewhat by sustained-release formulations. In addition, catechol-O-methyltransferase (COMT) inhibitors have recently shown some promise in increasing plasma levodopa levels and decreasing wearing-off symptoms.

There is currently some controversy about whether to start therapy with levodopa early in the course of Parkinson’s disease or to reserve it for later, when other agents are no longer effective. Other treatments used for Parkinson’s disease include anticholinergic agents such as benztropine mesylate (Cogentin) and trihexyphenidyl (Artane). The antiviral agent amantadine has an anticholinergic and antiglutaminergic effect and probably also increases the release of dopamine in the striatum. Dopaminergic agents such as pergolide, bromocriptine, ropinirole, and pramipexole are also sometimes used. Selegeline works by inhibiting the breakdown of dopamine. Early claims that selegeline may slow progression of Parkinson’s disease have not been substantiated, and there remains no known agent that alters the progression of this disease. Surgical treatments for Parkinson’s disease are discussed in KCC 16.4.

It should be apparent from reviewing Figure 16.7 how decreased dopaminergic input to the striatum in Parkinson’s disease results in increased inhibition of the thalamus by basal ganglia outputs (through both the direct and indirect pathways), causing a hypokinetic movement disorder. In addition, Figure 16.7 shows the beneficial effects of agents that enhance dopaminergic actions or inhibit cholinergic actions. However, it is important to recall that this simplified schematic is still incomplete; for example, it fails to account for the tremor seen in Parkinson’s disease.

Other Causes of Parkinsonism
Antipsychotic and anti-emetics: dopamineergic antagonists such as haloperidol (Haldol), and prochlorperazine (Compazine) commonly cause parkinsonian signs such as rigidity, hypokinesia, and even resting tremor. In Parkinson’s disease, onset is usually abrupt and symptoms are asymmetrical. Occasionally symptoms can persist for several weeks after the offending agent has been discontinued, making a careful review of prior medication history essential when evaluating patients with subacute onset of parkinsonism.

Several neurodegenerative conditions other than Parkinson’s disease are associated with parkinsonism (see Table 16.5). These are sometimes referred to as parkinsonism plus syndromes. They often produce atypical parkinsonism, which differs from idiopathic Parkinson’s disease by having relatively symmetrical symptoms, absence of resting tremor, and little response to dopaminergic agents. One group of neurodegenerative conditions, the atypical parkinsonism, falls under the heading of multisystem atrophy. These disorders include striatonigral degeneration, Shy–Drager syndrome, and olivopontocerebellar atrophy. In multisystem atrophy there is loss of dopaminergic neurons of the substantia nigra pars compacta (see Figure 16.7). However, there is also loss of striatal neurons projecting to the globus pallidus and substantia nigra pars reticulata. Therefore, even if dopaminergic transmission is enhanced pharmacologically, there will still be decreased inhibition of the basal ganglia output nuclei, resulting in increased inhibition of the thalamus, and parkinsonism (see Figure 16.7). This may explain the relative insensitivity of multisystem atrophy to levodopa compared to Parkinson’s disease. The most important differential diagnosis is with motor neuron disease, where the clinical presentation is often similar. In Shy–Drager syndrome there is marked atrophy of the intermediolateral cell column of the spinal cord (see Figures 6.4D, 6.12B). Therefore, patients with Shy–Drager syndrome have parkinsonism together with autonomic disturbances such as marked orthostatic hypotension, impotence, and urinary incontinence (see KCC 7.5). Olivopontocerebellar atrophy is characterized by parkinsonism together with ataxia. Often these different syndromes of multisystem atrophy overlap significantly.

Another important neurodegenerative condition in which parkinsonism is prominent is progressive supranuclear palsy (PSP), also known as Steele–Richardson–Olzewski syndrome. In this disorder there is degeneration of multiple structures around the midbrain–diencephalic junction, including the superior colliculus, red nucleus, dentate nucleus, subthalamic nucleus, and globus pallidus. The range of vertical eye movement is usually markedly limited, including both upward and downward saccades, relatively early in the illness (see Chapter 13). This finding should be distinguished from mildly decreased upward eye movements seen in numerous neurodegenerative conditions, and even in normal aging. Patients with PSP also have waxy rigidity, bradykinesia, and, and there remains no known agent that alters the progression of this disease. Surgical treatments for Parkinson’s disease are discussed in KCC 16.4.

Dementia with Lewy bodies (also called diffuse Lewy body disease) is increasingly being recognized as an important cause of parkinsonism and dementia. Lewy bodies in this disorder should be found in the substantia nigra and throughout the cerebral cortex. Patients often have prominent psychiatric symptoms, including visual hallucinations, relatively early in the course of the disorder, which tend to have episodic exacerbations. In cortical basal ganglionic degeneration, there is parkinsonism that resembles Parkinson's disease by being asymmetrical, together with marked cortical features such as apraxia (see KCC 19.7) and corticospinal abnormalities.

Machado–Joseph disease (also called spinocerebellar ataxia type 3) and dentatorubropallidoluysian atrophy are rare neurodegenerative disorders that often include parkinsonian features. Both are transmitted by autosomal dominant inheritance and are caused by expanded trinucleotide repeats (see KCC 16.3). Huntington’s disease, another trinucleotide repeat disorder, can present with predominantly parkinsonian features in the unusual patients in which onset is in childhood or early adulthood. Wilson’s disease (see KCC 16.1) can also cause tremor, rigidity, and bradykinesia. Illicit drug users who were exposed to the toxic MPTP, a synthetic heroin-like molecule, analog developed parkinsonism caused by destruction of pars compacta dopamine neurons.

In 1914–1980 there was an epidemic of von Economo’sencephalitis lethargica, a condition that has since disappeared. Many patients were left with severe parkinsonism following this illness. Boxers may develop dementia pugilistica, in which there is parkinsonism and cognitive decline.
There are numerous other causes of parkinsonism that are beyond the scope of this text (see the references at the end of this chapter for more details). We should mention, however, that bradykinesia, rigidity or paraesthesia, hypokinesia, and restless gait can be seen in hydrocephalus, frontal lobe lesions, and diffuse subcortical disorders, and these disorders can sometimes be difficult to distinguish from parkinsonism. In addition, severe depression can cause paucity of movement that may be mistaken for parkinsonism.

Huntington's disease is an autosomal dominant neurodegenerative condition characterized by a progressive, usually choreiform movement disorder, dementia, and psychiatric disturbances, ultimately leading to death. The pathologic hallmark of Huntington's disease is progressive atrophy of the striatum, especially involving the caudate nucleus. Clinical manifestations include abnormalities in all four domains of basal ganglia function discussed earlier (see Table 16.2, Figure 16.5). Specifically, Huntington's disease results in abnormalities of body movements, eye movements, emotions, and cognition.

The overall prevalence of Huntington's disease is about 4 to 5 cases per million people, although it is higher in those of northern European ancestry. Usual age of onset is between 30 and 50 years, although early-onset and late-onset cases are occasionally seen. Initial symptoms are usually subtle chorea (see KCC 16.1) and behavioral disturbances. These symptoms may be denied by the patient and brought to medical attention by family members or other contacts. While taking the history, the examiner can often elicit abnormalities extending back several years in retrospect. Interestingly, those experienced with Huntington's disease can often detect subtle eye movements and abnormalities before other manifestations become apparent. These include slow saccades, impaired smooth pursuit, sluggish optokinetic nystagmus (see Chapter 13), and a characteristic difficulty initiating saccades without moving the head or blinking.

Early movement abnormalities include clumsiness and subtle chorea as described in KCC 16.1, such as mild jerking, fidgety movements. Mild chorea may be voluntarily suppressed and examiner can make it more obvious by having patients walk or by asking them to hold their arms outstretched with eyes closed. In addition to chorea, other abnormal movements include tic, athetosis, and dystonic posturing. In the rare cases of juvenile onset, a more parkinsonian phenotype is often present.

Common psychiatric manifestations include affective disorders such as depression and anxiety, obsessive-compulsive disorder, impulsivity or destructive mannerism, and occasionally psychoses. Cognitive impairments are multiple and include decreased attention (see KCC 19.34), a memory disorder that affects both recent and remote memories, anosmia (see KCC 19.6), and impaired executive functions (see KCC 19.11). In advanced Huntington's disease, patients are profoundly demented and lose the ability to make nearly all purposive movements. They are mute, cannot speak, and usually die of respiratory infections. Median survival from the onset of first symptoms is about 15 years.

Pathologically, the most dramatic change in Huntington's disease is progressive atrophy of the caudate nucleus. The putamen is also involved, and to a lesser extent the nucleus accumbens atrophies as well. As already noted, the degeneration initially affects striatal neurons of the indirect pathway (see Figure 16.5), possibly explaining why a hyperkinetic movement disorder usually results. Atrophy of the caudate and putamen can lead to lateral ventricles to appear enlarged on CT and MRI scans. This condition is easily distinguished from hydrocephalus because in Huntington's disease the caudate head no longer forms the bulge normally seen on the walls of the lateral ventricles in coronal sections (see Figure 14.1C). As the disease progresses, milder atrophy of the cerebral cortex also occurs.

A landmark achievement for human genetics, the abnormal gene causing Huntington's disease was mapped in 1983 and cloned in 1993. The gene is located on chromosome 4, and it includes a region containing multiple repeats of the trinucleotide sequence CAG in tandem. Normal individuals have fewer than 30 CAG repeats in this gene. Individuals with over 40 CAG repeats either have Huntington's disease or will ultimately develop this disorder. The higher the number of CAG repeats, the earlier the onset of symptoms. The gene causing Huntington's disease encodes a protein called huntingtin. Active investigation is underway to clarify how an increase in CAG repeats, encoding multiple copies of the amino acid glutamine in the huntingtin protein, can lead to Huntington's disease. It is hoped that this information will suggest a cure for this devastating condition. In addition to the gene for Huntington's disease, several other genetic disorders, many of which have prominent neurologic manifestations, have also been found to be caused by expanded trinucleotide repeats.

A suspected diagnosis of Huntington's disease can be made on the basis of the appearance of typical clinical features, especially if there is a positive family history. Inheritance is autosomal dominant with complete penetrance. However, in many cases the family history is sketchy, or there may be only suggestive leads, such as a parent who died young or was institutionalized. Other causes of chorea should be considered in the differential diagnosis (see KCC 16.1). With the cloning of the Huntington's disease gene, it is now possible to perform a genetic test for Huntington's disease even before symptoms appear. Because the disorder remains incurable, however, such testing raises many ethical and philosophical issues. The test should therefore be performed only on consenting adults in a setting where specialized counseling is available.

Treatment for Huntington's disease is currently directed at alleviating symptoms and does not alter the course of the disease. Chorea can be reduced somewhat with antiparkinsonian agents. Psychiatric manifestations can be treated with counseling and psychotropic medications. The coming years may bring advances in molecular medicine that will enable more definitive treatments for Huntington's disease and other degenerative disorders.

Stereotactic surgery is a relatively old technique that has had increasing applications in neurosurgery in recent years. This method allows relatively precise localization in three-dimensional space of structures in the brain based on surface landmarks. There are several variations on this technique, and only the basic concept will be discussed here.

To establish a stereotactic coordinate system, reference points are first applied to the patient's head. Examples of reference systems used in stereotactic surgery include a series of small radiopaque markers placed on the patient's scalp, or a rigid frame affixed to the skull under local anesthesia. The patient, with the reference system in place, is then taken to the CT or MRI scanner, and images are obtained of the brain and reference system. A computer program then calculates the location of any point in the brain relative to the external reference system.

The patient is then taken to the operating room with the reference system still in place. Using the information provided by the scanned images, the surgeon can guide the tip of a needle or probe to a precise location in the brain through a small hole in the skull. This procedure can be performed under local anesthesia. Applications of this stereotactic technique in
neurosurgery have been numerous. For example, an instrument can be inserted through a narrow tube to obtain a biopsy of a lesion located deep within the brain. Prior to the development of stereotactic methods, a similar biopsy may have required highly invasive surgery or may have been impossible to perform. Fluid collections such as abscesses can be drained stereotactically, providing therapeutic benefit. In addition to surgery, stereotactic methods are used in radiation therapy. Known as stereotactic radiotherapy, this technique can be used to target highly focused beams of radiation such as the “gamma knife,” applied externally, to a specific location within the brain.

In the treatment of movement disorders, stereotactic methods are used to carefully place lesions or stimulators at specific points in basal ganglia pathways. Lesions are made by placing the tip of an electrode in a particular location, and then using electrical current to heat the tip sufficiently to cause a lesion. These lesions are placed in two main locations. For Parkinson’s disease that has progressed to severe on-off swings (see KCC 16.2), medical therapy, pallidotomy can provide substantial improvement in bradykinesia, rigidity, and medication-related dyskinesias. In this procedure, a lesion is placed stereotactically in the ventral posterior portion of the globus pallidus. The lesion interrupts the inhibitory output pathway carried by the ansa lenticularis from the medial globus pallidus to the ventral lateral nucleus of the thalamus (see Figures 16.7, 16.9). Removal of this inhibition may explain why bradykinesia and rigidity are improved. However, it is somewhat perplexing that this lesion does not cause deficits. It is also unclear why medication-related dyskinesias are improved with this treatment. The benefit of pallidotomy in patients with Parkinson’s disease is most dramatic contralateral to the lesion, although there is usually some temporary ipsilateral benefit as well.

For debilitating tremor (see KCC 16.1), especially in cases of severe essential tremor not responding to medications, thalamotomy can provide benefit. In this procedure a lesion is placed stereotactically in the posterior portion of the ventral lateral nucleus of the thalamus (see Figure 16.7). The mechanism for improvement in tremor produced by this lesion is not known. Also, like pallidotomy, it is not clear why this lesion does not cause a significant motor deficit.

Other recent surgical approaches to the treatment of movement disorders have involved the implantation of electrical stimulating electrodes in the thalamus, subthalamicus, or globus pallidus, instead of the creation of lesions. These devices can be turned on or off by the patient at will. When on, electrical current at the tip of the electrode apparently causes transient dysfunction of nearby neurons, resulting in improvement in the movement disorder. For example, subthalamicum stimulators have been shown to alleviate the bradykinesia and other symptoms of Parkinson’s disease, as might be predicted from the relative hyperkinesia usually produced by inhibited function in this nucleus (see Figure 16.7). Another surgical approach has been transplantation of fetal midbrain neurons or adrenal chromaffin cells into the striatum of patients with Parkinson’s disease. The long-term benefits of transplantation remain uncertain, and enthusiasm for these procedures has waned in recent years with the increasing popularity of stereotactically placed lesions or stimulators.

**CASE 16.1 UNILATERAL FLAPPING AND FLINGING**

**MINICASE**

A 65-year-old HIV-positive man began having involuntary flapping movements of the right arm and leg, which became progressively worse over the course of 1 month, making gait and use of the right hand difficult. On exam, he had continuous wild, uncontrollable flapping and circular movements of the right arm, and occasional jerky movements of the right leg, with an unsteady gait, falling to the right. The remainder of the exam was unremarkable.

**LOCALIZATION AND DIFFERENTIAL DIAGNOSIS**

1. On the basis of the symptoms and signs shown in bold above, where is the lesion?
2. What is the most likely diagnosis, and what are some other possibilities?

**Discussion**

The key symptoms and signs in this case are:

- Voluntary, wild flinging movements of the right arm and leg

1. This patient had a unilateral hyperkinetic movement disorder that could be described as hemiballismus or hemichorea (see KCC 16.1). As discussed in the section on hyperkinetic and hypokinetic movement disorders earlier in the chapter, and in KCC 16.1, hyperkinetic movement disorders are often caused by dysfunction of the contralateral subthalamic nucleus, or of indirect-pathway neurons in the striatum (see Figure 16.7). A review of Figure 16.7 should make it clear that a lesion in either location would result in less inhibitory output from the internal segment of the globus pallidus (and the substantia nigra pars reticulata) to the thalamus, resulting in increased excitatory activity traveling from the thalamus to the motor cortex.

The most likely clinical localization is left subthalamic nucleus or left striatum.

2. Given the patient’s age, a lacunar infarction in the left subthalamic nucleus or left striatum is the most likely diagnosis. A small hemorrage in these locations is also possible. Nevertheless, the history of gradual onset over the course of a month would be somewhat unusual for either an infarct or a hemorrhage. Especially because the patient has a history of HIV, other brain lesions should also be considered. The most common intracranial mass lesions in patients with HIV (see KCC 5.9) are toxoplasmosis and primary central nervous system lymphoma, either of which could occur in the subthalamic nucleus or striatum.

**Clinical Course and Neuroimaging**

A brain MRI with gadolinium (Figure 16.11) showed a ring-enhancing lesion in the region of the left subthalamic nucleus (compare to Figures 16.6D and 16.9). Given the clinical setting, the patient was treated empirically with the antiretroviral medications valganciclovir and sulfadiazine (see KCC 5.9). Serum and cerebrospinal fluid testing for toxoplasmosis were positive. Four weeks later the patient’s right-sided hemiballismus had subsided, but he still had some mild waveling movements of the left arm and leg.

A repeat MRI after 4 months showed the lesion to be nearly gone, with only a small homogeneous region of enhancement remaining.

*A description of this patient was published previously by Provenzale and Schwerzerfeld in 1994; see the references at the end of this chapter.*
CASE 16.2 IRREGULAR JERKING MOVEMENTS AND MARITAL PROBLEMS

CHIEF COMPLAINT
A 35-year-old man with a recent history of jerking movements went with his wife to see a psychiatrist for marital problems.

HISTORY
The wife reported that during recent months her husband had been having occasional irregular jerking movements of the head, trunk, and limbs. At night he sometimes would grind his teeth in his sleep, grip his wife's hand tightly without knowing it, or swallow noisily. The husband denied having any involuntary movements but said "they could be there." He did admit to occasional stumbling, having recently fallen down a flight of stairs. However, he denied that this represented any significant change in his gait over recent years. He worked as a salesman in a small business and denied any depression or problems due to intellectual function or psychiatric problems. In the army he was a high-70s golfer. At the time of consultation he was shooting 120, but he attributed this decrease in performance to practicing golf less often than previously. His wife felt something was wrong and urged him to seek medical attention, and his refusal led to bitter arguments.

FAMILY HISTORY
The wife's family history was unremarkable. The husband had no siblings. His father had died at age 50 years from Huntington's disease (diagnosed at 44 years). His mother's family was unaffected. The following pedigree gives further details:

- Unaffected male
- Unaffected female
- Female with Huntington's disease
- Male with Huntington's disease
- The man in this case

PHYSICAL EXAMINATION
At the end of the counseling session, the psychiatrist set aside some time to examine the husband.

Vital signs: T = 98.6°F, P = 76, BP = 140/80, R = 16.

Neck: Supple.

Lungs: Clear.

Heart: Regular rate with no murmurs.

Abdomen: Benign.

Extremities: Normal.

Neurologic exam:
MENTAL STATUS: Alert and fully oriented. Speech fluent. Good attention and calculation skills. Recalled 3/3 objects after 5 minutes. Affect slightly to moderately blunted, with some apathy regarding emotional impact of the consultation, stating, for example, "I've got it, I've got it."
CRANIAL NERVES: Normal, except that saccadic eye movements were moderately slowed.
MOTOR: Rare, brief, irregular, restless-appearing movements in the face, neck, trunk, and upper extremities. Tone was normal to slightly decreased in all extremities. SS power throughout.

COORDINATION: Normal on finger-to-nose and heel-to-shin testing.
Gait: Normal. Involuntary movements were not noticeably increased during walking. Tandem gait was slightly ataxic.
SENSORY: Intact.

LOCALIZATION AND DIFFERENTIAL DIAGNOSIS
1. On the basis of the symptoms and signs shown in bold above, which of the four parallel channels through the basal ganglia (see Table 16.2) are abnormal in this patient?
2. Does this patient have a predominantly hyperkinetic or hypokinetic movement disorder? Refer to Figure 16.7, identify the parts of the basal ganglia in which dysfunction could explain these movements.
3. Which mode of inheritance is suggested by the patient's pedigree, assuming he is affected by the same disorder as other family members? What is the most likely diagnosis? What genetic abnormality causes this disorder? What parts of the brain are predominantly affected?

**Discussion**
The key symptoms and signs in this case are:
- Irregular jerking movements, slightly decreased tone, and unsteady gait
- Moderately slowed saccadic eye movements
- flatt ataxic, argumentative, and denied having any involuntary movements

1. The abnormal movements suggest involvement of the motor channel; impaired saccades suggest involvement of the oculomotor channel (see Table 16.1). The patient's emotional changes and disoriented behavior suggest involvement of the limbic channel and possibly the prefrontal channel as well (see KCC 19.11).
2. This patient has a bilateral hyperkinetic movement disorder, best described as a mild tic or chorea (see KCC 16.1). Hyperkinetic movements of this kind may be caused by bilateral dysfunction in the subthalamic nucleus, or in the striatal neurons of the indirect pathway (see Figure 16.7).
3. The pedigree suggests an autosomal dominant inheritance pattern. The most likely diagnosis is Huntington's disease (see KCC 16.3). This disorder is caused by an expanded CAG trinucleotide repeat in the gene encoding the huntingtin protein, located on chromosome 4. In early Huntington's disease, the indirect-pathway neurons of the striatum are preferentially involved (see Figure 16.7). Later in the course of this disorder, there is gross degeneration of the bilateral caudate and putamen, with lesser involvement of the cerebral cortex as well.

**Clinical Course and Neuroimaging**

The psychiatrist was concerned that the husband in this couple could have early Huntington's disease, and he referred the patient to a neurologist. This occurred in the 1970s, before genetic testing for Huntington's disease was available. Treatment with levodopa had a modest effect in decreasing the patient's involuntary movements. Three years later his symptoms had progressed substantially, and he was briefly admitted to the hospital for further evaluation. In the interim he had lost his job as a salesman because "business was slow." He was then fired from work as a newspaper distributor because he "was robbed." In addition, he had recently divorced. On exam, mental status was normal for mild irritability, and slightly garbled speech when speaking at high speeds. In addition, he made some errors when asked to repeat nonsense syllables. He had developed frequent paroxysmal involuntary twitches of all four limbs, worse distally than proximally. Gait had a slight waddling character, with some dystonic arm carriage. Head CT was normal except for a very slight enlargement of the lateral ventricles. EEG was normal except for low voltage.

Eleven years after initial presentation the patient was readmitted after expressing suicidal thoughts when his driver's license was revoked. He said he was stopped by the police, but he was unable to say why, stating only that he was "trying to make a left turn." He had last worked about 1 year previously doing part-time paper delivery. He was still able to live independently at home. On exam, he was alert and oriented to 3. Speech was fluent but had an abnormal rhythm. He was able to follow complex commands. Memory and calculating skills were intact. He had a labsile affect, behaving in a frustrated, angry, and impulsive manner. For example, he threatened suicide if he could not drive. He had poor insight into his illness, denying any abnormalities in speech or movements. Motor exam was notable for hypotonia, motor
impeissence (see KCC 19.14), and continuous choreiform writhing movements of the tongue, arms, neck, and torso. The involuntary movements were worsened by walking, and he was unable to perform tandem gait.

A brain MRI performed at this time showed marked flattening of the lateral walls of the lateral ventricles (Figure 16.12A) when compared to an MRI from a normal individual (Figure 16.12B). This shape suggests bilateral atrophy of the head of the caudate nucleus, which normally bulges into the lateral ventricle in this location (Figure 16.12B). Note that some degree of cortical atrophy was present as well.

The patient was treated with additional medications, including dopamine antagonists such as haloperidol with little benefit. He was discharged home once it was ascertained that he was no longer suicidal, and he was followed by both a psychiatrist and a neurologist as an outpatient. Within 2 years he could no longer be managed at home and required admission to a chronic inpatient psychiatric facility, where he died soon afterward.

Related Case. Figure 16.13 shows coronal sections of two half brains. The right half is from the brain of a patient who died with Huntington’s disease (this is a different patient from the one presented in Case 16.1). The left half is from the brain of a normal individual who died in an automobile accident. Note that the patient with Huntington’s disease had severe atrophy of the caudate nucleus and putamen, as well as some atrophy of the nucleus accumbens and cerebral cortex.

CASE 16.1 UNILATERAL FLAPPING AND FLINING

Figure 16.11. Ring-enhancing toxoplasmosis lesion in left subthalamic nucleus. Coronal T1-weighted MRI with intravenous gadolinium.

CASE 16.3 ASYMMETRICAL RESTING TREMOR, RIGIDITY, BRADYKINESIA, AND GAIT DIFFICULTIES

CHIEF COMPLAINT

A 53-year-old right-handed man was referred for a second opinion regarding progressive bradykinesia, tremor, rigidity, and unsteady gait.

HISTORY

The patient had been well until 10 years previously, when, while working as a fireman, he had noticed some slowing and difficulty using his right arm. This symptom gradually progressed, and 2 years later he had to change jobs and begin working for the phone company. In the interim he developed occasional shaking of the right arm and right leg. He saw a neurologist, who diagnosed him with Parkinson's disease.

Treatment with levodopa plus carbidopa (Sinemet) provided significant benefit. Bromocriptine (a dopaminergic agonist) was also helpful. He was later enrolled in an experimental trial of deprenyl (selegiline) plus vitamin E, but his symptoms gradually continued to worsen. The tremor spread to involve his whole body, and he became progressively slower and stiffer, complaining that he often had difficulty initiating movements.

He had no family history of Parkinson’s disease, and no history of use of dopaminergic antagonist medications, toxin exposure, strokes, or encephalitis. CT and MRI scans were normal, and blood tests for Wilson’s disease were negative.

PHYSICAL EXAMINATION

Vital signs: T = 97.1°F; P = 80, BP = 130/80, R = 14.

Skin: Slightly oily and flaky, with ceruminous buildup in ear canals.

Nose: S Teresa with no crusts.

Lungs: Clear.

Heart: Regular rate with no murmurs, gallops, or rubs.

Abdomen: Normal bowel sounds; nontender.

Extremities: No edema.

Neurologic exam:


Cranial nerves: Normal, except for masklike decreased facial expression and slightly hoarse speech.

Motor: 4 Hz tremor of the head and all extremities, worse on the right side and worse at rest.

Cogwheel rigidity, especially of the right arm. Finger tapping and rapid alternating movements slow bilaterally. No pronator drift. 6/5 power throughout.

Reflexes: No extinction of the glabellar reflex (positive Myerson's sign).

Discussion

The key symptoms and signs in this case are:

- Asymmetrical bradykinesia, cogwheel rigidity, and resting tremor
- Stooped gait with short steps, decreased arm swing, in bloc turning, and retropulsion
- The significant benefit from levodopa
- Gradual progression over a period of years
1. This patient had all of the typical core features of idiopathic Parkinson’s disease listed earlier (see KCC 16.1, 16.2), so this is the most likely diagnosis. No atypical features, such as asymmetrical findings, absence of resting tremor, impaired vertical eye movements, orthostatic hypotension, or atypical psychiatric features, lack of response to levodopa were present. The gradual progression makes acute causes, such as drug exposure, unlikely. Other associated features seen in this patient, such as the masked facies, hypophonia, micrographia, and Meyerson’s sign are consistent with parkinsonism, but are not specific to idiopathic Parkinson’s disease.

2. Parkinson’s disease is caused by loss of dopaminergic neurons in the substantia nigra pars compacta. Pathologic changes typical of Parkinson’s disease are shown in Figure 16.10. Dopaminergic neurons in the substantia nigra normally project to the striatum. A review of Figure 16.7 shows that loss of dopaminergic innervation of the direct pathway and loss of dopaminergic inhibition of the indirect pathway both ultimately result in more arbitrary output from the internal segment of the globus pallidus (and the substantia nigra pars reticulata) to the thalamus. This, in turn, leads to less excitatory activity from the thalamus to the motor and premotor cortices, resulting in a hypokinetic movement disorder.

Problems with On-Off Fluctuations

In taking the history from this patient, the examiner uncovered another problem in addition to the hypokinesia. Escalating doses of Sinemet, amantadine, and dopaminergic agonists had helped his symptoms somewhat. However, he was having more and more problems with fluctuations, from being “on” after a dose of Sinemet to “off” just before a dose. When “off,” he could not rise from a chair unassisted, had some trouble walking, occasionally “freezing” in place, had difficulty rolling over in bed, was slow in using utensils and carrying out hygiene activities, and could not button his shirt without assistance. When “on,” he still had difficulties walking and carrying out his daily activities, as well as excessive jerky involuntary movements (dyskinesias) of all limbs. Despite the use of a sustained-release formulation, or frequent small doses, the therapeutic window had gradually narrowed, and his on-off symptoms were becoming more severe.

When examined at a different time in relation to his Sinemet dose from the exam described above, the patient had bilateral hypokinetic dyskinesias and no tremor. Rigidity and bradykinesia were improved but still present, worse on the right than the left.

1. How might excess dopamine cause the hypokinetic dyskinesias seen in this patient? (See Figure 16.17.)

2. Given the unacceptable response to medications in this patient, what nonsurgical procedure might be tried to improve his hypokinetic parkinsonian movements? Why is this procedure expected to benefit hypokinesia?

Discussion

1. We have just seen how too little dopamine in the nigrostriatal projections could cause the hypokinetic features of Parkinson’s disease (see Figure 16.7). Conversely, too much dopamine acting on striatal neurons of both the direct and the indirect pathways could inhibit the internal segment of the globus pallidus, thereby reducing the inhibitory output to the thalamus. With less inhibition of the thalamus, thalamocortical projections to motor and premotor cortex would be more active, resulting in hyperkinesia.

2. Pallidotomy has been used in recent years to treat medically refractory parkinsonism (see KCC 16.4). In this procedure a lesion is placed stereotactically in the ventral posterior globus pallidus (see Figures 16.7, 16.9). This interrupts the inhibitory output from the globus pallidus to the thalamus, leading to increased thalamocortical excitatory activity to motor and premotor cortex, and less hypokinesia. It is not known why this procedure does not produce a hyperkinetic movement disorder. In fact, for unclear reasons, pallidotomy actually causes a marked improvement in medication-related hyperkinetic dyskinesias. Another procedure that is beneficial and has been used more frequently in recent years for treating refractory parkinsonism is implantation of a subthalamic stimulator (see KCC 16.4).

Clinical Course and Neuroimaging

After reviewing this patient’s history and his increasingly narrow therapeutic window in response to medications, a stereotactic pallidotomy was recommended. This was performed on the left side because his parkinsonism was worse on the right. The surgery was done with mild sedation and local anesthetics so the patient could remain awake and be tested neurologically during the procedure. An MRI was done with the stereotactic frame in place, and he was then taken to the operating room without the frame being removed. The MRI was used to calculate the coordinates of the left globus pallidus with respect to the frame. A small burr hole was then placed in the left frontal bone, the dura was opened, and an electrode was advanced by 2 mm increments until it reached the internal segment of the left globus pallidus. After a permanent lesion was created in this area, the location of the electrode tip was tested by passage of a high-frequency electrical stimulus. This caused reversible dysfunction of the cells near the electrode tip, resulting in a dramatic improvement in the patient’s right-sided bradykinesia and rigidity. In addition, no visual changes or hemiparesis occurred, indicating that the electrode tip was not too close to the optic tract or internal capsule,

respectively (see Figure 16.4D). A permanent lesion was next created by the passage of sufficient current to heat the electrode tip to 70°C.

A postoperative brain MRI is shown in Figure 16.14A, just ventral to the left globus pallidus (see Figure 16.14B). One day after surgery, the patient no longer had any tremor on the right side, the tremor on the left was decreased, and he had only a single episode of mild dyskinesia lasting about 30 minutes. He also showed marked improvement in his rigidity, and his gait was faster, with larger steps and increased arm swing. Three months after surgery he was seen in follow-up while taking the same medications. He continued to enjoy a marked improvement in his symptoms, saying, “I’m doing a lot, lot better. I can walk. I can walk straight, and people don’t look at me like I’m a weirdo anymore.” He was on for about 14.5 hours per day, and off for only 2 hours per day. He had dyskinesias for about 5 to 10 hours, but these were much milder than preoperatively and did not interfere with his activities. On exam, his speech was normal, he had no tremor, he had mild facial bradykinesia, mild dyskinesias of the left leg, minimal rigidity on the right side, moderate rigidity on the left side, mild slowing of finger tapping. He was able to rise from a chair without difficulty and had a normal gait.
CASE 16.4 BILATERAL BRADYKINESIA, RIGIDITY, AND GAIT INSTABILITY WITH NO TREMOR

MINICASE
A 48-year-old woman gradually developed difficulty with handwriting and typing, saying that her fingers were stiff and slow. In addition, her gait became unsteady, and she had several falls. She was treated with levodopa plus carbidopa with no significant benefit. When examined 5 years after symptom onset, she had a normal mental status, slow saccades, masked facies, slow dysarthric speech, prominent bilateral bradykinesia and rigidity, especially of the axial and neck muscles, no tremor, and a slow shuffling gait with retropulsion. There was no evidence of autonomic dysfunction, ataxia, or dementia. Although saccades were slow in the vertical direction, there was no significant limitation of up- or downgaze.

LOCALIZATION AND DIFFERENTIAL DIAGNOSIS
1. On the basis of the symptoms and signs shown in bold above, is this patient more likely to have typical idiopathic Parkinson's disease or atypical parkinsonism (see KCC 16.1, 16.2)?
2. What is the most likely diagnosis?
3. Which neurons degenerate in this condition? How does this result in a hypokinetar movement disorder? Refer to Figure 16.7, explain why patients with this disorder usually do not respond very well to levodopa therapy.

Discussion
The key symptoms and signs in this case are:
- Bilateral bradykinesia and waxy rigidity
- No tremor
- Gait slow, shuffling with retropulsion (parkinsonian gait)
- No significant benefit from levodopa
- Gradual progression over a period of years
- Masked facies, slow saccades, slow dysarthric speech

1. Bilaterally symmetrical symptoms, absence of tremor, and lack of response to levodopa make this a case of atypical parkinsonism (see KCC 16.1, 16.2).

2. In most of the disorders listed in Table 16.5, there are other significant abnormalities in addition to atypical parkinsonism. Atypical parkinsonism alone, without other significant abnormalities, can be seen in striatal degeneration (a form of multisystem atrophy). Drug-induced parkinsonism is another possibility; however, the patient's gradual progression does not fit this etiology. The masked facies, slow saccades, and dysarthria are nonspecific findings present in most parkinsonian disorders. In conclusion, the most likely diagnosis is striatal degeneration.

3. In striatal degeneration, as in idiopathic Parkinson's disease, there is loss of dopaminergic neurons from the substantia nigra pars compacta. The result is more inhibitory activity to the thalamus from the internal globus pallidus and substantia nigra pars reticulata, causing a hypokinetar movement disorder (see Figure 16.7). In idiopathic Parkinson's disease, this dopamine deficiency can be corrected by the administration of levodopa. The medication levodopa is converted to dopamine in the brain, which can then act on striatal neurons (see Figure 16.7). In striatal degeneration, however, the striatal neurons degenerate as well. Therefore, administration of levodopa is usually not as beneficial to these patients as in Parkinson's disease.

Clinical Course and Postmortem Examination
The patient's dysarthria, dysphagia, bilateral bradykinesia, and rigidity without tremor continued to progress. Six years after symptom onset, she underwent pallidotomy (see KCC 16.4), which provided only some transient relief. As well, these findings are typical for Huntington's disease. (b) Normal MRI scan from a different patient at the same plane of section for comparison. Note the normal convex shape of the lateral ventricle walls, formed by the bulges of the heads of the caudate nuclei.

Figure 16.12 Atrophy of Caudate Head Associated with Huntington's Disease: (a) Coronal T1-weighted MRI scan. (b) The lateral ventricular walls have an abnormal concave shape due to severe atrophy of heads of the caudate nuclei as well as the putamen. The cortex is slightly atrophied.
Some cortical atrophy is present as well. For comparison, the left half-section is from a patient who died of Huntington's disease. The caudate and putamen are markedly atrophied.

Benefit. She eventually became bedridden and died of aspiration pneumonia, 7 years after initial symptoms.

In accordance with the patient's previously stated wishes, her family consented to an autopsy. On examination of brain sections by eye, the substantia nigra appeared somewhat pale (similar to left side of Figure 16.10A). In addition, the caudate, putamen, and external segment of the globus pallidus were markedly atrophied (Figure 16.15). Microscopic examination of the substantia nigra revealed marked loss of pigmented neurons, and an increase in glial cells (Figure 16.16A) when compared to a normal control (see Figure 16.16B). However, unlike the typical findings in Parkinson's disease, Lewy bodies were not present. Microscopic examination of the striatum also showed marked neuronal loss and gliosis (see Figure 16.16C) compared to a normal control (see Figure 16.16D). Some atrophy was also found in the external segment of the globus pallidus, subthalamic nucleus, and internal capsule, and cerebellum. These findings were compatible with a diagnosis of multisystem atrophy of the striatonigral degeneration type.

**CASE 16.3 ASYMMETRICAL RESTING TREMOR, RIGIDITY, BRADYKINESIA, AND GAIT DIFFICULTIES**

Figure 16.14 Left Pallidotomy Performed for Advanced Parkinson's Disease: Horizontal T1-weighted MRI scans. A and B are adjacent horizontal sections progressing from inferior to superior. (A) Stereotactically placed lesion is visible. (B) By comparison with A, it can be seen that the lesion was placed along the ventral edge of the globus pallidus.
CASE 16.4 BILATERAL BRADYKINESIA, RIGIDITY, AND GAIT INSTABILITY WITH NO TREMOR

Figure 16.15 Gross Pathologic Changes in a Patient with Striatonigral Degeneration. Coronal brain sections; A, B progress from anterior to posterior. Note the severe atrophy of the striatum, including the caudate and putamen. The external segment of the globus pallidus appears atrophied as well.

(A)  
(B)  

CASE 16.4 (CONTINUED)

Figure 16.16 Microscopic Pathologic Changes in a Patient with Striatonigral Degeneration. (A) Substantia nigra specimen from a normal control showing darkly pigmented dopaminergic neurons (arrow). (B) In a substantia nigra specimen from the patient in Case 16.4, no dopaminergic neurons are visible, and there is an increase in the number of glial cells: the small, darkly staining nuclei are in oligodendrocytes (black arrows); the paler ovoid nuclei are in astrocytes (white arrows). (C) Striatal specimen from a normal control showing many stained neurons (arrows). (D) Striatal specimen from the patient in Case 16.4 shows neuronal loss and gliosis, including oligodendrocytes (black arrows) and astrocytes (white arrows).
Brief Anatomical Study Guide

1. Like the cerebellum, the basal ganglia provide complex feedback loops that influence descending motor pathways, as well as other functions. The main components of the basal ganglia are the caudate nucleus, putamen, globus pallidus, subthalamic nucleus, and substantia nigra (see Table 16.1; Figures 16.1, 16.2). The striatum includes the caudate and putamen, while the lentiform nucleus includes the putamen and globus pallidus. The three-dimensional relationships of these structures are best appreciated through examination of horizontal (see Figure 16.3) and coronal (see Figure 16.4) brain sections. Note that in horizontal sections (see Figure 16.3), the internal capsule forms a sideways V-shaped demarcation with the thalamus and caudate nucleus lying medial to the internal capsule, and with the lentiform nucleus lying lateral.

2. The main input and output connections of the basal ganglia are summarized in Figures 16.5 through 16.7. Briefly, all inputs, including inputs from motor and premotor cortex, dopaminergic inputs from the substantia nigra pars compacta, and inputs from the thalamic intralaminar nuclei enter the basal ganglia circuitry via the striatum (see Figure 16.5). All outputs, including those to the thalamic ventral anterior (VA) and ventral lateral (VL) nuclei, other thalamic nuclei, brainstem reticular formation, and tectum leave via the internal segment of the globus pallidus and the substantia nigra pars reticulata (see Figure 16.6).

3. The intrinsic connections of the basal ganglia circuitry can be divided into a direct pathway from the striatum to the output nuclei, and an indirect pathway that reaches the output nuclei via a detour through the subthalamic nucleus (see Figure 16.7).

4. Understanding the neurotransmitters and intrinsic connections of the basal ganglia as depicted in Figure 16.7 provides a theoretical framework for understanding hyperkinetic movement disorders such as Huntington's disease, and hypokinetic movement disorders such as Parkinson's disease. In hyperkinetic movement disorders the inhibitory output from the basal ganglia to the thalamus (and hence to the cortex) is decreased, leading to a relative disinhibition of descending motor systems. Examples include lesions of the subthalamic nucleus such as stroke causing hemiballismus, or loss of inhibitory GABAergic neurons from the striatal neurons of the indirect pathway in early Huntington's disease. In hypokinetic movement disorders the inhibitory output from the basal ganglia to the thalamus is increased, resulting in a relative paucity of movements. Examples include degeneration in Parkinson's disease of dopaminergic neurons projecting from the substantia nigra pars compacta to the striatum.

5. In addition to general motor functions, the basal ganglia are also involved in ovo movements, fronto-executive function, and limbic pathways; these four parallel channels through the basal ganglia circuitry are summarized in Table 16.2 and Figure 16.8. The inputs to the general motor channel enter mainly via the putamen, while those for the oculo-motor and prefrontal channels enter via the body of the caudate and the head of the caudate, respectively.

Brief Anatomical Study Guide (continued)

Limbic channel involves ventral structures such as the nucleus accumbens (part of the ventral striatum) and ventral pallidum. Because of these multiple basal ganglia pathways, the clinical manifestations of basal ganglia disorders often include prominent oculomotor, cognitive, and psychiatric manifestations in addition to disorders of movement.

Additional Cases

Related cases can be found in other chapters for the following topics: movement disorders, ataxia, or related syndromes (Cases 5.7, 5.9, 13.2, 16.1, 14.4, 14.7, 15.1–15.4, 18.5, 19.7). Other relevant cases can be found using the Case Index.

References

Anatomy and Circuit Connections of the Basal Ganglia


General Movement Disorders


Hemichorea or Hemiballismus


Tourette's Syndrome


Wilson's Disease


Tremor


Parkinson's Disease and Related Disorders


Huntington's Disease


Stereotactic Surgery and Movement Disorders


CHAPTER 17

Pituitary and Hypothalamus

The hypothalamus and pituitary exert complex and fine control over the endocrine system, but because of their anatomical relations to adjacent structures, pituitary or hypothalamic lesions can cause visual deficits as well. A 50-year-old woman developed gradually worsening vision problems over the course of several months that eventually interfered with her driving. She also had a long-standing history of menstrual irregularity and infertility. Her examination was normal except for decreased vision bilaterally, primarily in the temporal portions of her visual fields. Eventually, it was discovered that this patient had a lesion in the pituitary region compressing her optic chiasm. In this chapter we will learn about the anatomy and neuroendocrine functions of the hypothalamus and pituitary and clinical ramifications of lesions in these structures.
ANATOMICAL AND CLINICAL REVIEW

The pituitary and hypothalamus constitute a unique region of the nervous system. In addition to communicating through conventional synaptic transmission, both of these structures utilize soluble humoral factors as a major source of afferent and efferent information. The pituitary and hypothalamus form the link between the neural and endocrine systems. In addition, the hypothalamus is the central regulator of homeostasis (mnemonic: Hypothalamic Homeostasis), and has been informally nicknamed the "homeostatic head ganglion." The hypothalamus maintains homeostasis in the body by interacting with and exerting important regulatory influences over four other systems, thereby participating in:

1. **Homeostatic mechanisms controlling hunger, thirst, sexual desire, sleep–wake cycles, etc.**
2. **Endocrine control, via the pituitary**
3. **Autonomic control**
4. **Limbic mechanisms** (see Chapter 18).

(Mnemonic: HEAL)

In the sections that follow, we will first review the overall anatomy of the pituitary and hypothalamus. Then we will discuss the major hypothalamic nuclei and their roles in each of the above functions, focusing in most detail on neuroendocrine control of pituitary hormones. Finally, we will review the clinical effects of pituitary and hypothalamic dysfunction.

Overall Anatomy of the Pituitary and Hypothalamus

The pituitary, or hypophysis, is derived from two different embryological pouches (Figure 17.1). The **anterior pituitary**, or **adenohypophysis**, is formed by a thickened area of ectodermal cells on the roof of the developing pharynx that invaginates, forming Rathke's pouch. The **posterior pituitary**, or neurohypophysis, forms from an evagination of the floor of the developing ventricular system. The anterior pituitary contains glandular cells that secrete a variety of hormones into the circulation. Release of hormones from the anterior pituitary is controlled by the hypothalamus through factors carried in a specialized vascular portal system, as we will discuss later (see Figure 17.5). The posterior wall of Rathke's pouch forms a small recess called the intermediate lobe of the pituitary (Figure 17.1D), which has less prominent endocrine functions in humans. The posterior pituitary does not contain glandular cells. Instead, it contains axons and terminals of neurons whose cell bodies are located in the hypothalamus. These terminals in the posterior pituitary secrete the hormones oxytocin and vasopressin into the circulation.

The **hypothalamus** is part of the diencephalon, and it is located under the thalamus (Figure 17.2A). The hypothalamus forms the walls and floor of the inferior portion of the third ventricle (see Figure 17.2A). The hypothalamus is separated from the thalamus by a shallow groove on the wall of the third ventricle called the portal hypophyseal sulcus. On the ventral surface of the brain (see Figure 17.2B), the hypothalamus can be seen just posterior to the optic chiasm (optic chiasm and mammillary bodies) although portions of the hypothalamus are located dorsal to the optic chiasm as well (see Figure 17.3). The **tuber cinereum**, meaning "gray protuberance," is a bulge located between the optic chiasm and the mammillary bodies. The mammillary bodies are paired structures that form the posterior portion of the hypothalamus. The **infundibulum**, meaning "funnel," arises from the tuber cinereum and continues inferiorly as the

**pituitary stalk** (see Figure 17.2A). The anterior portion of the infundibulum is slightly elevated and is called the **median eminence**. The median eminence is the region where hypothalamic neurons release regulating factors that are carried by portal vessels to the anterior pituitary (see Figure 17.3).

The pituitary gland lies within the **pituitary fossa** (see Figures 12.1, 12.2A). The pituitary fossa is bounded by the **anterior clinoid process** and the **posterior clinoid process**, which, together with the intervening portions of the sphenoid bone, form the fancifully named sella turcica, meaning "Turkish saddle." Just beneath the floor of the sella turcica lies the **sphenoid sinus**, allowing the pituitary fossa to be accessed by a transsphenoidal surgical approach (see KCC 17.1). Within the pituitary fossa the pituitary is surrounded by dura. The dura covering the superior portion of the pituitary fossa is called the **diaphragma sella**, and the pituitary stalk communicates with the main cranial cavity through a round hole in the middle of the diaphragma sella (see Figure 10.11B). The pituitary fossa is bounded laterally on both sides by the ** cavernous sinus** (see Figure 13.11). Note that the pituitary and other sellar and suprasellar structures lie just behind and inferior to the optic chiasm (see Figure 17.2). Tumors in this region therefore can compress the optic chiasm, causing visual problems, including **bitemporal hemianopia** (see KCC 11.2).

**REVIEW EXERCISES**

1. Which of the following is derived embryologically from Rathke's pouch and which from the prosencephalon?
   A. Anterior pituitary
   B. Posterior pituitary

2. Enlargement of the pituitary by a tumor may compress which structure of the visual pathway?
Important Hypothalamic Nuclei and Pathways

In this section we will discuss the anatomy of the major hypothalamic nuclei and the hypothalamic regions that specialize in homeostatic, autonomic, and endocrine functions. The neuroendocrine functions of the hypothalamus will be discussed in detail in the next section.

**Major Hypothalamic Nuclei**

The hypothalamic nuclei can be divided into four major regions, from anterior to posterior (Figure 17.3) and into two different medial and lateral areas (Figure 17.4). The fibers of the fornix pass through the hypothalamus on the way to the mammillary body, dividing the hypothalamus into a medial hypothalamic area and a lateral hypothalamic area (see Figure 17.4). The lateral hypothalamic area consists of the lateral hypothalamic nucleus and several smaller nuclei. The medial forebrain bundle is a diffuse group of fibers running rostrocaudally through the lateral hypothalamic area, which carries many connections to and from the hypothalamus, and between other regions. The medial hypothalamic area consists of several different nuclei (Table 17.1; see Figures 17.3, 17.4). Most medially, the periventricular nucleus is a thin layer of cells that lies closest to the third ventricle. The preoptic area is derived embryologically from the telencephalon, while the hypothalamus is derived from the diencephalon. Nevertheless, the preoptic area is functionally part of the hypothalamus. The lateral preoptic nucleus and medial preoptic nucleus (see Figure 17.4A) are the rostral continuations of the lateral and medial hypothalamic areas, respectively.

The remaining medial hypothalamic area can be divided into three regions, from anterior to posterior (see Table 17.1; Figures 17.3, 17.4). The anterior hypothalamic region, or supraoptic region, includes the anterior hypothalamic nucleus, supraoptic nucleus, paraventricular nucleus, and suprachiasmic nucleus (see Figures 17.3, 17.4B). Some neurons located in both the supraoptic and the paraventricular nuclei contain oxytocin or vasopressin and project to the posterior pituitary (see Figure 17.5). The suprachiasmic nucleus is the "master clock" for circadian rhythms. It receives inputs from retinal ganglion cells conveying information about day-night cycles. The middle hypothalamic region, or tuberal region (see Table 17.1; Figures 17.3, 17.4C), includes the arcuate nucleus, ventromedial nucleus, and dorsomedial nucleus. The arcuate nucleus is one of the hypothalamic nuclei projecting to the median eminence to control the anterior pituitary. The posterior hypothalamic region, or mammillary region (see Table 17.1; Figures 17.3, 17.4D), includes the medial mammillary nucleus, intermediate mammillary nucleus, lateral mammillary nucleus, and posterior hypothalamic nucleus.

**Hypothalamic Control of the Autonomic Nervous System**

The hypothalamus has important descending projections that influence both the sympathetic and the parasympathetic divisions of the autonomic nervous system. Descending autonomic fibers originate mainly from the paraventricular nucleus, but also from the dorsomedial hypothalamic nucleus and from the lateral and posterior hypothalamus. The descending autonomic fibers initially travel in the medial forebrain bundle, and then in the dorsolateral bundle to the brainstem and peripheral ganglia. Ultimately they synapse onto preganglionic parasympathetic nuclei in the brainstem and intermediolateral column of the spinal cord.

**REVIEW EXERCISE**

What are the four major types of functions carried out by the hypothalamus (mnemonic: HEAL)?
the sacral spinal cord, and orto preganglionic sympathetic neurons in the intermedio-lateral cell column of the thoracolumbar spinal cord (see Figures 6.12, 6.13). Aside from the descending autonomic pathways from the hypothalamus, there are also descending autonomic pathways from several brainstem nuclei, including the nucleus solitarius, rostroventromedial nucleus, raphe nuclei, and pontomedullary reticular formation. Many of these nuclei also receive inputs from the hypothalamus.

Inputs to the hypothalamus that regulate autonomic function come from numerous synaptic and hormonal sources. One important source of input is the amygdala and certain regions of the limbic cortex (see Chapter 18), including the orbital frontal, insular, anterior cingulate, and temporal cortex.

### Hypothalamic-Limbic Pathways

The limbic system and its connections with the hypothalamus will be discussed in detail in Chapter 18. Here we will simply mention the main input and output connections between the limbic system and the hypothalamus. The subiculum of the hippocampal formation, a limbic structure, projects to the mammillary bodies of the hypothalamus via the fornix. Meanwhile, the mammillary bodies project via the mammillothalamic tract to the anterior thalamic nucleus, which in turn projects to limbic cortex in the cingulate gyrus. The amygdala, another important limbic structure, has reciprocal connections with the hypothalamus via two pathways: the stria terminalis and the ventral amygdalofugal pathway. The limbic-hypothalamic interconnections are important for emotional influences on autonomic pathways (explaining why your palms get sweaty and your stomach churns when you are anxious) and on homeostatic pathways, including the immune system (explaining why depressed individuals may be more susceptible to infection). In addition, connections from the hypothalamus to limbic pathways may enable complex motivational and emotional programs to be activated in the service of homeostatic and reproductive functions.

### Other Regionalized Functions of the Hypothalamus

In addition to its roles in endocrine, autonomic, and limbic function, the hypothalamus is important in regulating a variety of appetitive, homeostatic, and other behaviors that are often essential to survival of the organism. The regional aspects of these functions have been studied predominantly through lesion and stimulation studies in animals. However, evidence is also accumulating for similar localization in many of these functions in human beings as well. As we have already mentioned, the suprachiasmatic nucleus in the anterior hypothalamus (see Figures 17.3, 17.4) is an important regulator of circadian rhythms. Recall also that GABAergic neurons in the ventral lateral preoptic area (VLPO) contribute to nonREM sleep by inhibiting histaminergic neurons in the tuberomammillary nucleus (TMMN) (see Figure 14.33, 14.15A). The lateral hypothalamus is important in appetite, and lateral hypothalamic lesions cause a decrease in body weight. Conversely, the medial hypothalamus, especially the ventromedial nucleus, appears to be important in inhibiting appetite, and medial hypothalamic lesions can cause obesity. Recently, leptin, a hormone that is produced by adipose tissue, was discovered. Leptin binds to receptors in the hypothalamic nuclei of the ventromedial hypothalamus (Ob receptors) and plays an important role in feedback regulation of food intake and obesity. Thirst appears to result from the activation of osmoreceptors in the anterior regions of the hypothalamus. Hypovolemia or elevated

**Body temperature can also activate thirst. Lesions of the lateral hypothalamus decrease water intake.**

**Thermoregulation** involves the control of multiple systems, including sweat production, smooth muscles that affect core and surface blood flow, skeletal muscles involved in shivering, panting, and other motor activity, and endocrine systems that control the metabolic rate. The anterior hypothalamus appears to detect increased body temperature and activates mechanisms of heat dissipation. Anterior hypothalamic lesions can cause hyperthermia. In contrast, the posterior hypothalamus functions to conserve heat. Bilateral lesions of the posterior hypothalamus usually cause poikilothermia, in which the body temperature varies with the environment because these lesions destroy both heat conservation mechanisms of the posterior hypothalamus and descending pathways for heat dissipation arising from the anterior hypothalamus. The hypothalamus probably also participates in circuitry involved in sexual desire and other complex motivational states. In addition, sexual development and differentiation involves an interplay of neural and endocrine signals, many of which appear to be regulated by the hypothalamus.

### Endocrine Functions of the Pituitary and Hypothalamus

The anterior pituitary produces six important hormones, many of which regulate endocrine systems in other parts of the body, such as the adrenal cortex, thyroid, and gonads. These anterior pituitary hormones are adrenocorticotrophic hormone (ACTH), growth hormone (GH), prolactin, thyroid-stimulating hormone (TSH), luteinizing hormone (LH), and follicle-stimulating hormone (FSH) (Table 17.2). The intermediate lobe is rudimentary in

| TABLE 17.2 Anterior Pituitary Hormones and Hypothalamic Releasing and Inhibitory Factors |
|---------------------------------|---------------------------------|---------------------------------|
| **PITUITARY HORMONE** | **HYPOTHALAMIC** | **HYPOTHALAMIC** |
| | **RELEASING FACTORS** | **INHIBITORY FACTORS** |
| Adrenocorticotrophic hormone (ACTH) | Corticotropin-releasing hormone (CRH), vasopressin, and other peptides |  |
| Thyroid-stimulating hormone (TSH) | Thyrotropin-releasing hormone (TRH) | Growth hormone-inhibiting hormone (GHI) |
| Growth hormone (GH) | Growth hormone-releasing hormone (GHRH) | Growth hormone-inhibiting hormone (GHI) |
| Prolactin | Prolactin-releasing factor (PRF) and thyrotropin-releasing hormone (TRH) | Prolactin-releasing-inhibiting factor (PIF) |
| Luteinizing hormone (LH) | Luteinizing hormone-releasing hormone (LHRH) |  |
| Follicle-stimulating hormone (FSH) | Follicle-stimulating hormone-releasing hormone (FSHRH) |  |

**REVIEW EXERCISE**

What are the effects of lateral hypothalamic lesions vs. medial hypothalamic lesions on body weight? What are the effects of anterior hypothalamic lesions vs. posterior hypothalamic lesions on temperature control?
Name 6 hormones released in the anterior pituitary and 2 hormones released in the posterior pituitary. What kind of cells (glandular cells or neurons) release the anterior pituitary hormones? Where in the hypothalamus are the inhibitory and releasing factors released and how do they reach the anterior pituitary? What kind of cells release the posterior pituitary hormones, and what are the names of the nuclei where their cell bodies are located?

Humans, produces pro-opiomelanocortin (POMC) and melanocyte-stimulating hormone (MSH), and has little known clinical significance. Two hormones are released in the posterior pituitary: (1) oxytocin and (2) vasopressin, which is also called arginine vasopressin (AVP) or antiuretic hormone (ADH).

Release of the anterior pituitary hormones by glandular cells is controlled by neurons in the hypothalamus through the hypophyseal portal system (Figure 17.5). The pituitary receives arterial blood from the inferior and superior hypophyseal arteries, which are both branches of the internal carotid artery. The first capillary plexus of the portal system occurs in the median eminence. Neurons lying adjacent to the third ventricle in several hypothalamic nuclei project to the median eminence, where they secrete inhibitory and releasing factors (see Table 17.2). Nuclei projecting to the median eminence include the arcuate nucleus, periventricular nucleus, medial preoptic nucleus, and medial parvocellular portions of the paraventricular nucleus.

Inhibitory and releasing factors enter the capillary plexus of the median eminence (see Figure 17.5; see also Figure 5.15) and are carried by the hypothyalamic portal veins to the anterior pituitary. Most of these factors are peptides, except for prolactin release-inhibiting factor (PIF), which is dopamin (see Table 17.2). Hormones released in the anterior pituitary are picked up by the secondary capillary plexus of the portal system and carried by draining veins to the cavernous sinus. Recall that the cavernous sinus drains primarily via the superior and inferior petrosal sinuses to reach the internal jugular vein (see Figure 10.11.A, B).

The posterior pituitary also has a capillary plexus (see Figure 17.5), which picks up oxytocin and vasopressin and carries these hormones into the systemic circulation. Oxytocin and vasopressin are secreted in the posterior pituitary by terminals of neurons whose cell bodies lie in the supraoptic and paraventricular nuclei. Both nuclei contain both hormones, but different neurons appear to contain either oxytocin or vasopressin.

We will now briefly review the most important functions of each of the pituitary hormones (Figure 17.6). ACTH stimulates the adrenal cortex to produce corticosteroids, especially the glucocorticoid hormone cortisol, and to a lesser extent the mineralocorticoid hormone aldosterone. These steroid hormones are important for maintaining blood pressure, controlling electrolyte balance, promoting glucose mobilization into the blood.
growth hormone release (see Table 17.2) and shrinks tumors. Treatment of prolactin-secreting or growth hormone-secreting tumors with medications has generally been disappointing. Surgical resection offers the advantages of potential immediate cure and relatively low risk. Surgery is also used for prolactin-secreting or growth hormone-secreting tumors that do not respond adequately to medical therapy. Usually, a transphenoidal approach is taken, in which, under general anesthesia, the floor of the pituitary fossa is entered through the roof of the sphenoid sinus (see Figure 12.1), with instruments inserted through the nose. With suprasellar pituitary tumors (extending above the sella turcica), an intracranial approach is often necessary to attain adequate tumor removal. Radiotherapy is used mainly for cases that fail to respond to surgery, although use of this treatment such as proton beam therapy and the gamma knife are being investigated as alternatives to surgery.

Let's discuss the clinical presentation and diagnosis of each type of hormone-secreting pituitary adenoma. Prolactin-secreting adenomas typically cause amenorrhea in women, hypogonadism in men, and galactorrhea, infertility, hair loss, decreased libido, and weight gain in both sexes. Some of these effects of elevated prolactin are mediated by inhibition of hypothalamic LHRH, which in turn leads to decreased LH and FSH levels (see Table 17.2). In normal women this effect of prolactin on LH and FSH delays the resumption of menses during lactation. As with all other pituitary tumors, headache and visual symptoms can also occur.

Elevated prolactin levels can have many causes, but very high levels (>150 micrograms per liter in nonpregnant patients) are virtually diagnostic of pituitary adenoma. MRI is useful for diagnosis and can now be used to detect microadenomas as small as 0.5 mm in diameter through indirect effects on pituitary shape, although smaller tumors may not be visualized despite significant endocrine abnormalities. Hypothalamic lesions can also sometimes cause elevated prolactin levels due to decreased PIF (dopamine) production, but the increase is not as high as is typically seen in pituitary adenomas.

Growth hormone-secreting adenomas cause acromegaly, a slowly progressive overgrowth of bones and soft tissues, with facial features and a protuberant jaw. Gigantism occurs if growth hormone excess begins before epiphyseal closure in adolescence. Other common problems in patients with growth hormone excess include carpal tunnel syndrome, arthropathy, infertility, hypertension, and diabetes. Diagnosis is by typical clinical features, elevated GH levels of greater than 2 micrograms per liter even after glucose administration, and MRI.

ACTH-secreting adenomas cause Cushing's disease. Cushing's syndrome is a general term for the clinical features of glucocorticoid excess of any cause, including endogenous cortisol excess or exogenous administration of glucocorticoid medications (as prednisone, methylprednisolone, dexamethasone, or hydrocortisone). Prolactinomas are most commonly associated with Cushing’s disease, and approximately 30% of all pituitary adenomas are associated with hyperprolactinemia. Nonfunctioning tumors account for about 15% of pituitary adenomas. The most common is growth hormone, followed by ACTH, TSH, LH, and PSH-secreting tumors. Nonfunctioning tumors account for about 30% of all pituitary adenomas. The most common is growth hormone, followed by ACTH, TSH, LH, and PSH-secreting tumors. Nonfunctioning tumors account for about 30% of all pituitary adenomas. The most common is growth hormone, followed by ACTH, TSH, LH, and PSH-secreting tumors. Nonfunctioning tumors account for about 30% of all pituitary adenomas. The most common is growth hormone, followed by ACTH, TSH, LH, and PSH-secreting tumors. Nonfunctioning tumors account for about 30% of all pituitary adenomas. The most common is growth hormone, followed by ACTH, TSH, LH, and PSH-secreting tumors. Nonfunctioning tumors account for about 30% of all pituitary adenomas. The most common is growth hormone, followed by ACTH, TSH, LH, and PSH-secreting tumors.
maria, psychosis, and depression. Cushings syndrome is caused by primary adrenal adenomas or adenocarcinomas in only about 15% of cases. The remaining 85% are caused by ACTH oversecretion by pituitary adenomas (70%), or by nonpituitary tumors that secrete ACTH, such as bronchial carcinoids (15%), referred to as "ectopic" ACTH production.

A series of endocrinological tests is done to localize the cause of endocrine cortisol excess. The dexamethasone suppression test works on the principle that administration of a dose of dexamethasone at midnight normally acts through negative feedback like cortisol (see Figure 17.7) to suppress cortisol levels or urine cortisol metabolites measured the next morning. A low-dose (1 to 3 milligram) overnight dexamethasone suppression test is often used as an initial screening test for excess cortisol production. If cortisol production is not suppressed with the low-dose test, the high-dose (8-milligram) dexamethasone suppression test is then helpful because ACTH-secreting pituitary tumors are usually suppressible with this dose, while ectopic ACTH-secreting tumors and adrenal tumors are not. Another strategy is to administer CRH (see Figure 17.7; Table 17.2), which causes an excessive rise in plasma ACTH and cortisol in pituitary adenomas but not in ectopic ACTH or adrenal tumors. MRI is useful in diagnosis as well. Finally, when results of these tests are equivocal, petrosal sinus sampling can be helpful to distinguish pituitary from nonpituitary ACTH overproduction. In addition, petrosal sinus sampling can often correctly localize the side of a microadenoma not visible on MRI. In this way, selective surgery on the side of the microadenoma may be possible while function of the remaining pituitary gland is spared.

In petrosal sinus sampling, catheters are inserted through a femoral vein and passed upward under radiological guidance through the internal jugular veins to reach the inferior petrosal sinuses on both sides (see Figure 10.1A,B). Aliquots are first removed to determine baseline ACTH levels. In ACTH-secreting pituitary adenomas, ACTH levels in at least one petrosal sinus should be more than two times the ACTH levels in a peripheral vein. An intravenous dose of CRH (see Figure 17.7) is then given, and ACTH measurements from each inferior petrosal sinus are taken approximately every 5 minutes. A threefold increase in ACTH is diagnostic of a pituitary adenoma. In addition, the ACTH rise is usually 2 to 3 times higher on the side of the tumor than on the contralateral side.

TSH-secreting adenomas are a rare cause of hyperthyroidism, Hyperthyroidism is much more commonly caused by primary thyroid disorders such as Graves' disease, thyroiditis, toxic multinodular goiter, and thyroid adenomas. Clinical manifestations of hyperthyroidism include nervousness, insomnia, weight loss, tremor, excessive sweating, heat sensitivity, increased sympathetic activity, and frequent bowel movements. Thyroid ophthalmopathy can occur, in which there is inflammatory involvement of orbital tissues leading to protrusion, and ultimately extraskeletal muscle fibrosis, which can mimic brainstem or cranial nerve disorders. Other important neurologic manifestations of hyperthyroidism include proximal muscle weakness, tremor, dyskinetias, and dementia. Particularly in the elderly, many of the other manifestations may be absent, and hyperthyroidism can mimic dementia (see KCC 19.16). In hyperthyroidism caused by primary thyroid disorders, TSH levels are completely suppressed, while in TSH-secreting pituitary adenomas, TSH levels are elevated.

Hyperthyroidism is also usually caused by primary thyroid disorders such as autoimmune thyroid disease, iodine deficiency, or previous ablative treatment for hyperthyroidism, and rarely is caused by pituitary or hypothalamic insufficiency. However, when lesions of the hypothalamus or pituitary are present, including medium-to-large pituitary adenomas of any type, it is relatively common for TSH production to be impaired, resulting in hypothyroidism. Manifestations of hypothyroidism of any cause include lethargy, weight gain, cold intolerance, smooth dry skin, hair loss, depression, and constipation. Eventually, myxedema coma and cardiac involvement can occur. Other important neurologic manifestations include neuropsychopathies, carpal tunnel syndrome, myalgias, ataxia, and dementia. Like hyperthyroidism, hypothyroidism can present in the elderly with a dementia or depression-like picture. Untreated hypothyroidism in utero or in infancy can cause cortinism, which is characterized by mental retardation, short stature, microphally, and other abnormalities.

Or FSH-secreting adenomas often cause hypogonadism and infertility, although tumors can reach a relatively large size before being detected clinically. Interestingly, these tumors may produce either high or low testosterone and estradiol levels; however, in either situation, patients have clinical hypogonadism. Because these tumors are often large, patients may present with headache and visual changes as the major manifestations.

Other lesions can also occur in the sellar and suprasellar region, causing endocrine disturbances or compressing the optic chiasm. Although pituitary adenomas are the most common, other lesions seen in this region include cranioopharyngioma, aneurysms, meningioma, optic glioma, hypothalamic glioma, dysembryoma, teratoma, epidermoid, dermoid, Rathke's pouch cysts, empty sella syndrome, sarcoidosis, lymphoma, and metastases.

Diabetes insipidus (DI) is the production of large amounts of dilute urine. This condition can be caused by deficiency of ADH (central or neurogenic DI) or by insensitivity of the kidneys to ADH (nephrogenic DI). Symptoms of DI include severe thirst, polyuria, and polydipsia. Patients who are able to drink consume large amounts of water to maintain fluid balance. Patients who cannot drink adequately become dehydrated rapidly and die if not treated. The diagnosis is made in a patient with polyuria by documentation of relatively low urine osmolality, despite increased plasma osmolality. To protect this condition, sometimes the patient must be asked to temporarily stop drinking while in a supervised setting. A dose of substitutable vasopressin will cause urine osmolality to rise in neurogenic but not in nephrogenic DI. Common causes of neurogenic DI include neurosurgery, head trauma, and infiltrative or neoplastic lesions in the pituitary-hypothalamic region (see KCC 17.1) or in the third ventricle. Interestingly, lesions of the posterior pituitary do not cause DI unless the lesion is high enough in the pituitary stalk to result in retrograde degeneration of hypothalamic neurons in the suprachiasmatic and paraventricular nuclei (see Figure 17.5). This suggests that neurons in these nuclei are capable of releasing vasopressin in locations other than the posterior pituitary. Treatment of DI is with substitutable or intranasal administration of synthetic vasopressin analogs.

In the syndrome of inappropriate antidiuretic hormone (SIADH), excess ADH production causes a low serum sodium (hyponatremia), together with inappropriately elevated urine osmolality. Note that hyponatremia with elevated urine osmolality is not always caused by SIADH, and it can also be seen in hypovolemia or in edematous states such as heart failure or cirrhosis. SIADH can be caused by many neurologic and non-neurologic conditions, including head trauma, meningitis, and numerous other neurologic disorders, pulmonary disorders, medication side effects, and ADH-secreting neoplasms. Severe hyponatremia can cause lethargy, coma, or seizures. When SIADH is
the cause of hypernatremia, it should be treated by restriction of daily fluid intake. In severe cases, infusions of hypertonic saline are sometimes used, but care must be taken not to correct hypernatremia too rapidly because central pontine myelinolysis can result from this approach.

Some conditions can cause the consecutive appearance of SIADH and DI in a single patient. For example, following surgery in the pituitary region there is occasionally a triphasic response, with DI shortly after surgery, followed by SIADH, and finally DI again, which may then gradually improve. Patients with other intracranial disorders, such as catastrophic hemorrhage or infarct, may initially have SIADH. If brain death then ensues, all ADH production ceases, resulting in DI.

17.3 Deficiency of multiple pituitary hormones can occur in several conditions of the pituitary and hypothalamic regions. When all pituitary hormones are involved, the condition is called panhypopituitarism. ACTH deficiency causes hypocorticism, with fatigue, weakness, decreased appetite, and impaired response to stress resulting in hypotension, fever, hypoglycemia, and a high mortality rate. TSH deficiency causes hypothyroidism (see KCC 17.1), and ADH deficiency causes diabetes insipidus (see KCC 17.2). LH and FSH deficiencies cause hypogonadism, including decreased libido, amenorrhea, and infertility. GH deficiency in children causes dwarfism. Prolactin deficiency in women causes inability to lactate.

There are multiple possible causes of panhypopituitarism. Lesions in this region include (see KCC 17.1) large nonfunctioning pituitary adenomas, hypothalamic tumors, metastases, and other infiltrative processes, including sarcoidosis, infections, and autoimmune diseases. On rare occasions, pituitary tumors can undergo spontaneous hemorrhage resulting in pituitary apoplexy. Patients with pituitary apoplexy often present with sudden headache, meningial signs, unilateral or bilateral cavernous sinus syndrome (see KCC 13.7), visual loss, hypotension, and depressed level of consciousness. Panhypopituitarism is a common sequel of pituitary apoplexy. Other causes of panhypopituitarism include head trauma, surgery, radiation therapy, pituitary infarct, and congenital abnormalities.

Panhypopituitarism is treated by exogenous replacement of pituitary hormones. ACTH insufficiency is treated by daily administration of steroids such as prednisone or hydrocortisone, with increased doses given in situations of stress such as infection or surgery. Diabetes insipidus is treated with synthetic ADH analogs, and hypothyroidism is treated with synthetic thyroid hormones. Hypogonadism is treated with testosterone or estrogen-progesterone combinations, and fertility can sometimes be achieved with LH and FSH substitution therapy. GH replacement is used in children; possible beneficial effects of GH replacement in adults are still under investigation.

### CLINICAL CASES

**CASE 17.1 MOON FACES, ACNE, AMENORRHEA, AND HYPERTENSION**

**CHIEF COMPLAINT**
A 33-year-old woman presented to an endocrinology clinic with multiple complaints, including truncal obesity, acne, amenorrhea, and hypertension.

**HISTORY**
Symptoms had begun 3 years previously with increased facial hair, new-onset acne, 45-pound weight gain especially in the abdomen, easy bruising, excessive sweating, and fatigue on her skin. Two years prior to presentation her menstrual periods stopped, and she developed hypertension requiring medication. During recent months she had become irritable and depressed, and had decreased energy, with difficulty walking up stairs.

**PHYSICAL EXAMINATION**
General appearance: Round face ("moon face"), truncal obesity with a "buffalo hump" of fat in the posterior neck, and thin legs.

**Vital signs:**
- **Blood Pressure:** 125/85.
- **Neck:** Supple, obese. Thyroid not enlarged.
- **Lungs:** Clear.
- **Breasts:** No masses.
- **Heart:** Regular rate with no murmurs.
- **Abdomen:** Obese; normal bowel sounds; no masses.
- **Extremities:** No clubbing or edema.
- **Skin:** Ruddy face, with facial hair, abdominal striae, ecchymoses, and thin-appearance skin in some areas.

**Genitalia:**
- **Female:** Normal female.
- **Neurologic exam:** Normal mental status, cranial nerves, motor exam, reflexes, coordination, gait, and sensation.

**DIAGNOSIS AND INITIAL LOCALIZATION**

1. On the basis of the symptoms and signs shown in bold above, what endocrinologic syndrome is present in this patient? This syndrome is caused by excess of which hormone?
2. What are the possible localizations for this disorder?

**Discussion**
The key symptoms and signs in this case are:

- **Truncal obesity, increased facial hair, new-onset acne, easy bruising, excessive sweating, and fatigue on her skin.**
- **Menstrual period stopped.**
- **Irritability and depression, decreased energy, and difficulty walking up stairs.**

These clinical features are all typical of Cushing's syndrome (see KCC 17.1). In the absence of exogenous glucocorticoid administration, Cushing's syndrome is caused by excess cortisol production by the adrenal cortex.

- **Cushing's syndrome can be caused by pituitary or extrapituitary hypersecretion of ACTH or by adrenal tumors.** The most common cause is ACTH-secreting pituitary adenoma.

**CASE 17.1 (CONTINUED)**

**INITIAL TEST RESULTS**
The patient's free cortisol level in the urine was 410 mg/dL (normal is <70). A low-dose overnight dexamethasone suppression test did not fully suppress the patient's free cortisol in the urine, but a high-dose dexamethasone suppression test did. Serum ACTH level was 35 pg/mL (normal is 6–86), which was not low despite high cortisol levels. The patient had an MRI scan with special attention to the pituitary region, which was entirely normal.

1. How do these results help with localization?
2. What does the MRI scan suggest about the diagnosis?
3. What test could be done to narrow the localization further?
Discussion
1. Elevated urinary cortisone, with suppression only with the high-dose dexamethasone test, suggests the presence of an ACTH-secreting pituitary adenoma (see KCC 17.1). Recall that nonpituitary sources of excess ACTH are usually not suppressed by the high-dose test, while pituitary sources are suppressed. In further support of an ACTH-secreting pituitary tumor, she had a normal ACTH level despite having elevated cortisone, suggesting that ACTH secretion was not under normal feedback inhibition (see Figure 17.2).
2. The normal MRI scan suggests that if a pituitary tumor were present, it would have to be a small microadenoma, probably less than 0.5 to 1 mm in diameter.
3. Petrosal sinus sampling (see KCC 17.1) can be used to confirm that excess ACTH is from a pituitary source and can often determine which side of the pituitary contains the adenoma.

CASE 17.1 (CONTINUED)

PETROSAL SINUS SAMPLING

Petrosal sinus sampling was performed in which catheters were passed up from the femoral vein through the vena cava to the internal jugular veins, to finally reach the right and left inferior petrosal sinuses. Catheter tip positions were then confirmed by the injection of a small amount of radiopaque dye through each catheter (Figure 17.8). Baseline ACTH in the inferior petrosal sinuses (in picograms per milliliter) was 573 on the right and 31 on the left, with ACTH peripherally measuring 26. Fifteen minutes after systemic administration of CRH, ACTH was 20,100 on the right, 580 on the left, and 255 peripherally.
1. Where is CRH normally produced, and how does it reach the anterior pituitary?
2. How do these results help further with localization?

Figure 17.8 Venous Angiogram for Petrosal Sinus Sampling
Contrast injection demonstrates the cavernous sinus and inferior petrosal sinuses draining into the internal jugular vein. Sampling catheters can be seen in the right and left inferior petrosal sinuses.

CASE 17.1 (CONTINUED)

TRANSPHENOIDAL SURGERY

The patient was admitted to the hospital for transphenoidal surgery on the pituitary gland. Under general anesthesia, an incision was made in the mucosa under the upper lip, and the tip was retracted upward so that the opening could be inserted through the incision into the nasal passages. In this way, access was gained to the sphenoidal sinus. The position in relation to the sella turcica was confirmed by the use of lateral fluoroscopic radiographs. The mucosa of the sphenoidal sinus was then removed to expose the bony roof of the sphenoidal sinus, or the floor of the sella turcica (Figure 12.1). This was penetrated by a small drill and bone tools to reveal dura. An incision in the dura provided access into the pituitary gland, which was inspected and showed no obvious evidence of tumor. Several small tissue samples were removed from the right anterior pituitary and sent to pathology for immediate examination using frozen sections. One of these contained a small pituitary microadenoma.

Postoperatively the patient did well, with no visual problems or other neurologic deficits. However, on the morning after surgery she began having increased urinary output, producing 2000 cc of urine in 8 hours. Serum sodium rose from 134 to 146 mEq/L (normal is 135-145), urine specific gravity was low at 1.001, and she felt very thirsty.
1. What neuroendocrinologic syndrome is associated with polyuria, polydipsia, increased thirst, and increased serum osmolality without a commensurate rise in urine osmolality? A decrease in which pituitary hormone can cause these changes?
2. Where are the cell bodies of the neurons that produce this hormone, and where is it released into the circulation?

Discussion
1. The patient has developed diabetes insipidus (DI) following surgery in the pituitary region (see KCC 17.2), which is caused by insufficient release of ADH (vasopressin).
2. Vasopressin is synthesized in neurons in the supraoptic and paraventricular nuclei of the hypothalamus, and transported via axons through the pituitary stalk to the posterior pituitary, where it is released into the circulation (see Figure 17.5).

CASE 17.1 (CONTINUED)

HYPONATREMIA

The patient was treated with an injection of the synthetic vasopressin analog DDAVP which immediately led to decreased urine output. Her diabetes insipidus then resolved spontaneously over the next day, requiring no further injections. Over the following few days, however, the serum sodium fell to 125 mEq/L (normal is 135-145), and urine specific gravity was 1.020, which is not low. She did not show signs of edema or hypovolemia.
1. What neuroendocrinologic syndrome can cause hyponatremia with a normal or increased urine osmolality?
2. Excess of which pituitary hormone is responsible for this condition?

Discussion
1. The patient's hyponatremia at this point was most likely caused by postoperative SIADH (see KCC 17.2).
2. This condition is caused by excessive ADH release.

Clinical Course
The patient was treated with restriction of free water intake, and her sodium gradually normalized. Soon afterward she again developed diabetes insipidus (pseudohypopituitarism response; see KCC 17.2), which required treatment with DDAVP for several months. She subsequently did well, with normal cortisol
levels, and her cushingoid features gradually resolved. One month postoperatively her normal menses resumed. Nine months after surgery she had lost 25 pounds, no longer had moon facies, and had only mild acne, and her abdominal striae had faded. She also no longer had irritability or depression, but instead had a calmer mood and improved energy level.

CASE 17.2 IMPOTENCE, ANOREXIA, POLYUORIA, BLURRED VISION, HEADACHES, AND HEARING LOSS

CHIEF COMPLAINT
Over a 6-month period, a 49-year-old man saw his physician for multiple complaints including impotence, anorexia, polyuria, blurred vision, headaches, and hearing loss.

HISTORY
Six to 12 months prior to presentation the patient had developed impotence, including no early morning erections and decreased sexual drive. He also developed fatigue, and his daily sleep requirement increased from 6 hours to 12 hours with naps. His muscle endurance decreased, and he became intolerant of cold temperatures. Five or six weeks prior to evaluation he began having increasing headaches over the vertex of his head, with light triggering of his vision. His hearing decreased, especially on the right side, making it difficult to understand phone conversations at work, and he noticed some blurring of his vision. He also had increased thirst, drinking approximately 1 gallon each night and urinating up to 16 times. Furthermore, he had marked anorexia, with no interest in food, and lost 22 pounds over the 3 weeks prior to presentation.

PHYSICAL EXAMINATION
Vital signs: T = 99.4°F; P = 80, BP = 110/70.
Mental status: Alert and oriented x3. Normal language and memory.
Cranial nerves: Normal, except for visual acuity 20/200 on the right, 20/40 on the left with intact fields, and hearing markedly decreased on the right, with air conduction greater than bone conduction.

Mental status: Alert and oriented x3. Normal language and memory.
Cranial nerves: Normal, except for visual acuity 20/200 on the right, 20/40 on the left with intact fields, and hearing markedly decreased on the right, with air conduction greater than bone conduction.

LOCALIZATION OF PITUARY-HYPOTHALAMIC ABNORMALITIES
1. Deficiency of which pituitary hormones can cause the following abnormalities seen in this patient?
   a. Polyuria, polydipsia, and excessive thirst
   b. Impotence, with bilateral decreased testicular volume
   c. Cold intolerance
   d. Fatigue and decreased muscle endurance
   e. Decreased appetite and weight loss
2. How does this information help with localization? A lesion in which region of the hypothalamus can also cause decreased appetite?

Discussion
1. a. ADH (vasopressin) deficiency
   b. LH and FSH deficiency
   c. TSH deficiency
   d. GH or ACTH deficiency
   e. ACTH deficiency

2. This patient has clinical evidence of panhypopituitarism (see KCC 17.3). The presence of ADH deficiency suggests that the lesion includes the high pituitary stalk or the hypothalamus (see KCC 17.2). In addition to ACTH deficiency, decreased appetite could also be caused by a lesion involving the lateral hypothalamus (see KCC 17.1). Note, however, that decreased appetite alone is a very nonspecific finding and can be caused by many medical disorders.

CASE 17.2 (CONTINUED)

RESULTS OF LABORATORY TESTS
The laboratory tests shown in the table below were performed, confirming that the patient had low levels of LH, FSH, testosterone, thyroxine, and cortisol. Elevated serum sodium and serum osmolality, with a low urine osmolality, was consistent with DI. Interestingly, prolactin levels were modestly elevated rather than decreased. Although elevated prolactin can have many causes, including hypothalamic lesions, which this patient had, one additional possibility, given the fact that a hypothalamic lesion is suspected based on the presence of DI, is that the presence of a hypothalamic lesion could lead to decreased PIF (dopamine) production (see Table 17.2; KCC 17.1). Growth hormone and oxytocin levels were not measured, and somatomedins were normal.

LOCALIZATION OF OTHER ABNORMALITIES IN THIS PATIENT, AND DIFFERENTIAL DIAGNOSIS
In addition to the above neuroendocrine findings, this patient had decreased hearing with a sensorineural pattern (see KCC 12.5) especially on the right side, decreased visual acuity, headache, and photophobia.

1. What space is shared by the hypothalamic-pituitary region, acoustic nerves, and optic nerves?
2. What are some possibilities for the diagnosis?

Discussion
The key symptoms and signs in this case are:
- Decreased hearing, especially on the right side (air conduction greater than bone conduction)
- Visual acuity 20/200 on the right, 20/40 on the left
- Headaches, with light blurring of the eyes

1. The adjacent space is shared by the hypothalamic-pituitary region and by the cranial nerves. Pathology in the adjacent space could also explain the presence of headache and photophobia, which are signs of meningeal irritation (see Table 5.5). The panhypopituitarism in this patient suggests a lesion in the hypothalamic or pituitary region. There are some clues but no definite
evidence that the lesion involves primarily the hypothalamus rather than the pituitary, including the presence of diabetes insipidus and the fact that prolactin levels were elevated rather than decreased. Involvement of CN II could be caused by direct extension of a hypothalamic or pituitary lesion, rather than by spread through the cerebrospinal fluid; however, involvement of CN VII cannot be explained in this manner. Therefore, a lesion of the hypothalamus or pituitary extending into the subarachnoid space to involve CN II and VII should be considered.

2. Possibilities for a lesion involving these areas include metastatic disease and chronic inflammatory or infectious disorders such as sarcoidosis or tuberculosis.

Clinical Course and Neuroimaging

A brain MRI scan showed a large enhancing lesion of the hypothalamus, with some involvement of the optic tracts bilaterally (Figure 17.9). Abnormal enhancement was seen in the septum pellucidum as well, suggesting that the lesion had possibly spread by CSF pathways. The patient was admitted to the hospital and underwent a lumbar puncture (see KCC 5.18), with CSF showing an elevated protein of 82 (normal is 15–45), normal glucose, no red blood cells, and an increased CSF white blood cell count of 18 (normal is <5), with 93% lymphocytes (see Tables 5.7, 5.9). CSF cytology was suspicious for lymphoma but not definitive. Repeat CSF cytology was also not definitive. Therefore, the patient underwent a needle biopsy of the enhancing lesion in the septum pellucidum (Figure 17.9) using a right frontal stereotactic approach (see KCC 16.4). Pathologic analysis showed B-cell lymphoma (see KCC 5.8). An HIV test was done and was negative.

The patient was treated for his pancreatitis (see KCC 17.3) with (1) synthetic vasopressin (DDAVP) nose spray for his diabetes insipidus, (2) the steroid prednisone for his hypoadrenalism, (3) thyroid hormone replacement therapy for his hypothyroidism, and (4) testosterone for his impotence and hypogonadism.

His lymphoma was treated with repeated cycles of intravenous chemotherapy with methotrexate about once per month, with an excellent response and no major toxicity. After 1 month his hearing in the right ear had improved, and he no longer had headaches. After 2 months his vision had improved, and he returned to work. Follow-up MRI scans showed complete disappearance of the enhancing lesion. Two years later an MRI scan showed recurrent enhancement in the original locations, as well as slight enhancement along the pons and midbrain. CSF showed lymphoma cells. He was switched to a different chemotherapy regimen, and the lesions on MRI again disappeared. At last follow-up, 3 years after diagnosis, he continued to do well.

Additional Cases

Related cases can be found in other chapters for the following topics: lesions of the sellar region (Cases 11.3, 13.5), and disorders of hypothalamic connections to autonomic or limbic circuits (Cases 14.1, 18.1–18.5). Other relevant cases can be found using the Case Index.

Brief Anatomical Study Guide

1. The pituitary and hypothalamus link the nervous system through both sympathetic and humoral forms of communication with numerous other systems in the body. The pituitary gland is connected to the bottom of the hypothalamus via the pituitary stalk (see Figure 17.2). This location of the pituitary gland just underneath the optic chiasm can result in compression of crossing optic nerve fibers by pituitary region tumors, classically causing bitemporal hemianopia or other visual deficits (see Figure 11.15).

2. The hypothalamus is located beneath the thalamus and can be divided from anterior to posterior into the preoptic region, anterior (supraoptic) region, middle (tuberal) region, and posterior (mamillary) region. The hypothalamus can also be divided from lateral to medial into a periventricular area, medial hypothalamic area, and lateral hypothalamic area (see Figures 17.3, 17.4). The main nuclei of the hypothalamus are listed in Table 17.1.

3. The hypothalamus participates in a variety of neural and non-neural systems that mainly regulate homeostasis through multiple complex feedback loops. The hypothalamus participates in these functions:

   A. Homeostatic control of appetite, thirst, thermoregulation, sleep-wake cycles, and sexual desire
   B. Endocrine control
   C. Autonomic nervous system
   D. Limbic system (Chapter 18)

4. Important nuclei and connections of the hypothalamus include:

   A. The paraventricular nucleus and other associated nuclei that control autonomic function (see Figures 13.10, 17.3, 17.4)
   B. Limbic inputs to the mammillary bodies from the hippocampal formation via the fornix (see Figures 18.9, 18.13)
   C. Limbic outputs from the mammillary bodies via the mammillothalamic tract to the anterior thalamic nucleus (see Figure 18.9)
   D. Reciprocal limbic connections with the amygdala via the stria terminalis and ventral amygdaloïd nuclear pathways (see Figure 18.17)
   E. Control of circadian rhythms by the suprachiasmatic nucleus (see Figures 17.3, 17.4)
   F. Release of oxytocin and vasopressin by the supraoptic and paraventricular nuclei into the posterior pituitary (see Figures 17.5, 17.6)
   G. Release of stimulatory and inhibitory factors by the arcuate nucleus, paraventricular nucleus, medial preoptic nucleus, and medial parvocellular portions of the paraventricular nucleus for control of the anterior pituitary (see Table 17.2; Figure 17.5)

5. The pituitary gland is composed of an anterior lobe, or adenohypophysis, derived embryologically from the roof of the pharynx (see Figure 17.1), and a posterior lobe, or neurohyophysis, derived embryologically from the diencephalon. The anterior pituitary is composed of endocrine tissue and secretes the following six hormones: adrenocorticotropic hormone (ACTH), growth hormone (GH), prolactin, thyroid-stimulating hormone (TSH), luteinizing hor-
**CASE 17.2 IMPOTENCE, ANOREXIA, POLYURIA, BLURRED VISION, HEADACHES, AND HEARING LOSS**

Figure 17.9 Enhancing Mass in the Hypothalamus Extending into the Optic Tracts. MR scans with gadolinium. A, B, C, D, G, and H represent progress from posterior to anterior.

(A) Forebrain of Mono

Thalamus

Enhancing hypothalamic lesion

Subarachnoid space

Optic tracts

(B) Lateral ventricle

Enhancing hypothalamic lesion

Right optic tract

Cavernous cisterna

MR scans with gadolinium. A, B, C, D, G, and H represent progress from posterior to anterior.

**Brief Anatomical Study Guide (continued)**

Methone (LH) and follicle-stimulating hormone (FSH). The posterior pituitary is composed of neural tissue extending from the hypothalamus and releases the two hormones oxytocin and vasopressin, also called arginine vasopressin (AVP) or antidiuretic hormone (ADH). Functions of these anterior and posterior pituitary hormones are summarized in Figure 17.5. Posterior pituitary hormones are released at axon terminals of magnocellular neurons located in the supraoptic and paraventricular nuclei of the hypothalamus (see Figure 17.5). The hypothalamic—pituitary axis is controlled by multiple feedback loops, as shown, for example, with the adrenocortical system in Figure 17.7.

**References**


CHAPTER 18

ANATOMICAL AND CLINICAL REVIEW
Overview of Limbic Structures
Olfactory System
Hippocampal Formation and Other Memory-Related Structures
KCC 18.1 Memory Disorders
The Amygdala: Emotions, Drives, and Other Functions
Other Limbic Pathways
KCC 18.2 Seizures and Epilepsy
KCC 18.3 Anatomical and Neuropharmacological Basis of Psychiatric Disorders

CLINICAL CASES
18.1 Sudden Memory Loss after a Mild Head Injury
18.2 Progressive Severe Memory Loss, with Mild Confabulation
18.3 Transient Dipsopia, Lethargy, and Hemiparesis, Followed by a Sustained Memory Deficit
18.4 Episodes of Panic, Olfactory Hallucinations, and Loss of Awareness
18.5 Episodes of Staring, Lip Smacking, and Unilateral Semipurposeful Movements
Additional Cases

BRIEF ANATOMICAL STUDY GUIDE

Limbic System: Homeostasis, Olfaction, Memory, and Emotion

The structures of the limbic system regulate emotions, olfaction, memory, drives, and homeostasis. A 40-year-old woman awoke from sleep and complained to her husband of an indescribable unpleasant odor, nausea, and a panicky, fearful sensation. During the following week, she had repeated stereotyped episodes of this kind followed by decreased responsiveness and slow, inappropriate speech lasting 2 to 3 minutes. As we shall see, limbic system abnormalities can cause paroxysmal disorders of the kind seen in this patient. In this chapter we will learn about this important and diverse neural system and the consequences of limbic system damage or dysfunction.
ANATOMICAL AND CLINICAL REVIEW

The limbic system includes diverse cortical and subcortical structures located mainly in the medial and ventral regions of the cerebral hemispheres. These structures are unified by their evolutionarily ancient origins, and they constitute the major portion of the forebrain in many species. Only in higher mammals has the larger neocortical mantle surpassed the limbic system in size.

The functions of the limbic system are also ancient, and they play an important role for survival in the animal kingdom. Limbic functions can be divided into the following four basic categories:

1. Olfaction
2. Memory
3. Emotions and drives
4. Homeostatic functions including autonomic and neuroendocrine control

An aid to remembering these functions is HOME (for Homeostasis, Olfaction, Memory, and Emotion). Numerous limbic structures participate in each of these functions, as we will see. The various components of the limbic system (Table 18.1) form a complex network, with multiple reciprocal connections (Figure 18.1). However, simplifying somewhat, one limbic structure can be thought of as central to each of these four functions (Table 18.2): the olfactory cortex is essential to olfaction, the hippocampal formation to memory, the amygdala to emotions and drives, and the hypothalamus to homeostasis (see Chapter 37). It cannot be emphasized enough that in reality, each of these structures participates in a complex network involving numerous limbic components to carry out these functions.

In this chapter we will first review the overall structure of the limbic system and briefly discuss each of its main components. Then we will discuss specific subsystems responsible for the four major categories of limbic function (see Table 18.2). Finally, we will review important clinical disorders of the limbic system, including memory loss and epileptic seizures.

**TABLE 18.1 Main Components of the Limbic System**

- **Olfactory cortex**
- **Parahippocampal gyrus**
- **Cingulate gyrus**
- **Medial orbitofrontal cortex**
- **Temporal pole**
- **Anterior insula**
- **Hippocampal formation**
- **Dentate gyrus**
- **Hippocampus**
- **Subiculum**
- **Amygdala**
- **Olfactory bulb**
- **Diencephalon**
- **Hypothalamus**
- **Thalamus**
- **Medial nucleus**
- **Medial medullary lamina**
- **Habenula**
- **Basal ganglia**
- **Nucleus accumbens**
- **Frontal cortex**
- **Insula**
- **Pallidum**
- **Septal nucleus**
- **Brainstem**

*Recall that a similar mnemonic (HEAL) was used to remember hypothalamic functions in Chapter 17. Limbic system and hypothalamic functions are strongly interconnected.*

**TABLE 18.2 Simplification of Limbic Functions and Corresponding Key Structures**

<table>
<thead>
<tr>
<th>Limbic Function</th>
<th>Key Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olfaction</td>
<td>Olfactory cortex</td>
</tr>
<tr>
<td>Memory</td>
<td>Hippocampal formation</td>
</tr>
<tr>
<td>Emotions and drives</td>
<td>Amygdala</td>
</tr>
<tr>
<td>Homeostatic functions</td>
<td>Hypothalamus</td>
</tr>
</tbody>
</table>

**Overview of Limbic Structures**

The limbic system includes a variety of structures extending from the forebrain to the brainstem (see Table 18.1). Most of these structures lie hidden within the medial and ventral regions of the cerebral hemispheres and are not readily visible from the lateral surface. Limbus means "border" or "edge" in Latin. The limbic cortex (Figure 18.2) forms a ringlike limbic lobe around the edge of the cortical mantle, which surrounds the corpus callosum and upper brainstem-diencephalic junction. This "grand lobe limbique" was first described by Broca in 1878. The main components of limbic cortex visible on a medial view are the cingulate gyrus (cingulum means "girdle" or "belt" in Latin) and the parahippocampal gyrus (see Figure 18.2A). The parahippocampal gyrus is separated from the remainder of the temporal lobe by the collateral sulcus, which continues anteriorly as the rhinal sulcus (see Figure 18.2B). The uncus is a bump visible on the anterior medial parahippocampal gyrus. The cingulate gyrus continues anteriorly and inferiorly as the subcallosal and paraterminal gyri. The cingulate gyrus joins the parahippocampal gyrus posteriorly at the isthmus (see Figure 18.2A).

In addition to the cingulate and parahippocampal gyri, other regions of limbic cortex include the medial orbitofrontal gyrus, the temporal poles, and the anterior insular cortex (see Figure 18.2A, C; Table 18.1). The limbic cortices share certain surface immunological markers. For example, the herpes simplex virus has a tropism for the limbic cortex and can cause severe encephalitis involving predominantly limbic cortical areas (Figure 18.3). In some texts, what we have called limbic cortex is referred to as paralimbic cortex or limbic association cortex.

The hippocampal formation (see Table 18.1) is the medial and dorsal continuation of the parahippocampal gyrus. It is buried within the medial temporal lobe, forming the floor of the temporal horn of the lateral ventricle (see Figure 18.8). The hippocampal formation is one of several C-shaped struc-
Figure 18.2 Limbic Cortex Blue regions represent limbic cortex, also known as paralimbic cortex, or limbic association cortex.

Figure 18.3 Herpes Encephalitis Affecting the Limbic Cortex Bilaterally Axial 1.7-T weighted MPR images from a patient with herpes encephalitis. Slices A-D progress from inferior to superior.
### TABLE 18.3 Terminology for Classifying Cerebral Cortex

<table>
<thead>
<tr>
<th>NAME</th>
<th>EQUIVALENT NAME(S)</th>
<th>DESCRIPTION</th>
<th>EXAMPLE(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neocortex*</td>
<td>Isocortex, neopallium</td>
<td>Six-layered cortex</td>
<td>Majority of the cerebral cortex</td>
</tr>
<tr>
<td>Neocortex</td>
<td>Limbic cortex, paralimbic cortex, transitional cortex</td>
<td>Forms gradual transition between three- and six-layered cortex</td>
<td>Parahippocampal gyrus, cingulate gyrus, anterior insula, orbital frontal cortex, temporal pole</td>
</tr>
<tr>
<td>Allocortex</td>
<td>—</td>
<td>Cortex with fewer than six layers</td>
<td>Archicortex, paleocortex</td>
</tr>
<tr>
<td>Archicortex</td>
<td>Aretipallium</td>
<td>Three-layered hippocampal cortex</td>
<td>Hippocampal formation</td>
</tr>
<tr>
<td>Palaeocortex</td>
<td>Paleopallium</td>
<td>Three-layered olfactory cortex</td>
<td>Priform cortex</td>
</tr>
<tr>
<td>Corticoid areas</td>
<td>—</td>
<td>Simple cortex that merges with subcortical nuclei</td>
<td>Amygdala, substantia innominata, septal region</td>
</tr>
</tbody>
</table>

*See Table 18.1 for additional details.

...and septal region. In fish and amphibians, the archicortex, paleocortex, and corticoid areas form the major portion of the cerebral hemispheres; only in mammals does the neocortex predominate.

The **amygdala** is a nuclear complex that lies in the anteromedial temporal lobe. It overlaps the anterior end of the hippocampus and lies dorsal to the tip of the temporal horn of the lateral ventricle (Figure 18.4B,C; see also Fig.

---

**Figure 18.4** Coronal Brain Sections through Basal Forebrain and Septal Region

The posterior amygdala and anterior hippocampus lie just underneath the uncus, a bump visible on the medial surface of the temporal lobe (see Figures 18.2 and 18.4B). The amygdala is composed of three main nuclei: the corticomedial, basolateral, and central nuclei. In addition, the C-shaped bed nucleus of the stria terminalis is considered part of the amygdala. The amygdala serves important functions in emotional, autonomic, and neuroendocrine circuits of the limbic system.

Diencerehalic structures (see Table 18.3) participate in all functions of the limbic system. These structures include the hypothalamus, the mesiodorsal nucleus of the thalamus, the anterior nucleus of the thalamus, and the habenula.

As we discussed in Chapter 16, the ventral portions of the basal ganglia process limbic information. Limbic inputs reach the basal ganglia arrive at the ventral striatum and nucleus accumbens (see Figure 18.4) and are then relayed via the ventral pallidum to the mediodorsal nucleus of the thalamus (see Figure 16.4D). The mediodorsal nucleus of the thalamus projects to the orbitofrontal and anterior cingulate limbic cortices (see Figure 16.8A).

The basal forebrain and septal region are contiguous and are sometimes lumped together in one category; however, we will discuss them separately here. The basal forebrain includes several structures that participate in limbic circuits. These structures lie just anterior and lateral to the hypothalamus, at the base of the frontal lobes near the midline (see Figures 18.4A, B). Although these structures are on surface of the forebrain, they are more histologically like gray matter nuclei than like cortex. Therefore, like the amygdala, the nuclei of the basal forebrain and septal region are corticoid structures.

The term substantia innominata is applied variably to the entire basal forebrain or to a nucleus within it called the nucleus basalis of Meynert, which lies just ventral to the anterior commissure (see Figure 18.4B).

The nucleus basalis contains cholinergic neurons that provide the major cholinergic innervation for the other cortical cortices. This includes the olfactory tubercle, which lies just underneath the anterior perforated substance (see Figure 18.6), and the following nuclei, which can be identified in Figure 18.4B: the ventral pallidum, which participates in limbic basal ganglia circuits; the nucleus of the diagonal band of Broca, which also contains cholinergic neurons; and the preoptic area, which is the rostral extension of the hypothalamus (see Figure 17.3). Portions of the amygdala also lie close to or within the region of the basal forebrain.

The septal region lies just dorsal to the basal forebrain, near the septum pellucidum, and it also participates in limbic pathways (see Figure 18.4B,C). The main septal nuclei lie within and just caudal to the subcallosal and paraterminal gyrus and are named the medial septal nucleus and the lateral septal nucleus. The medial septal nucleus contains cholinergic neurons (see Figure 14.90) that project to the hippocampal formation and may play a role in modulation of memory function. Inputs from the hippocampal formation are mainly to the lateral septal nucleus, and outputs are mainly from the medial septal nucleus. The lateral septal nucleus has a large projection to the medial septal nucleus, completing this circuit. The nucleus accumbens (see Figure 18.4A) is sometimes included in the septal region or basal forebrain and is involved in basal ganglia-limbic circuitry, as we have already discussed. Another nearby nucleus with limbic connections is the bed nucleus of the stria terminalis (see Figure 18.4B).

Numerous brainstem nuclei have reciprocal connections with limbic pathways and are sometimes considered part of the limbic system. Examples include the interpeduncular nucleus, superior central nucleus, dorsal tegmental nucleus, ventral tegmental nucleus, parabrachial nucleus, periaqueductal gray, reticular formation, nucleus solitarius, and dorsal motor nucleus of the vagus. These nuclei may help link limbic pathways to mechanisms for autonomic and behavioral arousal.

The gray matter structures of the limbic system are interconnected by white matter pathways, some of which form prominent tracts. These pathways are summarized in Table 18.4 and will be discussed further in the sections that follow.

**TABLE 18.4 Summary of Major Limbic Pathways**

<table>
<thead>
<tr>
<th>PATHWAY</th>
<th>FROM</th>
<th>TO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventral</td>
<td>Subiculum</td>
<td>Medial and lateral mammillary nuclei; lateral septal nuclei</td>
</tr>
<tr>
<td>Amygdala</td>
<td>Hippocampus</td>
<td>Lateral septal nuclei</td>
</tr>
<tr>
<td>Amygdala</td>
<td>Hippocampal formation</td>
<td>Anterior thalamic nuclei</td>
</tr>
<tr>
<td>Amygdala</td>
<td>Medial septal nucleus</td>
<td>Hippocampal formation</td>
</tr>
<tr>
<td>Amygdala</td>
<td>Nucleus of the diagonal band</td>
<td>Hippocampal formation</td>
</tr>
<tr>
<td>Amygdala</td>
<td>Medial mammillary nucleus</td>
<td>Anterior thalamic nuclei</td>
</tr>
<tr>
<td>Amygdala</td>
<td>Cingulate gyrus</td>
<td>Parahippocampal gyrus</td>
</tr>
<tr>
<td>Amygdala</td>
<td>Anterior olfactory nucleus</td>
<td>Contralateral anterior olfactory nucleus</td>
</tr>
<tr>
<td>Amygdala</td>
<td>Amygdala</td>
<td>Contralateral amygdala</td>
</tr>
<tr>
<td>Amygdala</td>
<td>Amygdala</td>
<td>Contralateral anterior temporal cortex</td>
</tr>
<tr>
<td>Amygdala</td>
<td>Amygdala</td>
<td>Contralateral amygdala</td>
</tr>
<tr>
<td>Amygdala</td>
<td>Amygdala</td>
<td>Contralateral anterior temporal cortex</td>
</tr>
<tr>
<td>Amygdala</td>
<td>Olefactory bulb</td>
<td>Anterior olfactory nucleus</td>
</tr>
<tr>
<td>Amygdala</td>
<td>Piriform cortex</td>
<td>Piriform cortex; periamygdaloid cortex; corticomedial amygdala</td>
</tr>
<tr>
<td>Amygdala</td>
<td>Hypothalamus</td>
<td>Hypothalamus</td>
</tr>
<tr>
<td>Amygdala</td>
<td>Septal nuclei</td>
<td>Septal nuclei</td>
</tr>
<tr>
<td>Amygdala</td>
<td>Orbifrontal olfactory cortex</td>
<td>Orbifrontal olfactory cortex</td>
</tr>
<tr>
<td>Amygdala</td>
<td>Orbifrontal and cingulate cortex</td>
<td>Orbifrontal and cingulate cortex</td>
</tr>
<tr>
<td>Amygdala</td>
<td>Medial diencephalon</td>
<td>Medial diencephalon</td>
</tr>
<tr>
<td>Amygdala</td>
<td>Hypothalamus; nucleus basalis; ventral striatum; brainstem nuclei</td>
<td>Hypothalamus</td>
</tr>
<tr>
<td>Amygdala</td>
<td>Amygdala</td>
<td>Amygdala</td>
</tr>
<tr>
<td>Amygdala</td>
<td>Brainstem nuclei</td>
<td>Brainstem nuclei</td>
</tr>
<tr>
<td>Amygdala</td>
<td>Amygdala, other forebrain structures</td>
<td>Amygdala, other forebrain structures</td>
</tr>
<tr>
<td>Amygdala</td>
<td>Brainstem nuclei</td>
<td>Brainstem nuclei</td>
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<tr>
<td>Amygdala</td>
<td>Medial septal nucleus</td>
<td>Medial septal nucleus</td>
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<td>Habenula</td>
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<td>Interpeduncular nucleus</td>
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<td>Brainstem</td>
<td>Brainstem</td>
</tr>
<tr>
<td>Amygdala</td>
<td>Dentate gyrus granule cells</td>
<td>Dentate gyrus granule cells</td>
</tr>
<tr>
<td>Amygdala</td>
<td>Hippocampal pyramidal cell</td>
<td>Hippocampal pyramidal cell</td>
</tr>
</tbody>
</table>

*For conclusions, many additional reciprocal connections have not been listed here.*
Hippocampal Formation and Para-hippocampal Gyrus

The key structures of the medial temporal lobe memory system are the hippocampal formation and the parahippocampal gyrus. The hippocampal formation has an elaborate convoluted or inverted S shape on coronal sections (Figures 18.7, 18.8). This appearance inspired the names hippocampus (meaning "sea horse" in Greek) and cornu Ammonis (Latin for "horn of the ancient Egyptian ram-headed god Ammon"). The three components of the hippocampal formation are the dentate gyrus (named for the toothlike bumps on its medial surface; Figure 18.9), the hippocampus, and the subiculum (Latin for "support"). Sometimes the term "hippocampus" is used to refer to all three components. During embryological development, the three-layered archichoroids of the medial temporal lobe folds over on itself twice (Figure 18.7). As a result of this double folding, the pial or gray matter surfaces of the dentate gyrus and subiculum fuse, and the ventricular or white matter surfaces of the subiculum and parahippocampal gyrus fuse.

The principal neurons of the dentate gyrus are called granule cells. The three layers of the dentate gyrus, moving inward from the pia, are the molecular layer, granule cell layer, and polymorphic layer (Figure 18.8A). Note the similarities of these names to the names for the six layers of neocortex (see Table 2.3). The principal

![Hippocampal Formation and Para-hippocampal Gyrus](image-url)
neurons of the hippocampus and subiculum are pyramidal cells, and the layers of these structures are the molecular layer, pyramidal cell layer, and polymorphic layer (see Figure 18.8A). The molecular layers of the dentate gyrus and subiculum are apposed, forming the hippocampal sulcus. The groove in the medial temporal lobe just dorsal to the hippocampal formation is called the choroid fissure (see Figures 18.8A, 18.9). The hippocampal formation is largest anteriorly, where it forms the pes hippocampi, also called the hippocampal head. The hippocampal formation curves back along the floor of the temporal horn, tapers to a smaller hippocampal tail, and finally disappears as it curves under the ventral posterior edge of the splenium of the corpus callosum. A minor vestigial remnant of the hippocampal formation, called the indusium griseum, continues along the dorsal surface of the corpus callosum (see Figure 18.9). The layers of the hippocampus can also be appreciated in sagittal sections (Figure 18.10).

The parahippocampal gyrus includes several cortical areas with connections to the hippocampal formation, the most important of which is the entorhinal cortex (see Figures 18.6, 18.8, 18.9, 18.11). The entorhinal cortex (Brodmann’s area 28; see Figure 2.15) lies in the anterior portion of the parahippocampal gyrus, adjacent to the subiculum, and serves as the major input and output relay between association cortex and the hippocampal formation. The posterior portion of the parahippocampal gyrus is simply called the parahippocampal cortex (see Figure 18.6). Laterally, the parahippocampal gyrus is delimited by the collateral sulcus, which continues anteriorly as the rhinal sulcus (see Figure 18.6). Along both medial and lateral walls of the rhinal sulcus, and continuing laterally onto the adjacent occipitotemporal gyrus, lies the perirhinal cortex (Brodmann’s areas 35 and 36). About two-thirds of the input to association cortex reaches the entorhinal cortex via relays in the adjacent perirhinal cortex and parahippocampal cortex (Figure 18.11; see also Figure 18.6).

For the sake of completeness, we will now briefly mention the names of the other parts of the parahippocampal gyrus aside from the entorhinal and perirhinal cortex (Table 18.5). (Knowledge of these other terms has no direct

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**Figure 18.10** Sagittal Section through the Hippocampal Formation and Amygdala

Myelin is stained dark. Compare to Figure 4.15C. (From Noth, 1995. The Human Brain in Photographs and Diagrams. Mosby, St. Louis, MO)
Figure 18.11 Summary of Hippocampal Input and Output Connections
S = subiculum; D = dentate gyrus; 
HC = hippocampus; EC = entorhinal cortex.

Intrinsic Circuitry of the Hippocampal Formation

The circuitry of the hippocampal formation has been the subject of intensive scientific investigation because of its possible important role in human memory. Figure 18.8B illustrates the major circuits for information flow from the entorhinal cortex, through the hippocampal formation, and back to the entorhinal cortex. Pyramidal cells in layers 2 and 3 of the entorhinal cortex project to the hippocampal formation via the perforant pathway and the alvear pathway (see Figure 18.8B, Suppase 1). The perforant pathway is named for its course through the subiculum and across the hippocampal sulcus to reach the granule cell layer of the dentate gyrus. The hippocampus has different pyramidal cell sectors named CA (for cornu Ammonis) 1 through 4 (see Figure 18.8A). CA4 lies within the limit of the dentate gyrus. CA3 is adjacent to CA4. CA2 comes next, and CA1 lies closest to the subiculum. Gruamal cells of the dentate gyrus give rise to axons called mossy fibers, which synapse on the dendrites of CA3 pyramidal cells (see Figure 18.8B, Suppase 2). The axons of CA3 pyramidal cells leave the hippocampal formation via the fornix. However, these axons also give rise to axons called Schaffer collaterals, which synapse on the dendrites of CA1 pyramidal cells (Suppase 3). Axons of CA1 pyramidal cells also leave the hippocampal formation via the fornix. In addition, CA1 pyramidal cells project to the next cell layer, which lies in the subiculum (Suppase 4). Finally, pyramidal cells of the subiculum project both into the fornix and back to neurons in the deeper layers of the entorhinal cortex, completing the loop (Suppase 5).

In addition to the perforant pathway, neurons of the entorhinal cortex project via the alvear pathway directly to CA1 and CA3 (see Figures 18.8B, 18.11). As in the perforant pathway, outputs in the alvear pathway are primarily from CA1 and CA3 to the subiculum.

An interesting form of synaptic plasticity called long-term potentiation (LTP) has been found in the perforant pathway–granule cell, mossy fiber–CA3, and Schaffer collateral–CA1 connections (Figure 18.12). High-frequency activity at any of these synapses causes a long-lasting increase in synaptic strength between the involved neurons. In particular, the perforant pathway–granule cell and Schaffer collateral–CA1 (but not mossy fiber–CA3) synapses require simultaneous pre- and postsynaptic activity for LTP to be elicited. This interesting property may allow these synapses to perform an associative function, similar to the learning rule proposed by the psychologist Donald Hebb in the 1940s. The Hebb rule states, “When an axon of cell A and an excitatory cell B repeatedly or persistently takes part in firing C, some growth process or metabolic change takes place in one or both cells so that A’s efficiency as one of the cells firing C is increased.” Since its initial discovery, LTP has also been demonstrated at synapses in several other areas of the nervous system. In addition, numerous other forms of excitatory and inhibitory, short-term and long-term synaptic modulation have been described. The cellular mechanisms underlying LTP and other types of synaptic plasticity are currently an important and very active area for further investigation and are thought to play an important role in memory formation.

Input and Output Connections of the Medial Temporal Lobe Memory System

The main input to the hippocampal formation arrives at the entorhinal cortex from association cortex in the frontal, parieto-occipital, and temporal lobes (see Figure 18.11). Much of this information is relayed in the adjacent pyramidal cortex and parahippocampal cortex before reaching the entorhinal cortex. These inputs are thought to contain higher-order information from multiple sensorimotor modalities that is processed further by the medial temporal structures for memory storage. The storage process itself is believed to occur not in the medial temporal structures, but back in the association and primary cortices that allow a particular memory to be reactivated. An important output pathway of the hippocampal formation is therefore...
The projection from the subiculum to the entorhinal cortex, and from there to the hippocampus through the hippocampal commissure (Figure 18.13). These pathways will be discussed in greater detail in the next subsection. Note that the subiculum is the main source of output fibers from the hippocampal formation to the fornix, as well as to the entorhinal cortex. The subiculum is thus an important structure in hippocampal outputs.

Some inputs reach the hippocampus from the contralateral hippocampus through the hippocampal commissure (see Figure 18.13). Finally, the hippocampal formation receives important modulatory inputs via the fornix arising from cholinergic neurons in the medial septal nucleus and the nucleus of the diagonal band. The entorhinal cortex and the remainder of the cerebral cortex also receive cholinergic inputs, which arise primarily from the nucleus basalis of Meynert (see Figure 18.4B). These cholinergic pathways activate muscarinic receptors and may be important in modulating neuronal excitability and synaptic plasticity. Additional modulatory influences also reach the medial temporal lobes from noradrenergic, dopaminergic, and serotonergic nuclei in the brainstem (see Chapter 14).

The Fornix and Medial Diencephalic Memory Pathways

Fornix means "arch" in Latin, which is an appropriate name for this white matter structure that courses through the ventricular system from the hippocampal formation to the diencephalon and septal area (see Figure 18.13). As we discussed in Chapter 5, there are several C-shaped structures that follow the curve of the lateral ventricles, including the fornix, corpus callosum, and cuneate nucleus. Please review the three-dimensional relations of the fornix to these structures, as discussed in the Brief Anatomical Study Guide in Chapter 5 and in "A Scuba Expedition Through the Brain."

Output fibers from the hippocampal formation form a white matter layer on the ventricular surface of the hippocampus called the alveus (see Figures 18.8A, 18.9A, 18.10, 18.13). As these fibers sweep medially, they form a discrete bundle called the fimbria of the fornix (see Figures 18.8A, 18.13). The cura (meaning "legs") of the fornix leave the hippocampal formation and curve under the corpus callosum (see Figure 18.9; see also Figure 16.3) to run adjacent to each other in the midline, at which point their names change to the body of the fornix (see Figure 18.13, see also Figure 16.4D). Between the curves of the fornix, on the undersurface of the corpus callosum, the hippocampal commissure provides a route for fibers arising from one hippocampus to reach the contralateral side. The body of the fornix curves anteriorly and downward to form the columns of the fornix (see Figures 18.4C, 18.9, 18.13; see also Figure 16.3). Axons traveling forward in the fornix have three main targets. The majority of the fibers arise from the subiculum and descend behind the anterior commissure in the postcommissural fornix to reach the medial and lateral mammillary nuclei of the hypothalamus (see Figures 18.9, 18.13). A smaller contingent of fibers, arising from both the subiculum and hippocampus, pass anterior to the anterior commissure in the precommissural fornix to reach the lateral septal nucleus. Finally, some fibers leave the fornix to terminate in the anterior thalamic nucleus (see Figure 18.9).

As has already been mentioned, some fibers travel back in the fornix, predominantly from cholinergic neurons in the medial septal nucleus and diagonal band of Broca, to reach the hippocampal formation (see Figure 18.11). This pathway can be influenced by projections from the hippocampal formation to the lateral septal nucleus because the lateral septal nuclei project strongly to the medial septal nucleus. These cholinergic projections, along with inhibitory GABAergic projections that also travel in the fornix from the septal nucleus to the hippocampal formation, may play an important modulatory role in memory function.

In 1937 the anatomist James Papez described a circuit involving several limbic structures, thereby stimulating the development of the concept of the limbic system in the 1950s. Although the structures in this circuit have subsequently been shown to have many important connections as well, the Papez circuit remains a useful heuristic device for reviewing some of the major limbic pathways (see Figure 18.9B). The Papez circuit begins with fibers arising from the subiculum of the hippocampal formation, which enter the fornix and travel forward to both the medial and the lateral mammillary nuclei. The medial mammillary nucleus then projects through the mammillothalamic tract to the anterior thalamic nucleus (see Figure 16.4D). Recall that the anterior thalamic nucleus also receives a direct projection from the fornix (see Figure 18.9D). The anterior thalamic nucleus next projects through the internal capsule to the cingulate gyrus. Finally, a prominent white matter pathway underlying the cingulate gyrus called the cingulate bundle or cingulum passes from the cingulate cortex to the parahippocampal gyrus, from which projections continue to the entorhinal cortex and hippocampal formation, completing the loop.

In summary, the medial temporal lobe memory systems communicate with the association cortex mainly through bidirectional connections via the entorhinal cortex (see Figure 18.11). The medial diencephalic memory systems communicate with the medial temporal memory systems through several pathways. The fornix connects the hippocampal formation with the...
mammillary bodies and septal nuclei, as well as with the anterior thalamic nuclei, both directly and indirectly, through the mammillothalamic tract. Other medial diencephalic structures implicated in memory function include the mediiodorsal nucleus of the thalamus, the internal medullary lamina, and the midline thalamic nuclei (see Figure 7.6). These medial diencephalic nuclei are connected to the limbic structures of the medial temporal lobe and insula via fibers of the inferior thalamic peduncle (see Table 18.4) traveling near the auditory radiation (see Figure 6.9B). The functional roles of individual medial diencephalic nuclei and their relative importance in memory are still under investigation.

In this section we will discuss memory disorders, beginning with a specific, well known case of amnesia. This case will be used to illustrate the different kinds of memory loss that can occur, before we discuss the differential diagnosis of memory loss.

Patient H.M.: A Landmark Case of Amnesia
In 1953 a 27-year-old man with the initials H.M. underwent an operation in which the bilateral medial temporal lobes, including the hippocampal formations and parahippocampal gyrus, were resected in an attempt to control his medically refractory epileptic seizures (Figure 18.14). Following the surgery, his seizures improved, but he had severe memory problems, with no other significant deficits. He was unable to learn new facts or recall new experiences. For example, when given a list of three or four words to remember, he was able to correctly recite them back immediately. Within 5 minutes, however, he had no recall of any of the words, even with hints, and he did not even remember being given the list to remember in the first place. In contrast, his memory of remote events from his childhood and up to several years before the surgery was intact; however, he had no recall of events from that point on. Despite his profound memory deficit, H.M.‘s personality and general intelligence assessed by IQ testing were normal. In addition, he retained the ability to learn certain tasks that did not require conscious recall. For example, his performance on a mirror drawing task (improved on successive days similarly to normal controls, despite his having no recollection of doing the task the previous day. Similarly, when primed by exposure to a word such as “DEFI” and then asked to complete the stem “DEF,” he chose the word he had seen previously at higher than chance levels, despite having no conscious recall of having seen the word before.

The selective yet devastating and permanent effects of this operation on H.M.’s memory led to intensive investigations of the medial temporal lobes’ role in human memory. H.M. continues to participate in these tests today. Patients today with medically refractory temporal lobe epilepsy can often be cured with unilateral medial temporal lobe resection (see KCC 18.2); after the unfortunate experience with patient H.M., bilateral medial temporal lobe resection is no longer performed.

Lessons Learned from H.M.: Classification of Memory and Memory Disorders
On the basis of studies of patient H.M. and numerous other studies of patients and experimental animals in subsequent years, several types of memory and memory disorders have been identified. Although many of these distinctions did not emerge until years after the original studies on H.M., we will review the case of patient H.M. to help illustrate and understand some of these distinctions.

Declarative versus Nondeclarative Memory. One major distinction is between declarative (or explicit) memory, which involves conscious recollection of facts or experiences, and nondeclarative (or implicit) memory, which involves unconscious learning of skills, habits, and other acquired behaviors (Figure 18.15). H.M. was severely impaired in his ability to recollect new facts or experiences; however, his behavior could be modified by previous experience in a nonconscious manner. Thus, H.M. suffered a loss of declarative memory, while his nondeclarative memory remained intact. The term amnesia is typically used for declarative memory loss. This form of selective loss of declarative memory is typical of bilateral medial temporal lobe or bilateral medial diencephalic lesions. Unilateral lesions do not usually produce severe memory loss. However, unilateral lesions of the dominant (usually

![Figure 18.14 MRI from Patient H.M. This patient underwent bilateral resection of the medial temporal lobe structures. (A) Axial T2-weighted MR image. (B) Coronal T1-weighted image. Regions of resection are indicated by arrows. (From Corkin S, Amaré RB, Gonzalez RG, Johnson KA, Hyman BT 1997: H.M.'s medial temporal lesion: findings from magnetic resonance imaging. /Neurosci 17(10): 3964-3975.)

![Figure 18.15 Classification of Memory (After Squire LR and Zola-Morgan S. The medial temporal lobe memory system. Science 253: 1380–1385, 1991.)

Declarative (explicit) Memory
- Facts
- Events
- Skills
- Habits
- Priming
- Simple classical conditioning
- Nonassociative learning

Nondeclarative (implicit) Memory
left) medial temporal or diencephalic structures can cause some deficits in verbal memory, while unilateral lesions of the nondominant (usually right) hemisphere can cause deficits in visual-spatial memory.

Unlike declarative memory, specific lesions do not usually result in clinically significant signs of declarative memory loss (consequential memory) (see Chapter 19). Learning of skills, such as mirror drawing by H.M., and of habits most likely involves plasticity in several areas, including the basal ganglia, cerebellum, and motor cortex. The caudate nucleus appears to be particularly important in habit learning, and interestingly, pathology in this region may be linked to obsessive-compulsive disorder (KCC 18.3). Priming, as exhibited by H.M. in the word stem completion test, depends on several cortical areas. Simple associative learning such as classical conditioning, and nonassociative learning such as habituation and sensitization, have been studied extensively in animals and appear to involve a variety of structures, including the cerebellum (in classical conditioning), amygdala (in conditioned fear), cerebral cortex, brainstem nuclei, and even spinal cord.

**Temporal Aspects of Memory and Memory Loss.** Although H.M. was able to repeat a short list of words immediately after hearing them, within 5 minutes he could not recall any of the words. How are memories converted from short-term to long-term storage? At least two classes of mechanisms appear to be involved (Table 18.6). First of all, a variety of different cellular mechanisms store information in the nervous system on different time scales (see Table 18.6A). Secondly, different anatomical regions of the brain are important for storing memories at different times. The brain regions thought to be involved in declarative memory at different times are listed in Table 18.6B. When exactly at the bedside, particular tests of immediate recall, attention, and working memory often by asking the patient to repeat back lists of digits or words forward and backward (see neuromex.com Video 4). These functions, which operate on the time scale of less than 1 or 2 minutes, must be in action in order to remember information and to encode it successfully in declarative memory. However, these functions do not depend on the medial temporal or medial diencephalic memory systems (see Table 18.6B). As we will discuss in Chapter 19, alertness and attention are mediated by an interaction of brainstem–diencephalic and frontoparietal networks, acting on the specific regions of cortex involved in portraying a particular concept in conscious awareness. In addition, working memory involves holding a particular concept briefly in awareness while a mental operation, such as the carrying function in arithmetic, is performed. Working memory requires the participation of dorsolateral prefrontal cortex (see Chapter 19). After testing attention and confirming the patient's ability to register new information, recent memory should be tested by giving the patient several words to remember and then testing for recall of these words 4 to 5 minutes later (see neuromex.com Video 6). Remote memory should then also be tested by asking the patient about either verifiable personal information such as previous addresses or schools, and about well-known current events (see neuromex.com Video 7). In addition, these simple bedside tests, more precise and quantitative neuropsychological testing, can often be useful in evaluating memory dysfunction (see also KCC 19.16).

H.M. and other patients with bilateral medial temporal or medial diencephalic lesions are unable to recall facts and events for more than a few minutes. Medial temporal and diencephalic structures appear to mediate a process by which declarative memories are gradually consolidated in the neocortex (see Table 18.6B). Ultimately, through this process, declarative memories can be recalled through activity of specific regions of neocortex without requiring medial temporal and diencephalic involvement.

**Anterograde amnesia** is the deficit in forming new memories that H.M. and other similar patients have from the time of their brain injury onward (Figure 18.16). For example, even since his surgery, H.M. has not been able to learn his address, and when asked, he still cites the address of his childhood; he cannot learn the date, and despite watching the news every day, he does not remember most events from after the time of the brain surgery. **Retrograde amnesia** is the inability to retrieve memories from the period of time before the brain injury. For example, H.M.'s memories of his childhood and adolescence are relatively normal, but they stop several years before the surgery (see Figure 18.16). This combination of retrograde and anterograde amnesia for declarative memories is typical of lesions of the medial temporal lobe or medial diencephalic memory systems (although it can also be seen in concussion or other diffuse disorders).

The phenomenon of retrograde amnesia suggests that recent memories, for a period of up to several years, are dependent on the normal functioning of medial temporal and diencephalic structures, while more remote memories are not. Retrograde amnesia is often graded, with the memories from the time just before the injury being the most severely impaired (although like most biological phenomena, the time gradient is not perfectly uniform). In patients with reversible causes of amnesia (described in the next subsection), the period of retrograde amnesia often gradually shrinks forward; older memories are recovered before more recent ones. Ultimately, these patients will have a short time period (several hours) of permanently lost memories from before the injury, and a period of lost memories from the injury until the time they recover from the retrograde amnesia.

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**TABLE 18.6 Memory Mechanisms in the Time Domain and in the Spatial Domain**

<table>
<thead>
<tr>
<th>A. Cellular Mechanisms Involved at Different Times in Memory Storage</th>
<th>SECONDS TO MINUTES</th>
<th>MINUTES TO HOURS</th>
<th>HOURS TO YEARS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing electrical activity of neurons: changes in intracellular Ca²⁺ and other ions: changes in second messengers systems</td>
<td></td>
<td></td>
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<tr>
<td>Protein phosphorylation and other covalent modifications: expression of immediate early genes</td>
<td></td>
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<td></td>
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<tr>
<td>Additional changes in gene transcription and translation resulting in structural changes of proteins and neurons</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>B. Anatomical Structures Involved at Different Times in Storage of Explicit Memories</th>
<th>LESS THAN 1 SECOND (&quot;ATTENTION&quot; OR &quot;REGISTRATION&quot;)</th>
<th>SECONDS TO MINUTES (&quot;WORKING MEMORY&quot;)</th>
<th>MINUTES TO YEARS (&quot;CONSOLIDATION&quot;)</th>
<th>YEARS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brainstem–diencephalic activating systems: parietal association networks: specific unimodal and heteromodal cortices</td>
<td>Frontal association cortex: specific unimodal and heteromodal cortices</td>
<td>Medial temporal structures: medial diencephalic structures: specific unimodal and heteromodal cortices</td>
<td>Specific unimodal and heteromodal cortices</td>
<td></td>
</tr>
</tbody>
</table>

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**Figure 18.16 Diagram of Anterograde and Retrograde Amnesia in Patient H.M.**
The expressions "short-term" and "long-term" memory are sometimes used for memories enduring less than or more than a few minutes, respectively. This terminology is not ideal because so-called long-term memory includes even recent memories that are disrupted by bilateral medial temporal or diencephalic disorders. Numerous cognitive models of memory function have been developed that are beyond the scope of this book. One common way that memory has been described is as a three-step process involving encoding, storage, and retrieval. However, it has proven very difficult to demonstrate a selective deficit in human or animal studies in just one of these processes.

**Differentiation of Memory Loss**

Impaired memory can have many causes, as summarized in Table 18.7. These can be conveniently divided into those in which there are usually anatomical abnormalities visible on conventional imaging studies, those in which there are not, and finally, "normal" forms of memory loss. We will comment on only a few of these conditions in detail.

**Cerebral contusions** caused by head trauma often involve the anteromedial temporal lobes, as well as the basal forebrain cortex (see Figure 5.21), resulting in permanent deficits in memory. In contrast, **concussion** (see KCC 5.5) can be associated with memory loss that is usually reversible, except for the hours around the time of the injury.

**Infarcts or ischemia** (see KCC 10.3, 10.4) can cause memory deficits, especially when bilateral medial temporal or medial diencephalic structures are affected. Recall that the medial temporal lobes are supplied by distal branches of the posterior cerebral arteries (see Figure 10.3). The medial thalamus is supplied by the paramedian thalamoperforator arteries, which arise from the internal segments of the posterior cerebral arteries (see Figures 10.8, 10.9). Thus, arterial lesions at the top of the basilar artery (see Figure 14.17A; KCC 14.3) are well positioned to cause either bilateral medial temporal or medial diencephalic infarcts. In addition, the bilateral medial thalamus are often supplied by a single paramedian thalamoperforator artery (or "artery of Percheron"), which bifurcates shortly after its origin from the top of the basilar. This provides another mechanism for bilateral infarctions in this area.

**Global cerebral anoxia**, such as that caused by cardiac arrest, memory loss is often prominent. This may be related to the particular vulnerability of the hippocampus to anoxic injury, especially CA1, in which marked loss of pyramidal cells can be seen. As has already been mentioned, rupture of an anterior communicating artery aneurysm can damage the basolateral forebrain, causing memory loss together with other deficits seen in frontal lobe lesions (see KCC 19.11). It is unclear whether the memory loss in these patients is due to damage to the basolateral forebrain, medial diencephalon, frontal lobes, or a combination of these locations.

**Wernicke-Korsakoff syndrome** is caused by thiamine deficiency, seen most often in alcoholics, but also occasionally in patients on chronic parenteral nutrition. Pathologically, these patients have bilateral necrosis of the mamillary bodies and of a variety of medial diencephalic and other periventricular nuclei. Acutely, patients with thiamine deficiency have a triad of ataxia, eye movement abnormalities ranging from horizontal gaze paresis, or nystagmus, to ophthalmoplegia, and a confusional state. Severe cases can result in coma or death. Patients who survive the acute stages are left with anterograde and retrograde amnesia, thought to be caused by the bilateral diencephalic lesions. In addition to amnesia, however, patients with Wernicke-Korsakoff syndrome usually have other neuropsychological deficits, that suggest frontal lobe dysfunction (see KCC 19.11). These include impairments in judgment, gainful, impulse control, and sequencing tasks. In contrast to patients with "pure" medial diencephalic or medial temporal lobe lesions, patients with Wernicke-Korsakoff syndrome often lack an awareness of their memory deficit, and in fact they tend to **confabulate**, providing spurious answers to questions rather than saying that they do not remember. Confabulation is also probably related to frontal lobe dysfunction, which causes disinhibition and a loss of self-monitoring capabilities.

Patients with complex partial and generalized tonic-clonic seizures (see KCC 18.2) usually have memory loss of events during the seizure and post-ictal period (the period immediately following the seizure). Memory between seizures may be normal, unless the seizures are severe or caused by lesions of the medial temporal lobe, such as hippocampal sclerosis (see KCC 18.2). **Electroconvulsive therapy** (ECT) is an effective mode of therapy for selected patients with refractory depression. In ECT, seizures are induced while the patient is under anesthesia during multiple sessions, usually over the course of several weeks. During the treatment period, patients develop retrograde and anterograde amnesia similar to that seen in patients with bilateral temporal or diencephalic lesions. The amnesia gradually resolves after the course of treatment is complete, but it typically leaves a gap, including retrograde and anterograde memory loss from around the treatment period.

**Transient global amnesia** is a somewhat mysterious disorder in which patients abruptly develop retrograde and anterograde amnesia with no obvious cause and no other deficits. Episodes often occur in the setting of physical exertion or emotional stress. During the amnesia, patients characteristically ask the same questions over and over, with no recollection of having asked them a few minutes earlier. The amnesia typically lasts for approximately 4 to 12 hours, after which the patient recovers fully, except for a permanent loss of memories for a period of a few hours before and after onset. In about 85% of patients, a similar episode never happens again.

**TABLE 18.7 Causes of Memory Loss**

<table>
<thead>
<tr>
<th>Scientific/Imaging</th>
<th>Clinical/Behavioral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilateral medial temporal lesions</td>
<td>Surgery</td>
</tr>
<tr>
<td>Cerebral contusions</td>
<td>Infarct (posterior cerebral arteries)</td>
</tr>
<tr>
<td>Hippocampal sclerosis (usually with chronic epilepsy)</td>
<td>Herpes encephalitis</td>
</tr>
<tr>
<td>Paraenephalic limbic encephalitis</td>
<td>Neoplasm</td>
</tr>
<tr>
<td>Inflammatory process, such as sarcoidosis</td>
<td>Bilateral medial diencephalic lesions</td>
</tr>
<tr>
<td>Wernicke-Korsakoff syndrome</td>
<td>Infarct (thalamoperforator arteries)</td>
</tr>
<tr>
<td>Whipple's disease</td>
<td>Diffuse disorders</td>
</tr>
<tr>
<td>Neoplasm</td>
<td>Multiple sclerosis</td>
</tr>
<tr>
<td>Basal forebrain lesions</td>
<td>Numerous other diffuse cerebral disorders (additional deficits common)</td>
</tr>
</tbody>
</table>

**NO ANATOMICAL LESIONS VISIBLY ON CONVENTIONAL IMAGING**

Seizures, including electroconvulsive therapy

Concussion

Ischemia (bilateral medial temporal) or medial diencephalic structures

Diffuse cerebral anoxia

Transient global amnesia

Early Alzheimer's disease and other degenerative disorders

Diffuse infectious or toxic/metabolic encephalopathies (additional deficits common), including those caused by medications such as benzodiazepines

Psychogenic amnesia

Disassociative disorders

Repression

Conversion disorder

Malnutrition

**"NORMAL" MEMORY LOSS**

Infantile amnesia

During or shortly after awakening from sleep

Passage of time (forgetting)

In some of these disorders, abnormalities may be visible on functional imaging studies such as PET or SPECT (see Chapter 4).
The cause of this intriguing syndrome is not known. It differs from other common causes of transient neurologic episodes (see KCC 10.5), such as seizures and transient ischemic attacks (TIAs). In several ways, seizures can cause periods of memory loss; however, other manifestations of seizures, such as abnormal movements or decreased responsiveness, are usually present as well. Complex partial seizures can occasionally cause brief episodes of amnesia with no other obvious behavioral changes. Unlike transient global amnesia, however, the duration of amnesia is only a few minutes, the episodes recur multiple times in a stereotyped fashion, and the EEG is often abnormal. EEG recordings during transient global amnesia do not show epileptic activity. TIAs can cause transient motor loss; however, the typical duration of TIAs is minutes, not hours. In addition, patients who have had an episode of transient global amnesia are not at increased risk for subsequent stroke compared to the general population. A migraine-like (see KCC 5.1) phenomenon has also been proposed as the mechanism for transient global amnesia, and indeed a history of migraine is common in patients with transient global amnesia. Functional imaging studies during transient global amnesia have demonstrated decreased blood flow or decreased glucose metabolism in the medial temporal lobes, as well as in other brain regions. In conclusion, the cause of transient global amnesia remains unknown. It is possible that this syndrome is produced by different etiologies in different patients, but the relative uniformity of this disorder argues for a common mechanism in at least the majority of cases.

In the early stages of several neurodegenerative disorders, especially early Alzheimer’s disease (see KCC 19.16), memory loss for recent events is often prominent, with no other obvious abnormalities. This phenomenon may occur because early Alzheimer’s disease tends to preferentially affect the bilateral hippocampal, temporal, and basal forebrain structures (see Figure 19.14). As Alzheimer’s disease progresses, other neurobehavioral abnormalities occur as well, as we will discuss in Chapter 19. Memory loss can also be seen as a part of numerous other diffuse or multifocal disorders of the nervous system stemming from many etiologies. In these disorders—which include multiple sclerosis, brain tumors, mucocerebral hemorhage, infarcts, CNS infections, various toxic or metabolic encephalopathies, CNS vasculitis, hydrocephalus, and many other conditions—a variety of other abnormalities are usually present in addition to memory loss. It is sometimes difficult to distinguish true memory disorders in these conditions from deficits in attention or language processing.

Psychogenic amnesia can occur in several settings, including dissociation, conversion, and malingering. In contrast to medial temporal lobe or diencephalic amnesia, patients with psychogenic amnesia usually do not have a pattern of retrograde and anterograde amnesia affecting mainly recent memories. Instead, patients with psychogenic amnesia often have memory loss for events of particular emotional significance. In psychogenic amnesia there may also be loss of autobiographical memories, such as one’s name and birthplace—memories that are ordinarily preserved in medial temporal lobe or diencephalic amnesia unless other severe cognitive deficits are present as well.

“Normal” memory loss occurs in several situations. Infantile amnesia is the inability for adults to recall events from the first 1 to 3 years of life. A variety of mechanisms have been proposed, but infantile amnesia is most likely the result of ongoing central developments in the brain. Another example of infantile amnesia is myelination, that are quite active during infancy and early childhood. At the other extreme of life, benign senescent forgetfulness is the presumably normal mind declining in memory function that occurs gradually over the decades. This should be contrasted with Alzheimer’s disease and other forms of dementia in which memory loss is more severe and occurs over the course of a few years.

In another normal form of memory loss, dreams can be recalled immediately after awakening from sleep, but they can no longer be remembered a few minutes later. Similarly, a common experience is being awakened from a deep sleep and having a conversation on the telephone that, the next day, one cannot recall. Finally, with the passage of time, forgetting normally occurs, in which memories gradually become less distinct and eventually may not be recalled.

The Amygdala: Emotions, Drives, and Other Functions

The amygdala (meaning “almond” in Greek), or amygdaloid nuclear complex, is a group of nuclei located in the lateral vertical temporal lobe, just dorsal to the anterior tip of the hippocampus and temporal horn. It has three main nuclei: the corticomedial, basolateral, and central nuclei (see Figures 18.4B, 18.6, 18.10). The bed nucleus of the stria terminalis (see Figure 18.4B) is also considered part of the amygdala. In humans, the basolateral nucleus is largest and is predominantly involved in direct and indirect connections of the amygdala to diverse cortical areas as well as to the basal forebrain and medial thalamus. The smaller corticomedial nucleus derives its name from its corticoid structure, located on the medial surface of the temporal lobe, near the basal forebrain and olfactory areas (see Figure 18.4A, B). The connections of the corticomedial nucleus are involved in olfaction, and interactions with the hypothalamus related to appetitive drives. The central nucleus is smallest and has connections with the hypothalamus and brainstem that are important in autonomic control.

As discussed in the beginning of the chapter, the amygdala plays a pivotal role in emotions and drives (see Table 18.2). However, through its extensive connections to other structures in the limbic network (see Figure 18.1), the amygdala is an active participant in all four major limbic functions (see Table 18.2). We will discuss functional roles of the amygdala and then review its main input and output connections.

Emotions and drives appear to be mediated by complex interactions among numerous brain regions, including the heteromodal association cortex, limbic cortex, amygdala, septal area, ventral striatum, hypothalamus, and brainstem autonomic and arousal pathways (Figure 18.17, A-B). The amygdala plays a central role, but the other components of the network are essential as well. On the basis of the effects of lesions in humans and experimental animals, the amygdala is important for attaching emotional significance to various stimuli perceived by the association cortex. When both amygdalas have been ablated, behaviour tends to be placid. Tame, nonaggressive behavior, together with other behavioral changes, constitutes the Klüver-Bucy syndrome studied in monkeys with bilateral lesions of the amygdala and adjacent temporal structures. (Klüver-Bucy syndrome has been observed only rarely in humans.) Seizures (see KCC 18.2) involving the amygdala and adjacent cortex cause powerful emotions of fear and panic.

Interestingly, while activity in the amygdala has been found to be important in states of fear, anxiety, and aggression, activity in the septal area appears to be important in pleasurable states. For example, experimental animals will press a lever repeatedly to obtain electrical stimulation of the septal area, even to the point of neglecting to eat in order to continue the stimulation. Increased activity has been recorded in the septal area during orgasm,
and lesions of the septal area in animals cause "sham rage," in which sudden outbursts of aggressive behavior occur. Sham rage behaviors have also been elicited by stimulating certain regions of the midbrain tegmentum.

Reciprocal connections between the amygdala and hypothalamic and brainstem centers for autonomic control mediate changes in heart rate, peristalsis, gastric secretion, piloerection, sweating, and other changes commonly seen with strong emotions. The limbic cortex, including the orbitofrontal, insula, anterior cingulate, and temporal cortex, (see Figure 18.2) has important connections with the hypothalamus as well. In addition, connections between the limbic cortex, amygdala, and the hypothalamus are important for neuroendocrinological changes seen in different emotional states. For example, patients with severe depression appear to have an increased susceptibility to infection, possibly resulting from endocrinological effects on the immune system. Although the amygdala was previously thought to be crucial for memory functions, more recent studies have instead emphasized the importance of the hippocampal formation. However, the amygdala does appear to play an important role in attaching emotional significance to memories. The role of the amygdala in olfaction, particularly in emotional and motivational aspects of olfaction, was mentioned earlier in this chapter.

Let's review the main input and output connections of the amygdala with these functional considerations in mind (see Figure 18.17). Most connections of the amygdala are bidirectional. In analogy to the hippocampal formation, the amygdala both receives and transmits information from diverse cortical areas, including heteromodal association cortex and limbic cortex (see Figure 18.17A). These connections occur through two pathways. Fibers pass posteriorly and laterally from the amygdala to reach most cortical areas, often via relay in the anterior temporal and insular cortices. In addition, the uncinate fasciculus passes anteriorly to connect the amygdala with the medial orbitofrontal and cingulate cortices (see Figures 18.4B, C, 18.17A). Table

Other Limbic Pathways

As should be clear by now, limbic circuits are fairly complex, and there are many other pathways in addition to those already mentioned. We will summarize only a few additional limbic pathways here (see Table 18.4), selected because they form prominent anatomical landmarks. The stria medullaris is a band of fibers that runs medially along the walls of the third ventricle, on the medial surface of the thalamus (see Figures 16.3A, 16.4D). It carries ventral amygdalofugal fibers that join the septal nuclei in the diagonal band of Broca, the diagonal band of Broca being an extension of the septum and the fornix, the posterior aspect of the hippocampus, and the stria terminalis. It contains fibers that join the prefrontal and limbic cortices. It continues posteriorly into the periaqueductal gray and eventually terminates in the medial geniculate nucleus.
fibers from the medial septal nuclei to the habenula, a small epithalamic structure located just lateral to the ponsial gland. The habenula, in turn, projects via the habenulo-interpeduncular tract (fasciculus retroflexus) to the interpeduncular nuclei in the midbrain. The interpeduncular nucleus projects to the mesencephalic raphe nuclei, which then project to the substantia nigra and other structures. These connections provide a network through which the habenula can influence other parts of the brain.

**KEY CLINICAL CONCEPT**

**SEIZURES AND EPILEPSY**

**TABLE 18.8 International Classification of Epileptic Seizures**

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Simple partial seizures</td>
<td>1. With motor signs 2. With sensory symptoms or signs 3. With autonomic symptoms or signs 4. With psychic symptoms</td>
</tr>
</tbody>
</table>

**Classification**

Seizures can be classified into several types, each with its own characteristics and implications for treatment. The International Classification of Epilepsy (Table 18.8) provides a framework for understanding these different types.

**A similar classification scheme is used for epilepsy syndromes. Specific epilepsy syndromes are defined based on the basis of the types of seizures that occur, together with other clinical features, such as age of onset, family history, and associated medical abnormalities other than seizures. In broad terms, however, epilepsy syndromes are divided into localization-related (partial, focal, or local) epilepsy and generalized, or primary generalized, epilepsy. Some seizures or epilepsy syndromes cannot easily be assigned to the local or generalized categories and remain unclassified. Ultimately, as our genetic and pathophysiological understanding of epilepsy improves, epilepsy syndromes will be defined on the basis of specific gene defects or cellular abnormalities.**

**Partial seizures** can be further subdivided into simple partial and complex partial seizures (Table 18.8). In simple partial seizures, consciousness is spared. For example, if a patient has rhythmic twitching movements of the left hand caused by a simple partial seizure in the right motor cortex hand area, they will remain at rest, talk normally during the seizure, and only become aware of the episode after it is over. Complex partial seizures can have positive symptoms, such as brief twitching, or negative symptoms, such as impaired language abilities. The combination of partial seizures depends on the anatomical regions of the brain in which the seizure activity occurs (Table 18.9). For example, as we discussed in Chapter 11 (see KCC 11.1), seizures in the primary visual cortex can cause simple partial seizures, whereas secondary generalized seizures in the extrastriate visual field, while seizures in visual association cortex can produce more elaborately formed visual hallucinations such as people's faces or complex scenes.

Patients with seizures in auditory cortex report simple sounds like a ringing engine or horn, most often coming from the direction opposite the involved cortex, or they may report having difficulty hearing, as if they were submerged underwater. Seizures in auditory association cortex can cause the patient to hear voices or music. Musical hallucinations are more common in nondominant hemisphere seizures (see KCC 19.13). Contralateral somatosensory phenomena occur during seizures in the somatosensory cortex.

The term aura means "breeze" and was originally used in ancient Greece by Galen's teacher Plineo to describe the sensation felt by one of his patients in his leg prior to having a large seizure. Aurae are brief simple partial seizures of any type that are experienced by a patient with no outward behavioral manifestations. They can occur in isolation, or they may serve as a warning for a larger seizure, with patients having seizures that typically begin in one region of the brain before spreading. Patients with seizures arising from medial temporal limbic structures (Table 18.9) often report a visceral sensation of rising in the epigastric area, a feeling of déjà vu, strange unpleasant odors, or feelings of extreme fear and anxiety. Odors and panic are thought to arise from the amygdala and nearby cortex, rather than from the hippocampus. Some reports suggest that olfactory phenomena during seizures can also arise from the orbital frontal olfactory cortex (see Figure 18.6).

As mentioned earlier, patients with seizures in primary motor cortex usually have simple rhythmic jerking tonic movements or sustained tonic contractions in the contralateral extremities. However, seizures in frontal motor association cortex, such as the supplementary motor area, can produce more elaborate movements, including a characteristic "fencing posture"; bilateral leg cycling movements; turning of the eyes, head, or entire body; and the production of unusual sounds. Typical duration for simple partial seizures is 5 to 10 seconds, although longer seizures are not uncommon. Recall that the time during a seizure is called the ictal period, and the time immediately after a seizure is called the post-ictal period. With brief simple partial seizures there are often no new post-ictal deficits. If the
## TABLE 18.9 Clinical Manifestations of Partial Seizures in Different Brain Regions

<table>
<thead>
<tr>
<th>TEMPORAL LOBE</th>
<th>LATERAL LOBE</th>
<th>FRONTAL LOBE</th>
<th>PARIETAL LOBE</th>
<th>OCCIPITAL LOBE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Temporal Lobe</strong></td>
<td><strong>Lateral Lobe</strong></td>
<td><strong>Frontal Lobe</strong></td>
<td><strong>Parietal Lobe</strong></td>
<td><strong>Occipital Lobe</strong></td>
</tr>
<tr>
<td>Medial: An indescribable sensation, rising epigastric (“better late in the stomach”), nausea, déjà vu, fear, panic, unpleasant odor, autonomic phenomena (tachycardia, pupillary dilation, ptosis, sweating, flushing, pallor, flushing), head with uncoordinated automatisms, stereotyped chewing, swallowing, or from the temporal lobes</td>
<td>Lateral: Vertigo (temporoparietal) or other auditory hallucinations (hearing or rousing engine, noise), elaborate auditory hallucinations (voices, music). Aphasias, including inability to understand what people are saying, to make overtures with dominant temporal seizures. Saying words or phrases repeatedly and having musical hallucinations are more common with nondominant temporal seizures.</td>
<td><strong>Frontal Lobe</strong></td>
<td><strong>Parietal Lobe</strong></td>
<td><strong>Occipital Lobe</strong></td>
</tr>
<tr>
<td><strong>Comments:</strong> Usual duration: 1 to 2 minutes, often with post-tetralamic amnesia, tingling, headache, emotional changes, or other focal deficits. Most common cause of complex partial seizures. Head or eye deviation probably results from spread to frontal or parietal lobes (see below). Medial temporal lobe seizures associated with hippocampal sclerosis usually do not generalize once treated with anticonvulsant medications; however, the complex partial seizures in this condition are often medically refractory and frequently require surgery.</td>
<td><strong>Supplementary motor area:</strong> Fencing posture with extension of contralateral upper extremity. Other tonic postures, speech arrest, uncoordinated sounds.</td>
<td><strong>Orbitofrontal and cingulate:</strong> Elaborate motor automatisms, making unusual sounds, sudden changes, laughter attacks (orbitofrontal, incontinence) (cingulate).</td>
<td><strong>Comments:</strong> Seizures are often brief, occur multiple times per day, and may have no post-tetralamic deficits. Nocturnal exacerbation is common. Elaborate motor automatisms without loss of consciousness or posttial deficits often lead to misdiagnosis of limbic epilepsy.</td>
<td><strong>Sparks, flashes, pulsating colored lights, scotomata, or hemianopsia in contralateral visual field (primary homonymous hemianopsia, ventrotemporal or occipito-temporal association cortex), nystagmus or oscillopsia, jerks, palatal jerks, eye blinking, sensations of eye oscillation.</strong></td>
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Note: Features of both simple partial and complex partial seizures are included here. Seizures may begin in one region and spread to another, producing signs and symptoms corresponding to multiple neuroanatomical areas.

Seizures are prolonged or recurrent, there may be post-tetralamic depression of the local region of cortex involved, producing focal weakness (Todd's paresis), or other deficits.

Unlike simple partial seizures, in complex partial seizures (see Table 18.8) there is impairment of consciousness. The impaired consciousness with complex partial seizures is presumably due to seizure activity affecting wider regions of cortex, or deep brainstem and subcortical regions. Impairment of consciousness in complex partial seizures may be complete or mild, sometimes making the distinction from simple partial seizures difficult. The most common localization for complex partial seizures is the temporal lobes; however, such seizures can arise from the frontal, parietal, or occipital lobes as well. Patients with complex partial seizures arising from the temporal lobes are sometimes said to have temporal lobe epilepsy, or psychomotor epilepsy. Medial temporal lobe-onset complex partial seizures (see Table 18.8) often begin with an aura, as described earlier, of an unusual, often indescribable sensation, or with epigastric, emotional, or olfactory phenomena, or déjà vu. Sometimes no aura can be recalled. The initial symptoms are followed by unresponsiveness and loss of awareness, during which the patient may have automatisms, which are usually repetitive behaviors such as lip smacking, swallowing, or stereotyped hand or leg movements such as stroking, wringing, or patting.

Interestingly, in temporal lobe seizures the ipsilateral basal ganglia are often involved, causing contralateral dystonia or immobility (see KCC 16.1), while the ipsilateral extremities remain free to exhibit automatisms. These behaviors can be falsely localizing to the unpracticed eye, since the side ipsilateral to the temporal lobe seizure shows movements (automatisms), while the contralateral side is relatively still (dystonia). Sometimes instead there is simply bland staring, immobility, and unresponsiveness. Autonomic phenomena such as tachycardia, pupillary dilation, and ptosis occur in up to 30% of patients. Post-tetralac deficits may last from minutes to hours and can include unresponsiveness, confusion, amnesia, tiredness, agitation, aggression, and depression. Headache is common. Patients with left temporal-onset seizures may have post-tetralamic language deficits, although care must be taken to distinguish such deficits from overall decreased responsiveness, which is nonlocalizing. There may also be some mild posttial weakness or hypereflexia contralateral to the side of onset. This is usually subtle, unless the seizure has spread to the motor cortex, in which case there would be unilateral tonic or clonic activity during the seizure.

The most common type of generalized seizure is a generalized tonic-clonic, or grand mal, seizure (see Table 18.8). A generalized tonic-clonic seizure can be generalized from the onset, or it may begin focaly and then secondarily generalize. It typically begins with a tonic phase characterized by loss of consciousness and generalized contraction of all muscles lasting for 10 to 15 seconds. This often results in stiff extension of the extremities, during which the patient may fall “like a tree” and injure themselves, and a characteristic expiratory gasp or moan may occur as air is forced past the closed glottis. Next is a clonic phase, characterized by rhythmic bilateral jerking contractions of the extremities, usually in flexion, at a frequency of about 1 hertz, which gradually slow down and then stop. Incoincidence or tongue biting is common. There is usually a massive intracranial autonomic outpouring with tachycardia, hypertension, hyperpneivation, and pupillary dilation. Typical duration is 30 seconds to 2 minutes. Immediately postictally, patients lie immobile, flaccid, and unresponsive, with eyes closed, breathing deeply to compensate for the mixed metabolic and respiratory acidosis produced by the seizure. Within a few minutes they usually begin to move and respond. Post-tetralamic deficits last from minutes to hours and include profound tiredness, confusion, amnesia, headache, and other deficits related to the location of seizure onset.
In addition to generalized tonic-clonic, or grand mal, seizures, there are a variety of other generalized seizure types (see Table 18.8). Most of these are relatively uncommon and will not be discussed further here, with the exception of absence seizures. Typical absence (petit mal) seizures are brief episodes of staring and unresponsiveness lasting for about 10 seconds or less. There are no post-ictal deficits, except for a lack of awareness of what occurred during the brief time of the seizure. These seizures are accompanied by a characteristic generalized 3-4 Hz spike and wave discharge on electroencephalogram (EEG) recordings (see Chapter 4).

Although absence seizures are generalized, they differ from grand mal seizures, which begin with a prolonged high-frequency electrical discharge that causes a more severe disruption of brain function. Absence seizures are most common in childhood and can occur multiple times per day, causing impaired school performance. They often can be provoked by hyperventilation, strobe lights, or sleep deprivation. About 40% of children with typical absence seizures remit spontaneously. It should be noted that both absence seizures and complex partial seizures can cause episodes of staring and unresponsiveness. Typical cases of medial temporal lobe complex partial seizures can usually easily be distinguished from typical absence seizures on clinical grounds (Table 18.10). However, in atypical absence seizures or brief complex partial seizures, the distinction may be more difficult.

When seizures of any type occur continuously, or repeatedly in rapid succession, the condition is referred to as status epilepticus. Generalized tonic-clonic status epilepticus is a medical emergency that requires immediate and aggressive treatment. When first-line agents such as benzodiazepines and phenytoin are ineffective, intubation and general anesthesia may be necessary. EEG recording should always be performed urgently in this situation to ensure that electrographic seizure activity has stopped. Blood tests (see the next subsection), head CT, and lumbar puncture (when appropriate) should be performed without delay so that specific treatments can be initiated. Prognosis depends mainly on the promptness of treatment and on the underlying etiology. Other forms of status epilepticus aside from tonic-clonic seizures should also be treated promptly, although the balance must be struck between the risks of aggressive treatment and the risks of ongoing seizures. The behavioral features of status epilepticus can sometimes be subtle, so the prompt performance of an EEG is often needed for the diagnosis to be made, and for treatment to be initiated.

**Diagnosis and Etiology**

The diagnostic evaluation of patients with epilepsy is essential because the correct diagnosis has a major impact on treatment. The first step is to ascertain whether the episodes are epileptic seizures or another type of transient event (see Tables 10.2, 16.3). Epileptic seizures are usually brief events that are stereotyped from one episode to the next in a given patient and often fit one of the typical seizure patterns already described. If the events are epileptic seizures, the next step is to determine the type of seizure (see Tables 18.8, 18.10), as well as the localization if the seizures are focal in onset (see Table 18.9). Finally, a cause for the seizures should be sought (Table 18.11).

The fundamental tools used for diagnosis in epilepsy include a detailed clinical history; physical exam; basic blood tests; MRI scan with special thin coronal cuts and pulse sequences used to view the medial temporal, cortical, and subcortical structures in detail; and an interictal EEG (see Chapter 4). When the diagnosis remains uncertain, additional tests can be helpful in diagnosis and localization. These include admission for continuous video and EEG monitoring in an attempt to obtain an ictal recording; ictal and interictal nuclear medicine tests, such as SPECT (single photon emission computed tomography) and PET (positron emission tomography) scans; and neuropsychological testing. In patients who are being considered for epilepsy surgery, additional tests, including a Wada test (see the next subsection), are often performed.

Let's briefly discuss some of the individual causes of seizures listed in Table 18.11. The most common causes vary with age, resulting in a bimodal age distribution for the risk of developing new-onset seizures. The risk of new-onset seizures is high in infancy and childhood, declines in adulthood, and then rises again in the elderly population. The most common causes of seizures in infancy and childhood are febrile seizures, congenital disorders, and perinatal injury. In contrast, the most common cause in patients over age 60 years is cerebrovascular disease, followed by brain tumors and neurodegenerative conditions.

The risk of seizures after head trauma increases with the severity of the injury. Minor head injuries with no clear structural damage and only brief confusion or loss of consciousness (for less than 30 minutes) do not pose a significant risk for subsequent seizures. Hypoglycemia, electrolyte abnormalities such as hyponatremia, hypernatremia, hypercalcemia, or hypoparathyroidism; metabolic abnormalities or exposure to a variety of endogenous or exogenous toxic substances can provoke seizures. It is therefore essential to check blood chemistries, including glucose, sodium, calcium, magnesium, liver function tests, creatinine, and a toxicology screen when assessing a patient with new-onset seizures, especially in the acute setting, so that these abnormalities can be corrected.

**Febrile seizures** are fairly common, occurring in 3 to 4% of all children, usually between the ages of 6 months and 5 years. These are usually brief, generalized tonic-clonic seizures called simple febrile seizures, which are not associated with increased risk of epilepsy. However, there is an increased risk of subsequent epilepsy in children with complex febrile seizures, defined as seizures lasting more than 15 minutes, or occurring more than once in 24 hours, or having focal features. Some of these children may have an underlying cause for epilepsy that is first unmasked in the setting of fever. It has also been hypothesized that prolonged febrile seizures cause subsequent temporal lobe epilepsy in some patients, through a pathologic process called mesial temporal sclerosis or hippocampal sclerosis, in which there is marked neuronal loss and gliosis, particularly in the CA1 sector of the hippocampus, as well as in other medial temporal structures. In addition to febrile seizures, mesial temporal sclerosis may also be triggered by other initial precipitating injuries in infancy and childhood, such as head trauma or...
CNS infections. Once established, there is often a latent period of up to several years between the precipitant and the onset of complex partial seizures. The seizures usually consist of a hard-to-describe aura of fear or epileptic sensation and other features typical of medial temporal lobe seizures (see Table 18.9). Once treated with anticonvulsant medications, seizures in patients with mesial temporal sclerosis rarely generalize. However, the complex partial seizures in these patients can be quite incapacitating, and are often associated with memory decline. In addition, unlike the seizures observed in patients with seizures, the complex partial seizures in these patients are often medically refractory. Based on the diagnostic methods discussed earlier, unilateral surgical resection of the medial temporal lobe structures has a cure rate of over 90% at patients localized to one temporal lobe.

Numerous other causes of focal brain lesions, some of which are listed in Table 18.11, can result in seizures, and many can be detected by a good-quality MRI scan. Family history is also essential in assessing patients with seizures. Many epilepsy syndromes, especially primary generalized epilepsies, but also some focal disorders, have a genetic component. Rolandic epilepsy is a common cause of focal, mostly nocturnal seizures in children that probably has autonomic inheritance with incomplete pene-

trance. The EEG shows characteristic centrotemporal spikes. Onset is usually between ages 3 and 13, and seizures are often mild, not always requiring medications. Remission is nearly always complete by age 15 years.

There are several familial primary generalized epilepsy syndromes, including childhood absence epilepsy (pyknotic), characterized by typical absence seizures (discussed earlier), juvenile myoclonic epilepsy, and other disorders. For a more detailed discussion of the many other causes of epilepsy, see the references at the end of this chapter.

Treatment
The basic goals of epilepsy treatment are to reduce the risk of seizures while minimizing side effects, to achieve the best possible overall quality of life. Major considerations include impact on driving (regulations vary from state to state), ability to work, the unfortunate public stigma associated with seizures, and effects on pregnancy and lactation.

Medications
Medications can be used to achieve satisfactory control of seizures in over 70% of cases. The first-line agents for treatment of localization-related epilepsy, with or without secondary generalization, are carbamazepine (Tegretol) and phenytoin (Dilantin). For childhood absence epilepsy, the first-line agent is ethosuximide (Zarontin). If treatment with ethosuximide is unsuccessful, or if grand mal seizures are present as part of a primary generalized epilepsy syndrome, valproate (Depakene) is preferred. After a period of 15 years in which no major new anticonvulsant medications were introduced in the United States, the pharmaceutical industry began in 1993 to reintroduce anticonvulsant medications. An average of 1 to 2 new anticonvulsants per year have appeared on the market since that time. Many of these new anticonvulsants have advantages over the medications already discussed, although the newer medications are still not typically used for first-line therapy (see References for additional details on epilepsy medications).

About 20 to 30% of patients with epilepsy have seizures that cannot be adequately controlled with medications and are considered medically refractory. Some children with refractory epilepsy may improve on a high-fat, low-carbohydrate ketogenic diet, but the effect is often temporary and does not always lead to significant reduction in seizure frequency. In appropriately selected candidates, several different surgical approaches can be used to treat medically refractory epilepsy. As we have already mentioned, the best candidates for surgical resection have epilepsy localized to a single temporal lobe; these patients have a surgical success rate of over 90%. Patients with confirmed localization to a single location other than the temporal lobe can also often be treated successfully.
with surgical resection. For these patients with extratemporal epilepsy, the best outcomes are usually seen when all diagnostic studies point to a single location; however, certain other features may also predict a favorable prognosis, including a focal lesion visible on MRI scan or seizure onset in the supplementary motor area. Surgery is considered successful if patients no longer have seizures and have no adverse effects from the surgery. Although many patients must continue anticonvulsant medications following surgery, to maintain freedom from seizures, this is still a major lifestyle improvement for patients who, prior to surgery, had frequent seizures even with medications. Following successful surgery, for example, many previously disabled patients are able to drive and to pursue productive employment.

In some patients, the seizure onset lies in a functionally critical area such as the motor or language cortex, and surgical resection cannot safely be performed. In these patients, multiple subpial transection may be helpful. In this procedure, a special sharpened probe is inserted under the pia and is used to sever the corticocortical connections, thereby making multiple parallel tracts that functionally disconnect the epileptogenic cortex. Patients with severe epilepsy arising from multiple locations in the brain may benefit from callosotomy. In this procedure, the corpus callosum is cut, preventing seizures from propagating from one hemisphere to the other. Callosotomy does not cure seizures. The procedure is reserved mainly for patients who have frequent falls and injuries when their seizures generalize. These patients may be helped if generalization is prevented, by allowing them to avoid such falls during seizures. Deficits associated with callosotomy are discussed in KCC 19.8.

In some patients, the seizure onset is not localized to a specific region but rather to multiple regions within a single hemisphere. In patients younger than 2 to 3 years, hemispheric specialization is still under development. Therefore, in some of these patients, hemispherectomy (surgical resection of an entire hemisphere) can be considered. Remarkably, many patients do quite well following hemispherectomy and are able to lead functional lives. Seizures are often cured, allowing language and motor development (often arrested by severe epilepsy) to proceed, with language and motor representation for both sides of the body forming in the single remaining hemisphere. In summary, the majority of patients with epilepsy can be successfully treated with either medications or other therapies discussed here and are able to resume their normal lives.

The neural basis of many psychiatric disorders is beginning to be better understood through a convergence of information derived from pathologic and anatomical imaging studies, functional imaging studies, neuropharmacological analysis, and other methods of investigation, such as molecular genetics. In this section we will briefly discuss some of the major pathophysiological findings for a few common psychiatric disorders on a basic level.

Schizophrenia
Patients with schizophrenia exhibit a variety of abnormalities of thought, including delusions, hallucinations, disorganized tangential speech, flat affect, and occasionally a profound decrease in spontaneous activity called catatonia. Studies of the pathophysiology of schizophrenia have suggested abnormalities in the limbic system, frontal lobes, and basal ganglia. Both pathologic studies and high-resolution MRI have demonstrated bilateral subtle decreases in the volume of the amygdala, hippocampal formation, and parahippocampal gyrus in patients with schizophrenia. More variable anatomical changes have also been reported in the basal ganglia and other regions.

Functional imaging studies such as PET scanning have shown decreased activation of the dorsolateral prefrontal cortex in patients with schizophrenia during tasks such as the Wisconsin Card Sorting Test. Much evidence suggests that an abnormality in dopamine is important in schizophrenia; for example, psychotic symptoms improve with antipsychotic agents. Recall from Chapter 16 that dopaminergic neurons in the ventral tegmental area project to the nucleus accumbens and ventral striatum, as well as to the prefrontal cortex and limbic cortex (see also Figure 14.10). Some other neurotransmitter systems may be important as well in the pathogenesis of schizophrenia, including glutamate, gamma-aminobutyric acid (GABA), serotonin, and norepinephrine. A complete pathophysiological understanding of schizophrenia is complicated by the fact that this disorder can include both positive symptoms such as psychotic delusions and hallucinations, and negative symptoms such as flat affect and impaired executive function. The most likely cause of schizophrenia is a combination of abnormalities in several anatomical areas and neurotransmitter systems.

Obsessive-Compulsive Disorder
In obsessive-compulsive disorder, recurrent intrusive obsessive thoughts cause the patient much anxiety, while the performance of repetitive compulsive behaviors such as hand washing or checking the door lock provide temporary relief. The improvement of obsessive-compulsive symptoms with serotonin-enhancing medications suggests a role for serotonin in this disorder; however, other neurotransmitters may be important as well. Functional imaging studies have shown abnormally increased activity in the basal ganglia, especially the head of the caudate, as well as in the anterior cingulate gyrus and orbital frontal cortex. These changes improve with pharmacological or behavioral treatment.

MRI studies have shown a subtle bilateral decreased volume in the head of the caudate, but these findings are not conclusive. Thus, obsessive-compulsive disorder appears to result from dysfunction in a network consisting of the caudate, cingulate gyrus, and orbital frontal cortex. This may be analogous to hyperkinetic movement disorders (see Chapter 16), but with unwanted thoughts or compulsions instead of movements. Indeed, there may be some overlap, since obsessive-compulsive disorder is present in about half of patients with Tourette's syndrome and can also occur in Huntington's disease, Sydenham's chorea, and other basal ganglia disorders.

Anxiety
Anxiety disorders encompass a variety of conditions, including panic disorder, phobias, posttraumatic stress disorder, and generalized anxiety disorder. Obsessive-compulsive disorder is also classified as an anxiety disorder. Anxiety is thought to be associated with an increase in noradrenergic and serotonergic transmitter systems in the central nervous system. In addition, anxiety symptoms can be controlled with benzodiazepines, which act on GABA_A receptors. Symptoms of anxiety, panic, and fear are also accompanied by increased peripheral sympathetic tone and increased release of epinephrine by the adrenal glands. Functional imaging studies during episodes of panic have shown inconsistent results, but they may demonstrate increased activation in the anterior cingulate and temporal cortices. Evidence from patients with panic as an epileptic phenomenon suggests involvement of the amygdalar region of the medial temporal lobes.

Depression and Mania
Patients with depression have a sad mood and lack of enjoyment, together with other findings, such as impaired concentration, increased or decreased
sleep, appetite, or level of activity, and feelings of worthlessness, guilt, and suicidal thoughts or actions. In contrast, patients with mania have an abnormally elevated, irritable mood, with other features including grandiosity, decreased sleep, pressured speech, racing thoughts, distractibility, increased activity, and impulsive behavior. A variety of evidence suggests that depression is marked by deficits in both the noradrenergic and serotonergic neurotransmitter systems. Other transmitters may be important as well, including dopamine, serotonin, and neuropeptides.

Structural and functional imaging studies in depression have produced contradictory results, but there is some evidence of a decrease in activity of the cerebral cortex, with a more prominent decrease in the parietal lobes. Neuropeptide changes occur in depression as well, including an increased release of cortisol in about 40% of patients with depression, resulting from increased release of corticotropin-releasing hormone by the hypothalamus. The effects of brain lesions on mood have also shed some light on possible mechanisms for mood disorders. Some studies suggest that left frontal lesions are more likely to produce a depressed mood, whereas right frontal lesions tend to produce an abnormally elevated mood, although these associations are not always consistent. Similarly, bilateral lesions of the diencephalic frontal cortex tend to produce a flat affect resembling depression (see KCC 19.11), while bilateral lesions of the medial orbitofrontal cortex may produce an abnormally elevated affect.

CLINICAL CASES

CASE 18.1 SUDDEN MEMORY LOSS AFTER A MILD HEAD INJURY

MINICASE

A 33-year-old neurology resident with a history of migraine fell backward while attempting a ski jump, struck his occiput on the snow, and suddenly developed amnesia. His wife witnessed the incident and reported that he had not lost consciousness from the fall. He stood himself up, skied part way down the slope, and then stopped skiing to tell his wife that he must have amnesia because he did not know the date, where he was, or how he had gotten there. He also reported seeing a scintillating scotoma in the left upper part of his visual field, like that accompanying his typical migraines.

At first his wife thought he was joking around, but when he began asking the same questions repeatedly, it soon became clear that he had a serious problem. He was unable to retain any new information for more than 1 to 2 minutes. In addition, he did not recall any events that had occurred during the previous approximately 1 year, including the fact that his wife was pregnant. Aside from the memory loss, he had no other significant deficits. He was taken to a local hospital, where a head CT was normal, and he was discharged in the care of his wife and friends. Being a neurologist, he constantly urged those around him to test his memory during the long car ride home. Meanwhile, he was able to enjoy the exciting "news" that his wife was pregnant, over and over again. Approximately 5 hours after onset, he was finally able to recall three words after a 3- to 4-minute delay, but this ability was still inconsistent. At about the same time, memories from the previous year began to return gradually, with the most remote memories generally returning first. By the next morning he was able to consistently recall new facts about as well as at baseline. In addition, he remembered everything from the previous year, except for a period extending from 2 to 3 hours before the injury to about 5 hours after the injury. An MRI scan performed a few days later was normal.

LOCALIZATION AND DIFFERENTIAL DIAGNOSIS

1. On the basis of the symptoms and signs shown in bold above, what type of memory was impaired in this patient? How would you describe the chronological features of his amnesia? Dysfunction in which locations in the brain could produce these findings (see KCC 18.1)?

2. What is the most likely diagnosis, and what are some other possibilities?

Discussion

The key symptoms and signs in this case are:

- Inability to retain any new information for more than 1 to 2 minutes, and asking the same questions repeatedly
- Inability to recall any events that had occurred during the previous approximately 1 year
- During recovery, return of the most remote memories generally first

1. The patient was unable to remember facts and events; therefore, he had a deficit in declarative (explicit) memory (see Figure 18.15). He had anterograde amnesia, since he was unable to learn new information, and retrograde amnesia for a period of about 1 year prior to the injury (see Figure 18.16). This pattern of selective declarative memory loss with anterograde and retrograde amnesia is characteristic of bilateral medial temporal or bilateral medial diencephalic dysfunction (see KCC 18.1). Asking the same questions repeatedly is also typical of acute dysfunction in these areas, and recovery of remote memories prior to more recent ones is often seen when the memory loss is reversible.

   The most likely clinical localization is bilateral medial temporal or bilateral medial diencephalic structures.

2. Given the onset after a head injury, concussion must be considered as the cause of amnesia in this patient (see KCC 18.1; see also KCC 19.5). No loss of consciousness was observed; however, it may have been too brief to be noticed. Interestingly, it is unclear whether concussion causes amnesia due to direct impact to the medial temporal structures, or whether the mechanism is diffuse dysfunction of the white matter pathways necessary for normal function of the medial temporal and medial diencephalic memory systems.

3. Alternatively, the clinical features of the memory loss and recovery in this patient could represent transient global amnesia (see KCC 18.1) that occurred coincidentally following a minor head injury. The onset in the setting of stress and history of migraine are also suggestive of this diagnosis, as are the typical migraine symptoms of a scintillating scotoma (see KCC 5.1) reported by the patient during the episode. Other causes of transient amnesia, which are less likely, given the history in this patient, include transient ischemic attack, seizure, Wernicke's encephalopathy, psychogenic amnesia, or administration of a benzodiazepine or other medication (see Table 18.7).

Clinical Course

The patient resumed work a few days later and had no further episodes of amnesia. On follow-up over 5 years, he had no deficits except for continued lack of memories for the period of a few hours before and after onset of his amnesia.
CASE 18.2 PROGRESSIVE SEVERE MEMORY LOSS, WITH MILD CONFABULATION

MINICASE

A 75-year-old semiretired businessman was brought to the emergency room by his friends because of several weeks of severe progressive memory problems. At baseline, the patient had normal cognition, exercised avidly, and maintained an active schedule, driving himself to appointments with friends and business associates. Ten days prior to admission he met a friend for lunch and had a normal, clear, precise conversation, except that he did not remember the name of the hostess, whom he had known for several years. Four days later, the same friend spoke with the patient on the phone and discovered that the patient had no recollection of having lunch or of any of their conversation. He seemed normal otherwise. The next day the patient missed an important business meeting. When the patient's son contacted him over subsequent days, his conversation seemed appropriate except that he was totally unaware of current events, including a recent highly publicized plane crash. There was no known history of alcoholism.

Exam was normal except for profound problems with recent memories and milder problems with remote memories. He said the year was 1964 (it was 1994) and realized he was in a hospital but did not know which one. Attention and immediate recall were normal, with a digit span forward of 7 and backward of 5. He was able to repeat three words immediately when asked to memorize them. After 3 minutes, however, he did not even recall the task, and he got 0/3 words correct even with multiple choice. When the examiner left the room and came back a few minutes later, the patient had no recollection of having met him before.

The patient had no knowledge of recent current events and was completely unaware of the highly publicized O. J. Simpson trial going on at the time. More remote memory was better but still not perfect. For example, he was able to describe his hometown, childhood, family members, marriage, and the fact that he had fought in World War II. However, he could not recall any battles he fought in, and he was surprised to hear that John F. Kennedy had been shot. He did not know that Johnson and Nixon were presidents during the Vietnam War, or that his wife had died a few years back. With some prompting, however, he was able to generate the name of the current president: "Clinton." There was also a mild tendency to confabulate. For example, when asked why he was in the hospital, he said he "came here to pick up some things and leave," and when asked if anyone had visited him, he mentioned several names despite having had no visitors. The remainder of the mental status exam was normal, including normal attention span (see above), pleasant affect and behavior, normal language, good calculations, normal reading and writing, normal drawing of a clock face and cube, and good interpretation of similarities and proverbs. The rest of the neurologic exam was likewise normal.

LOCALIZATION AND DIFFERENTIAL DIAGNOSIS

1. On the basis of the symptoms and signs shown in bold above, where is the lesion?
2. What is the most likely diagnosis, and what are some other possibilities?

Discussion

The key symptoms and signs in this case are:

- Severe progressive problems with recent memory and milder problems with remote memory
- Tendency to confabulate

1. As in Case 18.1, this patient had anterograde and retrograde amnesia affecting declarative memory, which could be caused by dysfunction of the bilateral medial temporal or bilateral medial diencephalic structures (see KCC 18.1). Unlike the patient in Case 18.1, however, this patient also had a mild tendency to confabulate. This symptom suggests additional dysfunction affecting the frontal lobes (see KCC 19.11).

2. The time course of the memory decline in this patient was too rapid to be a neurodegenerative disorder such as Alzheimer's disease, which progresses over months to years, rather than over weeks as in this case (see KCC 19.16). Wernicke-Korsakov syndrome resulting from thiamine deficiency should be considered, since this disorder causes declarative memory loss, often with confabulation (see KCC 18.1). However, there was no known alcoholism or nutritional deficiency in this case, and onset in Wernicke-Korsakov syndrome is often more abrupt. Given the insidious onset, other important possibilities to consider are those listed in Table 18.7, including tumor, paranocaplastic limbic encephalitis, or other inflammatory or infiltrative disorders affecting the bilateral medial temporal or medial diencephalic structures and extending to the frontal lobes. Other, less likely possibilities include an anterior communicating artery aneurysm that had a small hemorrhage followed by a larger hemorrhage, or several transient ischemic attacks or small infarcts followed by a larger infarct.

Clinical Course and Neuroimaging

The patient was given thiamine with no benefit and was admitted to the hospital, where a brain MRI with gadolinium (Figure 18.18) revealed markedly abnormal enhancement in the bilateral medial temporal lobes, including the anterior hippocampal formations and amygdalae. In addition, there was less dramatic enhancement in the fornix, bilateral periventricular regions of the third ventricle, and fornix of the Monro (see Figure 18.13) and extending to the bilateral basal forebrain and medial orbital frontal cortex (see Figure 18.18C). Several hyperintense areas (see KCC 5.3) and blood tests were done but did not yield a diagnosis. A follow-up examination revealed that the patient had lost his sense of smell, suggesting that the lesion had spread to involve adjacent olfactory structures such as the bilateral pituitary cortex or olfactory bulbs (see Figures 18.5, 18.6). Over the course of several days he became more disoriented, stating that his location was "Israel," and he responded more slowly to questions. This change raised concerns about more diffuse spread, and a stereotactic biopsy (see KCC 16.4) of the right orbital frontal cortex was therefore done. Pathologic examination revealed an atypical-appearing B cell lymphoma (see KCC 5.8).

The patient was treated with steroids and multiple cycles of intravenous chemotherapy with methotrexate and had a dramatic improvement in his memory. One month after diagnosis he was able to recall 3/4 words at 5 minutes, and 4/4 with hints. Formal neuropsychology testing revealed that he still had some subtle residual memory deficits in both verbal and visual-spatial domains. Repeat MRI scan 3 months after diagnosis showed complete disappearance of the enhancing lesions, and the patient had resumed most of his previous activities. He continued chemotherapy, and at last follow-up, 15 months after diagnosis, he was doing well, recalling 3/3 words after 10 minutes.
CASE 18.3 TRANSIENT DIPLOPIA, LETHARGY, AND HEMIPARESIS, FOLLOWED BY A SUSTAINED MEMORY DEFICIT

MINICASE
A 45-year-old right-handed research technician woke up late for work on Monday and noticed that he had horizontal diplopia, which disappeared if he covered one eye. His wife found him in the bathroom with his head resting on the sink. He helped her back to bed and thought he seemed unusually somnolent, with slurred speech, so she called 911. In the emergency room the patient was initially back to baseline, but then he had a transient episode of right-sided weakness lasting approximately 30 minutes. Neurologic exam, after he recovered from this episode, was entirely normal except for a deficit in recent memory. He was alert and oriented × 3, with good attention, spelling "world" forward and backward correctly, and he knew the names of the past three presidents. However, he recalled 0/3 words after 3 minutes.

LOCALIZATION AND DIFFERENTIAL DIAGNOSIS
1. Dysfunction in which part of the brain could account for all of the transient symptoms listed in bold above (excluding the memory loss)?
2. In what locations could a lesion produce memory loss as described in this case?
3. What is the most likely diagnosis, and what are some other possibilities?

Discussion
The key symptoms and signs in this case are:
- **Horizontal diplopia**
- **Somnolence**
- **Dysarthria**
- **Transient right-sided weakness**
- **Deficit in recent memory**

1. Horizontal diplopia, together with somnolence and dysarthria, strongly suggest brainstem dysfunction involving, respectively, horizontal eye movement pathways (see KCC 138), the pontomesencephalic reticular activating system (see KCC 142), and corticobulbar or cerebellar pathways (see KCC 143). The episode of transient right-sided weakness could also be explained by involvement of brainstem corticobulbar fibers (see KCC 6.3, 14.3). These abnormalities together suggest dysfunction of the medial pons (abducens fasciculus or nucleus, paramedian pontine reticular formation, or medial longitudinal fasciculus reticular activating system; corticobulbar or pontocerebellar fibers; and corticospinal tract), or of the midbrain (oculomotor fasciculus or nucleus, convergence center, or medial longitudinal fasciculus reticular activating system; corticobulbar, corticospinal, or subcortical fibers; and corticospinal tract). Note that horizontal diplopia with no vertical component, and hemiparesis, are more common with pontine than with mesencephalic lesions (see KCC 163).

2. After recovering from the initial transient episode, this patient had anterograde amnesia for declarative memories. He was more mildly affected than the patients in Cases 18.1 and 18.2, since he was able to remember some recent information, such as his location and the correct date. Some retrograde amnesia may have been present as well, although this was not specifically described. This patient's deficit in declarative (explicit) memory, with preserved attention and other cognitive skills, suggests bilateral medial temporal or bilateral medial diencephalic dysfunction (see KCC 18.1).

3. The transient neurologic symptoms in this patient (see KCC 103) affecting the pons or midbrain were most likely caused by transient ischemic attack, or possibly migraine. Given this, the sudden onset of a permanent memory deficit suggests that the transient episodes heralded a subsequent infarct in the medial temporal lobes or diencephalon. Together these findings could indicate a "basilar scarp" syndrome (see KCC 143), with an embolus migrating up the basilar artery causing transient symptoms. Various penetrating arteries were temporarily occluded, followed by an infarct when the embolus lodged at the top of the basilar, obstructing bilateral thalamoperforator arteries or branches of the bilateral PCAs supplying both medial temporal lobes.

Clinical Course and Neuroimaging
A head CT revealed no hemorrhage or infarct, and the patient was admitted and treated with intravenous heparin while an embolic workup was pursued. A brain MRI done the day after admission (Figure 18.19) showed bilateral T2-bright areas consistent with infarcts in both medial thalami, larger on the left than on the right side. An magnetic resonance angiogram, echo-cardiogram, and 24-hour cardiac Holter monitor were negative. However, a hypercoagulation profile showed activated protein C resistance, a disorder that can predispose affected individuals to blood clot formation. Heparin was therefore changed to aspirin and coumadin with Coumadin by the time of discharge. By hospital day 2 the patient was able to recall 3/5 words after 5 minutes.

Neuropsychology testing was done on hospital day 3 and repeated on hospital day 5. Subtests of the Wechsler Memory Scale—Revised were used to test verbal and visual memory. To test verbal memory, two paragraphs were read to the patient, and he was scored on his ability to recall items from the paragraphs immediately after they were read and after a 20-minute delay. To test visual memory, the patient was shown three cards with printed geometric designs, and he was scored on his ability to draw the designs from memory immediately and after a 20-minute delay. The results are shown in the table below.

<table>
<thead>
<tr>
<th>Results of the Wechsler Memory Scale Test*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Verbal memory</strong></td>
</tr>
<tr>
<td>Immediate</td>
</tr>
<tr>
<td>1%</td>
</tr>
<tr>
<td>21%</td>
</tr>
<tr>
<td>Delayed</td>
</tr>
<tr>
<td>2%</td>
</tr>
<tr>
<td>8%</td>
</tr>
<tr>
<td><strong>Visual memory</strong></td>
</tr>
<tr>
<td>Immediate</td>
</tr>
<tr>
<td>9%</td>
</tr>
<tr>
<td>72%</td>
</tr>
<tr>
<td>Delayed</td>
</tr>
<tr>
<td>16%</td>
</tr>
<tr>
<td>45%</td>
</tr>
</tbody>
</table>

*Scores are expressed as the percentile of the normal population. Scores that were significantly lower than the normal range are shown in bold.

On hospital day 2 the patient had severe deficits in verbal memory and a barely significant deficit in delayed visual memory. On hospital day 5, he continued to have a significant deficit in delayed verbal memory. The discrepancy between verbal and visual memory in this patient was likely due to the larger lesion on the left side (see Figure 18.19). Similar discrepancies are seen in patients with asymmetrical lesions in medial temporal memory structures. Repeat neuropsychology testing 2 months later showed further improvements in his verbal memory. At a follow-up appointment 6 months after the stroke, he was still able to recall only 3/5 words after 5 minutes, but he was back to his previous level. He was not aware of any language or memory difficulties.
CASE 18.4. EPISODES OF PANIC, Olfactory Hallucinations, and Loss of Awareness

MINICASE
A 40-year-old right-handed woman came to the emergency room because of unusual episodes. She had been healthy until 2 weeks previously, when she awoke one night from sleep and complained to her husband of an indescribable unpleasant odor, nausea, and a panicky, fearful sensation. This lasted for 2 to 3 minutes, after which she felt very tired and went back to sleep. During the following week, while traveling with a Girl Scout troop, she began having stereotyped episodes about three times per day. These always began with panic, nausea, and a strong unpleasant odor “like smelling salts,” followed by decreased responsiveness and slow, inappropriate speech lasting 2 to 3 minutes. After each episode she had a bifrontal headache and felt very tired. On the day of presentation, she had six episodes of this kind, so her husband brought her to the emergency room. General exam and a detailed neurologic exam were normal.

LOCALIZATION AND DIFFERENTIAL DIAGNOSIS
1. On the basis of the symptoms shown in bold above, where in the brain is dysfunction occurring during the episodes?
2. What type of transient neurological episode was this patient most likely experiencing (see KCC 10.3)?
3. What is the most likely diagnosis, and what are some other possibilities?

Discussion
The key symptoms and signs in this case are:
- Episodes of an indescribable unpleasant odor, nausea, and a panicky, fearful sensation
- Decreased responsiveness and slow, inappropriate speech

1. Episodes of olfactory phenomena, nausea, and panic could arise from dysfunction in the amygdala and adjacent cortex in the medial temporal lobe. Decreased responsiveness can be caused by dysfunction of the brainstem-diencephalic activating systems or of bilateral diffuse regions of the cerebral hemispheres (see KCC 14.2). The slow, inappropriate speech could either signify involvement of language areas in the left hemisphere (see KCC 19.6), or it could be secondary to the impaired responsiveness, as already mentioned.

The overall clinical presentation in this patient is focal dysfunction of the amygdala and adjacent cortex (most likely of the left hemisphere), as well as milder, more diffuse dysfunction of both hemispheres or of the activating systems.

2. The transient episodes in this patient (see KCC 10.3) could be caused by seizures arising from the medial temporal lobe. Since there was decreased responsiveness, these events would be classified as complex partial seizures (see KCC 18.2). Additional support for this diagnosis comes from the fact that the episodes were stereotyped, had the appropriate duration for complex partial seizures, and were followed by post-ictal dizziness and headache. The slow, inappropriate speech may have been caused by language dysfunction resulting from spread of left mesial temporal-occipital seizures to the left lateral temporal neocortex. However, since the patient was not examined during an actual seizure, one cannot exclude speech difficulties simply caused by decreased responsiveness.

Psychogenic episodes, such as panic attacks, could also be considered in this case (see Table 18.11). However, panic attacks are not accompanied by olfactory phenomena, usually last longer, and do not have post-ictal deficits.

Other causes of transient neurologic episodes listed in Table 10.2, such as migraine or transient ischemic attack, are less likely to have this time course or to be accompanied by positive olfactory phenomena.

Numerous focal lesions in the medial temporal lobe could produce seizures of the type seen in this patient (see Table 18.11). The most likely possibilities in a 40-year-old woman are a tumor such as glioblastoma, metastatic breast or lung cancer, other neoplasms (see KCC 5.8), a bacterial brain abscess, toxoplasmosis, cytomegalovirus (see KCC 5.9), vascular malformation, previous head trauma, sarcoidosis, or other infectious or inflammatory disorders. For unknown reasons, neuronal developmental disorders can sometimes present with seizure onset in adulthood. Onset at age 40 years would be older than usual, but not impossible. In mesial temporal (hippocampal) sclerosis, seizure onset is typically at a younger age than in this patient, there is often an initial precipitating injury such as prolonged febrile seizures in childhood, and olfactory aurae are not commonly present.

Clinical Course and Neuroimaging
A head CT with contrast was performed in the emergency room, and a subsequent brain MRI with gadolinium confirmed the presence of a large enhancing mass in the left anterior temporal lobe, involving the amygdala (Figure 18.20A) and extending to the left orbitofrontal region (Figure 18.20B). Note that the mass had a heterogeneous, hypointense center, suggesting central necrosis. There was also surrounding hypointensity on T1-weighted images, with effacement of the Sylvian fissure and temporal horns, consistent with edema and mass effect (see Chapter 4). This appearance was felt to be most compatible with a glioblastoma multiforme, or less likely a metastasis or other tumor. The patient was started on the anticonvulsant medication phenytoin, which stopped her seizures, and she underwent a surgical resection of the left anterior temporal lobe. Pathology revealed a glioblastoma multiforme (see KCC 5.8). She was treated with radiation therapy and multiple cycles of chemotherapy. On this regimen she remained stable for a while, but then she developed progressive deficits as the tumor grew. At last follow-up, 9 months after presentation, she had lethargic and disoriented, with a right visual field cut and right-sided hemiparesis (2/5 to 3/5 strength). Glioblastoma multiforme, unfortunately, remains a relatively common, yet incurable brain tumor.
CASE 18.2 PROGRESSIVE SEVERE MEMORY LOSS, WITH MILD CONFAJULATION

Figure 18.18 Bilateral Medial Temporal Lymphoma
T1-weighted MR scan with intravenous gadolinium.

(A) Axial image. (B,C) Coronal images progressing from posterior to anterior.

Lateral rectus
Optic nerve
Sphenoid sinus
Medial rectus
Midbrain
Choroid plexus
Atresia of lateral ventricle
Occipital lobe
Enhancement in bilateral medial temporal lobes

MINICASE
A 26-year-old right-handed woman was evaluated at an epilepsy referral center for medically refractory seizures. She was the product of a normal birth and delivery, but at age 9 months she had two prolonged febrile seizures in one day. These consisted of generalized tonic-clonic activity, with the first seizure lasting nearly 2.5 hours and the second seizure, after arrival in the hospital, lasting about 1 hour. She was treated with anticonvulsant medications, which initially stopped the seizures. Within a few years, however, she began having stereotyped episodes that continued into adulthood and were refractory to multiple medicatations. Her episodes typically began with an aura of a "vague" and "scary feeling," followed by loss of awareness. Her mother has witnessed many of her seizures and described her as next having staring, unresponsiveness, lip smacking, rigid posturing of the left arm, and groping, purposeless movements of the right arm lasting for about 1 minute. Sometimes she spoke during the episodes without grammatical errors, but what she said was inappropriate for the questions being asked. Post-ictally she was fatigued and somewhat confused but had no other deficits. These episodes occurred two to three times per week, occasionally up to three times per day. She also had occasional isolated auras, without progression to full-blown episodes.

Her longest seizure-free interval in adulthood was about 3 months. Rarely (at intervals of greater than about 3 to 5 years), mostly in the setting of missing her medications, she had an episode that progressed to a generalized convulsion. Numerous medications, including phenobarbital, phenytoin, carbamazepine, mephobarbital, valproate, gabapentin, and felbamate were tried in various combinations, without effective seizure control. Aside from the febrile seizures, she had no other seizure risk factors, such as head injury, CNS infections, or family history of seizures. She graduated from high school, worked briefly as a cashier,
CASE 18.3 TRANSIENT DIPLOPIA, LETHARGY, AND HEMIPARESIS, FOLLOWED BY A SUSTAINED MEMORY DEFICIT

Figure 18.19 Bilateral Medial Thalamic Infarcts Axial T2-weighted MRI images. A, 8 progress from inferior to superior.

Discussion
The key symptoms and signs in this case are:
- *Aura* of a "vague" and "scary feeling"
- Loss of awareness, staring, and unresponsiveness
- Lip smacking, rigid posturing of the left arm, and groping, purposeless movements of the right arm
- Ability to produce speech during the episodes that was inappropriate, but without grammatical errors
- Post-ictal fatigue and confusion without other deficits
- Rare generalized convulsions

1. According to the classification in Table 18.8, the auras in this patient were simple partial seizures, since consciousness was spared. The episodes with loss of consciousness but no generalized convulsion were complex partial seizures. Finally, the febrile convulsions in infancy and the rare generalized convulsions in adulthood were generalized tonic-clonic seizures.

2. A simple partial seizure beginning in one part of the brain can spread to become a complex partial seizure, and then spread further to become a generalized tonic-clonic seizure.

3. A vague feeling and fear are features typically seen in seizures arising from the medial temporal lobe (see Table 18.9). In addition, complex partial seizures with staring, unresponsiveness, oral automatisms, unilateral gestural automatisms, and contralateral dystonia are commonly seen in temporal lobe seizures. The fact that dystonic posturing occurred on the left and automatisms on the right suggests that the seizures arose from the right side (see KCC 18.2). The fact that the patient had nonphasic speech during the seizures and no post-ictal aphasia also suggests that the seizures arose from the nondominant (usually right) hemisphere. The most likely clinical localization is right medial temporal lobe.

4. The history of prolonged febrile seizures in infancy, followed by the development of medial temporal-onset complex partial seizures is the classic presentation of hippocampal (mesial temporal) sclerosis (see KCC 18.2). Although only a small number of children with febrile seizures go on to develop epilepsy, children in the subgroup with complex febrile seizures are at increased risk for epilepsy. In addition, about 30 to 40% of patients with epilepsy and hippocampal sclerosis have a known history of febrile convulsions. Other features in this patient that are typical of hippocampal sclerosis are complex partial seizures that are notoriously refractory to medication therapy, and only rare secondary generalization while on medications. Other possible lesions in the medial temporal lobe that could be the cause of epilepsy in this patient are listed in Table 18.11.
**Clinical Course and Neuroimaging**

Given this patient's frequent, medically refractory seizures, a comprehensive evaluation was pursued in an effort to localize the region of onset and to determine if she was a suitable candidate for epilepsy surgery. She was admitted to the hospital for continuous video and simultaneous EEG monitoring. Ten stereotyped seizures were recorded, with loss of consciousness, lip smacking, left-sided dystonia, and right-sided automatisms. EEG during the seizures showed rhythmic 8 Hz activity over the right temporal lobe. Interictal EEG showed occasional right temporal spikes and right temporal slow waves. A brain MRI was performed, with special thin coronal sections used to evaluate epilepsy patients. This technique is capable of demonstrating detailed hippocampal anatomy (Figure 18.21A). The MRI revealed marked atrophy of the right hippocampal formation compared to the left (see Figure 18.21C-F). In addition, signal intensity in the right hippocampal formation was increased, suggesting gliosis (Figure 18.21B). The volumes of the right and left hippocampal formations were 562 and 983 (arbitrary units), respectively, based on measurements performed on the entire sequence of coronal MRI images. This discrepancy between the two sides was over five standard deviations greater than normal. A fluorodeoxyglucose PET scan (see Chapter 4) performed interictally showed markedly reduced glucose metabolism in the right temporal lobe, especially medically and anteriorly (Figure 18.22), a finding commonly seen in medial temporal lobe epilepsy.

Neuropsychology testing revealed decreased visual-spatial memory on the Wechsler Memory Scale, with preserved verbal memory. In addition, on selective remediation tests (another measure of recent memory), the patient had visual-spatial memory that was two standard deviations below normal, and verbal memory that was normal. A Wada test (see KCC 18.2) was performed as well. Following injection of the right carotid with amytal, the patient developed left hemiplegia and was shown 10 test items. Her speech was not aphasic. Ten minutes later the hemiplegia had worn off, and the patient was able to remember 5/10 items spontaneously, and 10/10 with multiple choice. These results demonstrated good memory in the left hemisphere. Injection of the left carotid produced right hemiplegia and global aphasia. The patient was shown 10 test items. During recovery she had paraphasic errors and comprehension difficulties that resolved, as did the hemiplegia, within 30 minutes. She was then able to recall 0/10 test items, and got only 2/10 correct with multiple choice. These results demonstrated poor memory in the right hemisphere. In addition, the Wada test results demonstrated that language dominance was in the left hemisphere.

These findings were discussed by the multidisciplinary team at the epilepsy referral center, and all results were felt to be concordant, indicating onset of her seizures in the right medial temporal lobe. Given this location and the results of the patient's Wada test and neuropsychology testing suggesting that the left temporal lobe could support adequate memory functions, it was felt that surgical treatment of her right mesial temporal sclerosis could be offered with a low risk of producing deficits and a good chance of curing her seizures. She decided to pursue this option and underwent a right anterome-dial temporal resection.

She had no deficits as a result of the surgery, and her seizures stopped completely. Pathology revealed right hippocampal cell loss and gliosis, consistent with hippocampal sclerosis. About 1 month after surgery and again 6 months after surgery, she tried briefly to discontinue her antiepileptic medications, but on both occasions she had recurrent seizures. As long as she took her medications, she remained without seizures or aura at last follow-up, a year and a half after surgery.
CASE 18.5 EPISODES OF STARING, LIP SMACKING, AND UNILATERAL SEMIPURPOSEFUL MOVEMENTS

Figure 18.21 Right Hippocampal Sclerosis
(A) Enlarged view of coronal thin-slice, T1-weighted MRI done with a special epilepsy protocol revealing normal structures of the left medial temporal lobe (compare to Figure 18.8A). (B) Coronal T2-weighted image. Increased signal intensity is evident in the right hippocampal formation, compatible with gliosis. (C-F) Coronal thin-slice, T1-weighted images. Atrophy is seen in the right hippocampal formation compared to the left. Images C-F progress from posterior to anterior.

(A)

Hippocampal gyrus
Subiculum

(B)

Parahippocampal gyrus
Rhinal (collateral) sulcus
CASE 18.5 (CONTINUED)

Figure 18.22  Right Temporal Hypometabolism
Fluorodeoxyglucose (FDG) PET scan for patient in Case 18.5, showing right medial temporal hypometabolism. Darker colors indicate regions of decreased metabolism. (A, B) Axial sections progressing from inferior to superior. (C, D) Coronal sections progressing from posterior to anterior.

Brief Anatomical Study Guide

1. In this chapter, we have reviewed the main neuroanatomical structures and functions of the limbic system. The limbic system can be defined as a network of brain structures lying on the medial and inferior aspects of the brain (see Figures 18.1, 18.2), involved in four general functions: homeostasis, olfaction, memory, and emotions and drives (mnemonic HOME). Simplifying somewhat, the most important structure for each of these functions is listed in Table 18.2, although in reality these functions are mediated by a widely distributed network (see Figure 18.1).

2. Limbic cortex, also called paralimbic cortex or limbic association cortex, forms a ring on the medial aspect of the brain consisting mainly of the cingulate gyrus and the parahippocampal gyrus (see Figure 18.2). Within this ring and in the temporal lobe lies the simple three-layered archicortex of the hippocampal formation (see Table 18.3, Figure 18.9). The hippocampal formation consists of three gyri, named, from medial to lateral, the dentate gyrus, hippocampal gyrus, and subiculum (see Figures 18.7, 18.8). Unlike the six-layered neocortex making up most of the brain surface, these gyri of the hippocampal formation each consist of three layers (see Figure 18.8).

3. The hippocampal formation is crucial to memory function and has many input and output network connections (see Figure 18.11). The connections with the association cortex may be particularly important for memory, and they occur mainly via the perirhinal and parahippocampal cortex, connected to the adjacent entorhinal cortex (see Figure 18.6), which in turn is connected to the hippocampal formation. Inputs from the entorhinal cortex to the hippocampal formation reach the dentate gyrus via the perforant pathway, and the CA1 and CA3 fields of the hippocampal gyrus via the alvear pathway (see Figure 18.88). Outputs from the hippocampal forma-

Additional Cases

Related cases can be found in other chapters for the following topics: impaired olfaction (Case 12.1); abnormal emotions (Cases 12.8, 16.2, 19.7); memory decline (Cases 5.8, 14.8, 19.7, 19.11); and seizures (Cases 10.13, 12.3, 19.10). Other relevant cases can be found using the Case Index.

References

General References
Seizures and Epilepsy

Wyllie E (ed.). 1997. The Treatment of Epilepsy. 2nd Ed. Williams & Wilkins, Baltimore, MD.

Psychiatric Disorders


CHAPTER 19

Higher-Order Cerebral Function

A 64-year-old woman progressively developed difficulties with reading, along with a right visual field defect. When she presented at the clinic, she was completely unable to read, but was able to write normally. For example, she wrote “Today is a nice day” and “It is a sunny day in Boston,” but was unable to read her own writing a few minutes later. As we shall see, higher-order cerebral functions (such as reading) depend on both local cortical functions (vision), together with more distributed cortical network functions (language). In this chapter, we will learn about the local higher-order functions of the cerebrum, and about the network connections that are essential for distributed functions such as language and cognition.
ANATOMICAL AND CLINICAL REVIEW

In humans, the majority of the brain surface is composed of association cortex. The functions of this vast cortical mantle are perhaps more difficult to understand than those of any other brain area, yet they are also what make us uniquely human. Functions of the association cortex include sophisticated operations such as higher-order sensory processing, motor planning, language processing and production, visual-spatial orientation, determining socially appropriate human behavior, and perhaps even what we would call "abstract thought."

Although the emphasis of this chapter is association cortex, it should be noted that numerous subcortical structures participate in these functions as well. We saw in Chapter 19 that lesions of the medial diencephalon can mimic the memory deficits seen in medial temporal lobes. Similarly, lesions of the basal ganglia, thalamus, subcortical white matter, and other structures can produce deficits that resemble those of the association cortex. Although cerebral cortical localization will be emphasized in this chapter, in reality networks of both cortical and subcortical structures mediate virtually all brain functions. For example, we have learned that the thalamus and basal ganglia participate in association cortex networks (see Figures 7.8, 16.8), that brainstem activating systems are crucial for behavioral arousal (see Figure 14.17), and that the amygdala has widespread connections participating in emotions and drives (see Figure 18.17). Thus, in addition to deficits arising from focal cortical lesions, specific neurocognitive deficits can be caused by lesions that involve only subcortical structures, or by lesions that disrupt cortical-cortical or cortical-subcortical network connections.

Historically there has been a dichotomy in theories of brain function. Some investigators have attributed brain functions to distributed networks, while others have assigned functions to specific localizations. In reality, both network and localized mechanisms participate in brain function, and therefore, these will both be discussed in this chapter. We will begin by reviewing the overall structure of the mental status examination introduced in Chapter 3. Next, we will discuss localized aspects of cerebral function and focal clinical disorders in four general regions of the association cortex: dominant (usually left) hemisphere, nondominant (usually right) hemisphere, frontal lobes, and visual association cortex. Finally, we will discuss more widely distributed functions such as attention and awareness and clinical disorders resulting from more global brain dysfunction.

The epilogue that follows this chapter will briefly present an overview of the integrated functions of the nervous system, including the various systems discussed throughout this book. An attempt will be made to unify these into a simple working model of the mind. *

KEY CLINICAL CONCEPT
THE MENTAL STATUS EXAM

591 In Chapter 3, we introduced the mental status exam. This part of the neurological exam, like all other parts, should be performed and interpreted in the context of a more general clinical assessment that includes the patient's history, general physical examination, and appropriately selected diagnostic tests. The mental status exam provides a useful bedside evaluation of mental performance. Formal neuropsychological testing can provide more detailed, accurate, and quantitative information when needed. There are many variations in the mental status exam, depending on the clinician's style and on the specific clinical situation. However, the mental status exam usually includes the basic elements listed in Table 19.1.

The patient's level of alertness, attention, and cooperation will influence virtually every other part of the exam. Therefore, the exam usually begins with an evaluation of these functions, which tend to depend on more widely distributed networks. Any abnormalities should be carefully documented, since they will affect the interpretation of all other parts of the exam and could lead to false diagnosis of a focal condition. For example, patients who are in a global confusional state because of a toxic or metabolic disorder (see KCC 19.15) are often inattentive and may perform poorly on writing tests. Unless the level of alertness and attention is carefully tested, this poor performance could be misinterpreted as a focal deficit in written language.

Next, the patient's orientation and memory should be tested. Memory is a crucial element of mental status that was covered in detail in Chapter 18. The remaining parts of the mental status exam (see Table 19.1) mainly test functions in brain regions such as the dominant (usually left) hemisphere (language and related functions), right hemisphere (neglect and constructions), and frontal lobes (sequencing tasks and frontal release signs). In the sections that follow, we will discuss the anatomy and testing of each of these brain regions in greater detail. In addition, we will discuss testing and disorders of visual processing, not listed explicitly in Table 19.1. Finally, the examiner should evaluate the patient for several additional, more global functions (logic and abstractions) and for psychiatric disorders (see KCC 18.3).

To avoid confusion, note that the general organization of this chapter does not follow the order of Table 19.1, but instead begins with localized functions and then later continues with more global functions such as attention. The mental status exam is described in greater detail in Chapter 3 (and in neuroexam.com Videos 3-23) and should be reviewed carefully at this point before reading the rest of this chapter, since it will make the material presented here much easier to understand.

Unimodal and Heteromodal Association Cortex

Association cortex can be divided into unimodal (modality-specific) association cortex and heteromodal (higher-order) association cortex (Figure 19.1; Table 19.2). Examples of unimodal association cortex include somatosensory association cortex, visual association cortex, auditory association cortex, and motor association cortex (premotor cortex and supplementary motor area).

TABLE 19.1 Overview of the Mental Status Exam

| Level of alertness, attention, and cooperation |
| Orientation |
| Memory |
| Recent memory |
| Remote memory |
| Language |
| Spontaneous speech |
| Comprehension |
| Naming |
| Repetition |
| Reading |
| Writing |
| Calculations, right-left confusion, finger agnosia, apraxia |
| Apraxia |
| Neglect and constructions |
| Sequencing tasks and frontal release signs |
| Logic and abstraction |
| Delusions and hallucinations |
| Mood |

TABLE 19.2 Terminology Used for Classifying Neocortex

<table>
<thead>
<tr>
<th>NAME</th>
<th>EQUIVALENT NAME(S)</th>
<th>EXAMPLES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary sensory and motor cortex</td>
<td>Idiotype cortex, heterotype cortex</td>
<td>Primary somatosensory cortex, primary visual cortex, primary auditory cortex, primary motor cortex</td>
</tr>
<tr>
<td>Primary sensory cortex</td>
<td>Koniocortex, hypergranular cortex, granular cortex</td>
<td>Primary somatosensory cortex, primary visual cortex, primary auditory cortex, primary motor cortex</td>
</tr>
<tr>
<td>Primary motor cortex</td>
<td>Macropyramidal cortex, agranular cortex</td>
<td>Primary somatosensory cortex, primary visual cortex, primary auditory cortex, primary motor cortex</td>
</tr>
<tr>
<td>Association cortex</td>
<td>Homotype cortex</td>
<td>Somatosensory, visual, or auditory association cortex, premotor cortex, supplementary motor area</td>
</tr>
<tr>
<td>Unimodal association cortex</td>
<td>Modality-specific association cortex</td>
<td>Somatosensory, visual, or auditory association cortex, premotor cortex, supplementary motor area</td>
</tr>
<tr>
<td>Heteromodal association cortex</td>
<td>Higher-order association cortex</td>
<td>Preferential cortex, parietal and temporal heteromodal association cortex</td>
</tr>
</tbody>
</table>

*See layered cortex, analogous to ancestors or overlap. See Table 19.3 for classification of other types of cortical columns.
*Meaning cortex in which the layers are unequal. *
*Meaning cortex in which the layers are relatively equal. *
[Unimodal] sensory association cortex receives its predominant input from primary sensory cortex of a specific sensory modality and performs higher-order sensory processing for that modality. Unimodal motor association cortex projects predominantly to primary motor cortex, and it is important in formulating the motor program for complex actions involving multiple joints.

In contrast, heteromodal association cortex has bidirectional connections with both motor and sensory association cortex of all modalities. In addition, heteromodal association cortex has bidirectional connections with limbic cortex. This anatomical arrangement enables heteromodal association cortex to perform the highest-order mental functions. These functions apparently require integration of abstract sensory and motor information from unimodal association cortex, together with emotional and motivational influences provided by limbic cortex. Heteromodal association cortex is found in the frontal lobes and at the parieto-occipitotemporal junctions (see Figure 19.1).

In the sections that follow, we will survey some of the main functions of unimodal and heteromodal association cortex in different brain regions and study disorders that result from lesions in these areas.

**Principles of Cerebral Localization and Lateralization**

As we have already mentioned, in the 1800s and early 1900s there was a controversy between those who described the brain as a network and those who described it as a collection of specialized areas. In reality, the brain is both. Localized regions of the brain do carry out specific functions, but they also communicate through networks with many other regions of the nervous system. Focal brain lesions can cause specific deficits, as we will see in the sections that follow. By understanding the main functions of the different cortical regions, deficits such as aphasia, unilateral neglect, impaired executive function, or inability to process visual information normally, can often be localized based on the neurological exam. However, because brain functions are mediated by networks involving not single, but multiple areas, false localization can sometimes occur. For example, so-called frontal lobe functions involve networks that encompass diverse regions including the frontal, parietal, and limbic cortices, the thalamus, basal ganglia, cerebellum, and brainstem. Therefore, lesions in these other structures, or in their white matter connections, can sometimes produce deficits that mimic frontal-lobe lesions. Disconnection syndromes (see KCC 19.8) are another result of the network properties of brain function. For example, when a lesion in the white matter disconnects the network connections between visual cortex and the language processing areas, a patient may lose the ability to read.

Another important principle that can help localize deficits on clinical grounds is the tendency of some functions to be lateralized to the left or right hemisphere, resulting in hemispheric specialization. The human brain appears fairly symmetrical anatomically between the left and right hemispheres, and many basic sensory and motor functions in the brain are distributed symmetrically. Homologous regions of cerebral cortex on either side of the brain are connected to each other via long association fibers carried by the corpus callosum. For unknown reasons, however, there are marked asymmetries in several brain functions. It has been postulated that these asymmetries allow certain functions to be processed mainly within one hemisphere, eliminating delays caused by long callosal transmission times.

The most obvious asymmetry in cerebral function is handedness. Approximately 90% of the population is right-handed. The degree of asymmetry in manual dexterity varies, but most individuals are remarkably clumsy
in performing tasks such as writing or closing buttons with the nondom-
inant (usually left) hand. Functional neuroimaging and the results of lesions
have suggested that although each hemisphere controls simple movements
of the contralateral limbs, skilled complex motor tasks for both right and left
limbs are programmed mainly by the dominant hemisphere. Les-
sions of the dominant hemisphere therefore are more commonly associated
with apraxia, a disorder of formulating skilled movements (KCC 19.7).

Language is another well-known example of hemispheric specialization.
In most individuals, language function depends predominantly on the left
hemisphere. The left hemisphere is dominant for language in over 95% of
right-handers, and in over 60 to 70% of left-handers. Thus, lesions of the
left hemisphere language areas usually cause language dysfunction even
in left-handed individuals. However, many left-handed individuals have
significant bilateral representation of language, especially if there is a family
history of left-handedness or ambidexterity. Thus, after a left hemisphere le-
sion, left-handed individuals tend to recover language more quickly than
right-handers.

The nondominant hemisphere is specialized for certain nonverbal
functions and appears to be generally more important for complex visual-
spatial skills, for imparting emotional significance to events and language,
and for music perception. Although the right and left hemispheres are each
involved in attention to the contralateral environment, only the right hemi-
sphere is significantly involved in attending to both sides. Lesions of the
right hemisphere usually cause marked inattention to the contralateral (left)
side even in individuals who are right hemisphere dominant for language.
Right hemisphere specialization for spatial attention may therefore be even
more highly conserved than left hemisphere dominance for language.

To summarize the "flavor" of lesions of each hemisphere, dominant (usu-
ally left) hemisphere lesions cause impairments of language, detailed analyti-
cal abilities, and complex motor planning (praxis), while nondominant (usu-
ally right) hemisphere lesions cause impairments of spatial attention and
complex visual-spatial abilities, especially those involving spatial orientation
and perception of the overall gestalt, or big picture. As Table 19.3 shows, many
important activities are carried out by combinations of different specialized
skills of the left and right hemispheres. These functions of the dominant and
nondominant hemispheres are mediated by distributed networks involving
fronto-parietal connections, connections with limbic memory structures,
and reciprocal connections with subcortical nuclei. Lesions that
disconnect these networks, either within one hemisphere or between
hemispheres at the corpus callosum, can cause specific disconnection
syndromes (see KCC 19.6).

The anatomical basis for hemi-
spheric specialization is only just
beginning to be investigated. Al-
though it has been known since
the 1960s that the left superior temporal plane (planum temporale) is larger in
the left hemisphere in most indi-
viduals, the functional significance
of this finding is still debated. Some
preliminary evidence suggests that
portions of the parietal lobe are larger in the right hemisphere. Functional and
structural asymmetries in the brain are not unique to humans and have been
demonstrated in other primates, and even in amphibians. Handedness and
erother lateralized aspects of cerebral function are not apparent in humans until
or 4 years of age, suggesting that developmental processes play a crucial role
in hemispheric specialization. When lesions of the dominant hemisphere
occur early in life, language and other functions often move to the nondom-
ninant hemisphere resulting in a remarkable preservation of function.

In the sections that follow, we will move through the brain from left to
right, and then from front to back. Thus, in the next section of the next section
we will discuss the processes generally associated with the dominant hemisphere, followed by functions associ-
ated with the nondominant hemisphere. Then we will turn to the frontal
lobes, and finally to visual association cortex.

The Dominant Hemisphere:
Language Processing and Related Functions

In this section, we will describe the components of the language network and
then discuss disorders of the dominant hemisphere affecting language.
We will also discuss language and other typical functions of the dominant hemisphere (see Table 19.3).

<table>
<thead>
<tr>
<th>TABLE 19.3 Functions of the Dominant and Nondominant Hemispheres</th>
</tr>
</thead>
<tbody>
<tr>
<td>DOMINANT (USUALLY LEFT) HEMISPHERE FUNCTIONS</td>
</tr>
<tr>
<td>Language</td>
</tr>
<tr>
<td>Skilled motor formulation (praxis)</td>
</tr>
<tr>
<td>Arithmetic, sequential, and analytical calculation skills</td>
</tr>
<tr>
<td>Musical ability: sequential and analytical skills in trained musicians</td>
</tr>
<tr>
<td>Sense of direction: following a set of written directions in sequence</td>
</tr>
</tbody>
</table>

A Historical Note:
The anatomical study of language disorders has had considerable historical impor-
tance over the past two centuries in the development of theories of cerebral localiza-
tion in general. In the 1860s and 1870s, when Pierre Paul Broca and Karl Wernicke
described language disorders caused by focal lesions in the brain, these descrip-
tions were taken as important support for the notion that localized regions of the brain are
specialized to perform specific cognitive functions. This concept fell into disfavor
around the turn of the twentieth century, in the face of more holistic schemes of
brain function proposed by Sigmund Freud and Pierre Marie, only to be revitalized
eventually by Norman Geschwind and others in the 1960s and subsequent decades.
Currently, the most widely accepted model is based on localized regions of cortex
that have specialized functions but also participate in networks employing multiple
brain regions to perform cognitive tasks.

As mentioned in the previous section, the left hemisphere is dominant
for language in over 95% of right-handers and in over 60 to 70% of left-handers.
Important areas for language processing and production are shown in Figure
19.2. Figure 19.2A shows the core structures associated with basic linguistic
processes, such as hearing a word and then repeating it aloud. Auditory in-
formation reaches primary auditory cortex on the superior bank of the Syl-
vian fissure in the temporal lobe (see Figure 19.1A). The initial steps of lan-
guage processing that enable particular sequences of sounds to be identified and
comprehended as meaningful words are performed in the adjacent asso-
ciation cortex, which has been named Wernicke's area (see Figure 19.2A).
Wernicke's area corresponds to Brodmann's area 22 (see Chapter 2), which
echoes the posterior two-thirds of the superior temporal gyrus in the
dominant hemisphere. Many authors also include in Wernicke's area a rim of
adjacent association cortex from Brodmann's areas 37, 39, and 40 because
lesions extending to these areas produce Wernicke's aphasia (see KCC 19.5).

Articulation of the sounds that constitute speech depends on the face
area of the primary motor cortex, located in the interior portion of the precentral
gyrus (see Figure 6.2). The motor program that activates particular se-
Figure 19.2 Anatomy of Language Areas (A) Core language circuit composed of Broca’s area, Wernicke’s area, and the arcuate fasciculus. (B) Network of areas involved in language, including interactions with adjacent anterior and posterior association cortex, subcortical structures, and callosal connections to the contralateral hemisphere.

Accurate fasciculus and other peri-Sylvian connections

Broca’s area
Wernicke’s area
Premotor and supplementary motor cortex (6)
Prefrontal cortex (8, 9, 10, 14, 16, 47)
Supramarginal gyrus (40)
Angular gyrus (39)
Inferior temporal language area (37)

Non-dominant hemisphere
Corpus callosum

Connections through the corpus callosum (see Figure 19.2B) allow the non-dominant hemisphere to participate in the language-processing network. The non-dominant hemisphere appears to be important in both the recognition and the production of the affective elements of speech. Thus, patients with lesions of the non-dominant hemisphere usually have no obvious language disturbance. However, they may have difficulty judging the intended expression imparted by a particular tone of voice, or they may have difficulty producing emotionally appropriate expression in their own voice. Perhaps more importantly, in lesions of the dominant hemisphere, callosal connections may allow the non-dominant hemisphere to take over some functions of the damaged areas, and to participate in at least partial recovery.

The language network also has important reciprocal connections with subcortical structures such as the thalamus, basal ganglia, and subcortical white matter in the dominant hemisphere that can produce aphasia that can sometimes be mistaken for a cortical lesion.

For each of the following: state whether it is more closely associated with Broca’s or Wernicke’s area.
1. Superior temporal gyrus
2. Areas 44, 45
3. Language formulation and planning
4. Inferior frontal gyrus
5. Area 22
6. Lexicon
7. Syntax
8. Language comprehension

KEY CLINICAL CONCEPT DIFFERENTIAL DIAGNOSIS OF LANGUAGE DISORDERS

Aphasia, or dysphasia, is a defect in language processing caused by dysfunction of the dominant cerebral hemisphere. Because aphasia is a disorder of language, and not a simple sensory or motor deficit, both spoken language and written language are affected. Aphasia is not caused by impaired audition or articulation, although deficits in these modalities may coexist.
TABLE 19.4 Disorders Commonly Mistaken for Aphasia

<table>
<thead>
<tr>
<th>Disorder of speech production</th>
<th>Aphasia (verbal aphasia)</th>
<th>Mutism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Auditory disorders</td>
<td>Peripheral hearing loss</td>
<td>Pure word deafness</td>
</tr>
<tr>
<td></td>
<td>Cortical deafness</td>
<td>Auditoryagnosia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Uncooperative patient</td>
</tr>
</tbody>
</table>

with aphasia. The definition of aphasia will become more intuitively clear as we discuss specific examples in the sections that follow.

It is important to distinguish aphasia from several other disorders that affect language but are not specific disorders of language itself (Table 19.4). In motor disorders such as dysarthria (see KCC 12.9) and epilepsy (verbal aphasia) (see KCC 19.7), speech may be difficult to comprehend; however, it has normal content and grammar, and written language is often normal. Mutism may result from severe aphasia or from motor disorders, which can sometimes be distinguished by other clues, such as writing. Similarly, peripheral (see KCC 12.5) or central (see KCC 19.7) auditory disorders, perception of spoken language is impaired, but reading and other aspects of language are normal.

Disorders of arousal and attention from a variety of causes (see Chapter 14), including toxic or metabolic disorders, post-ictal state, brainstem ischemia, and sleep disorders, are occasionally mistaken for aphasia because of the impaired comprehension and incoherent speech seen in these conditions. Finally, psychiatric disorders are sometimes confused with aphasia. In particular, schizophrenic patients may have very disordered, noncoherent, clanging speech, full of neologisms, which may resemble aphasia. It is important to recognize that the opposite situation can also be hazardous, in which a patient with aphasia is incorrectly given one of the diagnoses in Table 19.4. Through careful examination of the patient, as discussed in the following sections, it is usually possible to make these critical distinctions.

The most common cause of acute onset of aphasia is cerebral infarct, as we will discuss through multiple examples in this chapter. However, aphasia can also be caused by a wide variety of other disorders of the dominant hemisphere. (see KCC 19.5) (1)

**KEY CLINICAL CONCEPT**

BEDSIDE LANGUAGE EXAM

Comprehension

**TABLE 19.5 Causes of Aphasia**

<table>
<thead>
<tr>
<th>Cerebral contusion</th>
<th>Subdural or epidural hematoma</th>
<th>Ischemic or hemorrhagic vascular events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ictal or post-ictal data with focal seizures in dominant hemisphere</td>
<td>Mass lesions such as brain tumor, abscess, or toxoplasmosis</td>
<td>Infarctary or autoimmune disorders such as multiple sclerosis or vasculitis</td>
</tr>
</tbody>
</table>

Developmental disorders such as language delay or autism

Degenerative disorders such as primary progressive aphasia, moderately advanced Alzheimer’s disease, or Huntington’s disease

(1) Following the format of Figure 1.1.

**Broca’s aphasia** is usually caused by lesions affecting Broca’s area and adjacent structures in the dominant frontal lobe (Fig. 19.2). The most common etiology is infarct in the territory of the left middle cerebral artery (MCA) superior division (Fig. 19.3A); see also KCC 10.1). Although other lesions in this location can produce Broca’s aphasia as well,Clinically, the most salient feature of Broca’s aphasia is decreased fluency of spontaneous speech (see Table 19.6). The impaired fluency in Broca’s (in contrast to Wernicke’s) aphasia can be remembered by the mnemonic Broca’s broken bowl (“bowl” means “mouth” in Spanish). Fluency can be surprisingly difficult to define and assess in an objective manner. Some helpful guidelines are that patients with decreased fluency tend to have a phrase length of fewer than five words, and the number of content words (e.g., nouns) exceeds the number of function words (e.g., prepositions, articles, and other syntactic modifiers). Word generation tasks, such as FAS (see KCC 19.11) can be useful for detecting subtle decreases in verbal fluency. In addition, prosody (the normal melodic intonation of speech that conveys the meaning of sentence structure) is lacking in patients with Broca’s aphasia. The resulting speech in Broca’s aphasia has an effortful, telegraphic quality, with a lack of grammatical structure and a monotonous sound. *Speech output is often better for certain overlearned, semantically loaded tasks, such as naming the days of the week or singing familiar songs like “Happy Birthday,” and performance is often improved by cueing—that is, providing the first sound of a word during naming tests. Paraphasic errors (see KCC 19.5) occasionally occur, although these are less common than in Wernicke’s aphasia.

The decreased fluency of Broca’s aphasia is associated with marked naming difficulties. In addition, lesions in Broca’s area cause a disconnection of this structure from Wernicke’s area (Fig. 19.3A). Therefore, in Broca’s aphasia repetition is impaired as well. Patients tend to have the most difficulty repeating phrases with a high content of function words, such as “No ifs, ands, or buts” or “If I were here, she would be there.” In contrast, because the posterior language structures are spared, comprehension is relatively intact in Broca’s aphasia. The one notable exception is impaired comprehension of syntactically dependent structures. For example, when given a passive sentence such as “The lion was killed by the tiger,” a patient with Broca’s aphasia often incorrectly chooses the tiger as the animal that is dead. Writing and reading aloud in Broca’s aphasia have a slow, effortful, grammatical quality that is similar to the deficits in spoken language. Reading comprehension is often relatively spared, except for syntactically dependent structures.

Commonly associated features in Broca’s aphasia include dysarthria, and right hemiparesis affecting the face and arm more than the leg, especially when left MCA superior division infarct is the cause. Visual fields are usually normal. Other common features are frustration and depression. Aphasia (see KCC 19.7) may also be present, often affecting the nonparetic left side of the body and mental-linguistic structures.

A distinction is often made between so-called little Broca’s aphasia and big Broca’s aphasia. Big Broca’s aphasia is caused by large lesions, such as MCA superior division infarcts (see Figure 19.3B).

**TABLE 19.6 Bedside Language Exam**

<table>
<thead>
<tr>
<th>Test and Procedure</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous speech</td>
<td>Fluency</td>
</tr>
<tr>
<td>Proseody</td>
<td>Grammar and meaning</td>
</tr>
<tr>
<td>Paraphasia</td>
<td>Articulation</td>
</tr>
<tr>
<td>Naming</td>
<td>Visual confrontation naming</td>
</tr>
<tr>
<td>Repetition</td>
<td>Visual confrontation naming</td>
</tr>
<tr>
<td>Articulation</td>
<td>Objects and parts</td>
</tr>
<tr>
<td>Writing</td>
<td>Nouns, verbs, proper nouns, colors, etc.</td>
</tr>
</tbody>
</table>

1. Spontaneous speech
2. Proseody
3. Grammar and meaning
4. Paraphasia
5. Articulation
6. Visual confrontation naming
7. Naming
8. Repetition
9. Articulation
10. Writing
11. Nouns, verbs, proper nouns, colors, etc.
12. Paraphasia
13. Articulation
14. Writing
15. Nouns, verbs, proper nouns, colors, etc.
16. Proseody
17. Grammar and meaning
18. Paraphasia
19. Articulation
20. Naming
21. Visual confrontation naming
22. Repetition
23. Articulation
24. Writing
25. Nouns, verbs, proper nouns, colors, etc.
26. Paraphasia
27. Articulation
28. Writing
29. Nouns, verbs, proper nouns, colors, etc.
30. Proseody
31. Grammar and meaning
32. Paraphasia
33. Articulation
34. Naming
35. Visual confrontation naming
36. Repetition
37. Articulation
38. Writing
39. Nouns, verbs, proper nouns, colors, etc.
40. Paraphasia
41. Articulation
42. Writing
43. Nouns, verbs, proper nouns, colors, etc.
44. Proseody
45. Grammar and meaning
46. Paraphasia
47. Articulation
48. Naming
49. Visual confrontation naming
50. Repetition
51. Articulation
52. Writing
53. Nouns, verbs, proper nouns, colors, etc.
54. Paraphasia
55. Articulation
56. Writing
57. Nouns, verbs, proper nouns, colors, etc.
speech deficits in Wernicke’s aphasia, and consist of fluent, but meaningless, paraphasic renditions.

Commonly associated features in Wernicke’s aphasia include a contralateral visual field cut, especially of the right upper quadrant (see Figure 11.15E). Apraxia may be present (see KCC 19.7), but it can be difficult to demonstrate because of impaired comprehension. Dysarthria and right hemiparesis are usually absent or very mild. In addition, in marked contrast to Broca’s aphasia, patients often appear unaware of their deficit ( anosognosia), behaving as if carrying on a normal conversation despite their markedly abnormal speech. Angry or paranoid behavior may occur, causing Wernicke’s aphasia occasionally to be misdiagnosed as a psychiatric disorder (recall that patients with schizophrenia may also have abnormal speech).

Examine a patient with severe Wernicke’s aphasia can be difficult because the patient may respond to all questions or commands with nothing but incomprehensible paraphasic jargon. When examining the patient with Broca’s aphasia the patient often feels frustrated, while when examining the patient with Wernicke’s aphasia, the examiner may feel frustrated.

Other names are sometimes used to refer to Broca’s aphasia and Wernicke’s aphasia, respectively, including expressive and receptive aphasia, motor and sensory aphasia, anterior and posterior aphasia, and nonfluent and fluent aphasia. However, these terms each have drawbacks. For example, Broca’s aphasia is not simply an expressive deficit, since comprehension of syntactically dependent structures is impaired. Conversely, Wernicke’s aphasia is not simply a receptive deficit, since speech expression is highly paraphasic and largely uninterpretable. Similarly, although Broca’s and Wernicke’s aphasia are usually caused by anterior and posterior lesions, respectively, this is not always the case. The simple syndromic names Broca’s aphasia and Wernicke’s aphasia are preferable.

19.6 Broca’s aphasia and Wernicke’s aphasia are prototypical aphasia syndromes that, once understood, allow for easier classification of other aphasia syndromes. In this section we will present a simplified scheme for classifying aphasias that is useful because it is easy to apply and makes anatomical sense (Figure 19.4). Note, however, that aphasias do not always fit neatly into these categories. Left-handed patients, in particular, have more variable distribution of their language areas between the two hemispheres, and they may have aphasia syndromes that do not fit the classification presented here. In addition, many aphasia researches consider this classification to be oversimplified. Nevertheless, this scheme is useful for most basic clinical purposes.

When examining patients with aphasia, recall that neurologic deficits are not all-or-none phenomena. In addition to deciding on the absence or presence of a deficit such as decreased fluency or impaired comprehension, it is important to assess its severity. This assessment can help both to clarify the diagnosis and to track the clinical progression of the disorder. For example, consider a patient with normal fluency who can comprehend and repeat simple phrases, but who has difficulty comprehending and repeating more complex phrases and has occasional paraphasic errors. Despite the fact that some comprehension is present, this patient would be considered to have Wernicke’s aphasia (see KCC 19.5), but in a relatively mild form.

The classification scheme is based on three parts of the language exam: fluency, comprehension, and repetition (see Figure 19.4). The other portions of the exam are important as well, to complete the clinical picture and to distinguish aphasia from other disorders. For example, naming difficulty and paraphasia do not appear explicitly in Figure 19.4 because these two disorders of language can occur in virtually any aphasia syndrome and have little
Aphasia is one possible cause of ACA–MCA watershed infarct (see Figure 19.3B). This lesion destroys connections to other regions of the frontal lobe that are needed for Broca’s area to function in language formulation (see Figure 19.3B). However, peri-Sylvian connections from posterior to anterior language areas are left intact, enabling repetition.

A patient with normal fluency but impaired comprehension, as in Wernicke’s aphasia, but with intact repetition, has transcortical sensory aphasia. MCA–PCA watershed infants (see Figure 19.3B) are one possible cause of this disorder. Connections to structures in the parietal lobe and temporal lobe that are needed for Wernicke’s area to function are destroyed (see Figure 19.3B), while the peri-Sylvian area is left intact. The result is a condition that resembles Wernicke’s aphasia, except that repetition is spared.

A patient with impaired fluency and impaired comprehension, as in global aphasia, but with intact repetition, has mixed transcortical aphasia, also called isolation of the language areas. One possible cause is combined MCA–ACA and MCA–PCA watershed infants (see Figure 19.3B), although this form of aphasia is often seen in subcortical lesions as well.

Finally, let’s consider patients who show normal fluency, normal comprehension, and normal repetition but, like the other patients described here, have some naming difficulties and occasional paraphasias. This disorder is called anomia or dysnomia (see Figure 19.4). Naming difficulties can be severe or relatively mild. Careful testing for subtle dysnomia can be a sensitive indicator of language dysfunction because naming is often the first function to be impaired and the last to recover in language disorders. A careful test of naming is thus an excellent screening test for aphasia. Patients with subtle dysnomia often have particular difficulty naming lower-frequency words or parts of objects (see neuroscience.com Video 10). For example, the parts of a watch (face, band, clasp) or a shirt (collar, pocket, sleeve, cuff) are a useful bedside test. Sometimes a similar but incorrect word will be used, such as “clock” for watch or “pencil” for pen (semantic paraphasias). Causes of anomia are numerous and include subcortical or cortical lesions in the dominant hemisphere, and recovery from more severe forms of aphasia.

Recovery from Aphasia

Although the nature of recovery from aphasia is variable, the nature of recovery tends to follow certain common patterns. Global aphasia seen in big Broca’s usually recovers to a Broca’s aphasia, Broca’s aphasia may recover to a transcortical motor aphasia, and eventually to a subcortical dysnomia. Similarly, Wernicke’s aphasia may recover to a transcortical sensory aphasia, and then to a dysnomia. Other patients have primarily naming and repetition difficulties following recovery, resembling a conduction aphasia. Dysnomia is the most common long-term deficit, although some patients have other more severe residual deficits as well. Subtle decreases in fluency can be tested for with word generation tasks, as discussed in KCC 19.11.

Some important syndromes are related to the aphasic disorders of the dominant hemisphere. These disorders can occur either together with aphasia or in isolation.

Alexia and Agraphia

Alexia and agraphia are impairments in reading or writing ability, respectively, that are caused by deficits in central language processing and not by simple sensory or motor deficits. Alexia and agraphia can each occur in isolation, or they can occur together. In patients with aphasia, agraphia is invariably
**Agnosia** has been defined by Teuber as "a normal percept stripped of its meanings." Specific agnosias have been described for a variety of visual, auditory, and other percepts, as we will see in this chapter. Each of the single components of Gerstmann's syndrome, when found in isolation, has little specific localizing value and can be found in a variety of brain disorders. However, when all four components are present in the absence of a global confusional state or other diffuse disorder, this syndrome is strongly localizing to the dominant inferior parietal lobule, in the region of the angular gyrus. Gerstmann's syndrome can occur alone as a pure syndrome, but it is more often accompanied by other deficits localizing to the dominant inferior parietal lobule, such as a contralateral visual field cut (see Figure 11.15), alexia, apraxia, or more severe aphasia.

**Apraxia**

Apraxia, or more specifically, ideomotor apraxia, is the inability to carry out an action in response to verbal command, in the absence of any comprehension deficit, motor weakness, or incoordination. It is caused by an inability to formulate the correct movement sequence. In testing for apraxia, the patient is usually asked to carry out imaginary actions, such as saluting the flag, brushing their hair, lighting a match and blowing it out, and so on (see neuroexams.com Video 15). Patients with apraxia make awkward-looking attempts and perform tasks ineffectually. In mild apraxia, patients may exhibit body part substitution—e.g., using their index finger like a toothbrush instead of holding an imaginary toothbrush between their fingers in the normal fashion. Intact comprehension of the command should be confirmed by multiple choice, with different actions demonstrated by the examiner. In addition, the patient should have intact motor skills that would allow performance of the task, which can be demonstrated if the patient spontaneously performs the same task or a similar task involving the same muscles at another time. These strict criteria are hard to meet, and sometimes a patient's inability to perform a task is best described as "probably" resulting from apraxia.

Apraxia is not a well-recognized disorder, and it can be caused by lesions in many locations. However, there is an association between apraxia and aphasia: At least one-third of patients with aphasia also have apraxia. Apraxia can affect orofacial, proximal, or distal limb movements differentially. Thus, some patients may have particular difficulty packaging their lips or sticking out their tongues on command, while others may have more difficulty with other body movements.

In addition to ideomotor apraxia (usually known simply as apraxia), the term "apraxia" has been applied to a variety of other, seemingly unrelated disorders. For discussion of conditions such as dressing apraxia, ocular apraxia, constructional apraxia, gait apraxia, ideational apraxia, and so on, consult the references at the end of this chapter.

**Aphemia (Verbal Apraxia)**

In aphemia, patients have severe apraxia of the speech articulatory apparatus, with a language disturbance. Aphemia is usually caused by a small lesion of the dominant frontal operculum restricted to Broca's area. In contrast to patients with Broca's aphasia, these patients have normal written language. Patients with aphemia have effortless, poorly articulated speech sometimes referred to as foreign accent syndrome. Severe aphemia can cause muteness, with preserved writing ability. Aphemia also occurs as a developmental disorder in children, often without a visible lesion on imaging studies. It is referred to as verbal apraxia in this context.
Cortical Deafness. Pure Word Deafness, and Nonverbal Auditory Agnosia

Patients with cortical deafness have bilateral lesions of the primary auditory cortex in Heschl's gyrus (see figure 19.1). These patients are often aware that a sound has occurred but are unable to interpret verbal stimuli and cannot identify nonverbal stimuli such as a telephone ringing or a ticking clock. In contrast, patients with pure word deafness, or verbal auditory agnosia, can identify nonverbal sounds but cannot understand any spoken words. Unlike Wernicke's aphasia patients, these patients can read and write normally. Although a few paraphasic errors may occur early on, speech is usually normal within a few days of onset.

The lesion in pure word deafness is usually an infarct in the auditory area of the dominant hemisphere that extends to the subcortical white matter, cutting off auditory input from the contralateral hemisphere as well (another disconnection syndrome; see KCC 19.8). Some patients with pure word deafness have also been reported with bilateral lesions of the superior temporal gyrus. In nonverbal auditory agnosia, patients understand speech but cannot identify nonverbal sounds. The lesion in nonverbal auditory agnosia is usually located in the nondominant hemisphere.

The Nondominant Hemisphere: Mechanisms of Attention and Spatial Processing

Exploring the functions of the nondominant (usually right) hemisphere brings us tantalizingly close to the fundamental mechanisms of consciousness. While the dominant hemisphere is specialized for language and step-by-step formulation and execution of motor tasks, the nondominant hemisphere is more important for attention and for generating an integrated visual-spatial gestalt. In this section we will emphasize the more localized functions of the nondominant hemisphere in directed attention to the contralateral hemispace and in visual-spatial processing. The role of the nondominant hemisphere, and of other more distributed networks in global attentional mechanisms (such as generalized vigilance, concentration, and behavioral arousal), will be discussed later in this chapter.

Lateralized Aspects of Attention

Attention includes two major components:

1. Global attention (discussed later in this chapter) includes functions such as vigilance, concentration, and generalized behavioral arousal.

2. Selective, or directed attention involves focusing attention on a particular domain above others.

The circuits involved in these two aspects of attention share many common components and mechanisms. We began learning about these networks through discussions of brainstem and diencephalic activating systems in Chapter 14. Thus, attention (like alertness) depends on activating systems such as the pontomesencephalic reticular formation (see Figures 14.7, 14.8), thalamic intralaminar nuclei and other diencephalic structures, widespread projecting neuromodulatory systems (see Figures 14.9-14.13), as well as the oculomotor gyrus and other limbic, frontal, and parietal higher-order association cortices (see Figure 19.1).

Although both hemispheres are involved, there is a marked asymmetry in the relative importance of the two hemispheres, and the right hemisphere is more important for attentional mechanisms in most individuals. As we will discuss in KCC 19.9, lesions of the right hemisphere often lead to prominent and long-lasting deficits in attention to the contralateral side, while in left hemisphere lesions, contralateral neglect is relatively mild or undetectable. In studies of normal individuals using functional neuroimaging or electrophysiological investigations, the left hemisphere responds to stimuli on the right side, while the right hemisphere responds to both left and right-sided stimuli rather more strongly to stimuli on the left. This is analogous to the involvement of the right premotor cortex in movement of the left hand and of the left premotor cortex in movement of both the right and left hands, discussed earlier.
The hemispheric asymmetry of attentional mechanisms, and the effects of lesions, are shown schematically with "attention rays" in Figure 19.7. Under normal conditions (Figure 19.7A), the right hemisphere attends strongly to the left side and less strongly to the right side, while the left hemisphere attends mainly to the right side. The result is a very slight net attentional bias toward the left in most individuals, which may explain why many languages are written from left to right. With right hemisphere lesions (see Figure 19.7B), the left hemisphere is still able to attend to the right side, but there is a profound deficit in attention to the left. In addition, there is a milder deficit in attention on the right side (ipsilateral to the lesion) as well. With left hemisphere lesions (see Figure 19.7C), the right hemisphere is still able to attend to the right side, so only mild right-sided deficits or no deficits in attention are seen. Finally, with bilateral partial lesions (see Figure 19.7D), there is some residual ability of the right hemisphere to attend to the left side only, resulting in a marked deficit in attention to the right. As we discussed in the section on central lateralization earlier in this chapter, the reasons for left hemisphere specialization for language and right hemisphere specialization for attention and spatial analysis are not known.

**Spatial Analysis and Integration**

Spatial analysis depends on integration of information from multiple sensory modalities; however, since vision plays such an important role in human perception, the term "visual-spatial analysis" is often used. Like other mental functions, visual-spatial analysis is performed by a distributed network and depends on bilateral regions of the frontal and parietal association cortex. However, the parietal association cortex at the junction of the parietal, temporal, and occipital lobes is especially important for spatial analysis, and the *non-dominant* (usually right) hemisphere is more important than the left.

As we discussed in Chapter 11, and we will further discuss later in this chapter, visual information is analyzed by two streams of higher-order information processing: a "What?" stream in the medial occipital, temporal, and parietal cortex, and a "Where?" stream in the dorsal occipital, parietal, and prefrontal cortex (see Figure 19.12). The parietal association cortex at the junction of the parietal, temporal, and occipital lobes (see Figure 19.1) lies directly in the dorsal stream, analyzing location and movement of visual objects in space. The posterior parietal cortex is also ideally situated to integrate other sources of spatial information from adjacent cortical areas. Spatio-analysis thus encompasses both the surrounding environment and the relative position of the individual's body in space, using visual, proprioceptive, vestibular, auditory, and other information from adjacent cortical areas (see Figure 19.1). As we will discuss in KCC 19.10, disorders of spatial analysis, such as impaired visual-spatial judgment or spatial constructional abilities, are most commonly seen in lesions of the right parietal cortex, but can be seen with lesions on other areas as well.

**Figure 19.7 Hemispheric Asymmetry in Attention Demonstrated through Attentional Rays**

**Review Exercise**

What deficits in attention are expected with:
- Right hemisphere lesions?
- Left hemisphere lesions?
- Bilateral partial lesions?

**Key Clinical Concept**

**HEMINEGLIGENCE SYNDROME**

One of the most dramatic syndromes in clinical neurology is hemineglect syndrome, seen most often with infants or other acute lesions of the right parietal or right frontal lobes. Patients with this syndrome often exhibit profound neglect for the contralateral half of the external world, as well as for the contralateral half of their own bodies. Most strikingly, despite their profound deficits, these patients are often unaware that anything is wrong, and they sometimes even fail to recognize that the left sides of their bodies belong to them.

Contralateral hemineglect occurs most often with lesions of the right parietal or frontal cortex (Figure 19.8). Cases of contralateral neglect also occasionally occur with lesions of the cingulate gyrus, thalamus, basal ganglia, or midbrain reticular formation. As we have already discussed, neglect is usually much more pronounced and lasts longer with right hemisphere lesions, but milder forms of neglect can occur with left hemisphere lesions as well (see Figure 19.7).

Neglect is most severe in lesions of sudden onset such as infarct, hemorrhage, seizures, or head trauma, but it can also be seen in more slowly developing lesions, such as brain tumors or other space-occupying lesions. In large strokes, recovery from hemineglect can take weeks to months, and...
some patients remain with a permanent deficit in contralateral attention. During the recovery period, patients with hemineglect are more prone to injury and falls, and they may inadvertently bump or injure their contralateral side. Driving should be avoided until patients are able to demonstrate normal attention to both sides.

Testing for Hemineglect on Patient Examination

Close examination of the presence of hemineglect include a history of the patient’s bumping into objects on one side, ignoring food on one side of the plate, or being unaware of deficits. In addition, obvious examination of the patient’s behavior, movements, and grooming (some patients may comb or shave only their right side!) can be helpful. Other associated features of nondominant hemisphere lesions are discussed in KCC 19.10.

Four main types of testing can be performed on patient examination to evaluate different aspects of the hemineglect syndrome (Table 19.7). Tests usually evaluate sensory neglect, in which patients ignore visual, tactile, or auditory stimuli in the contralateral hemisphere; motor-intentional neglect, in which patients perform fewer movements in the contralateral hemisphere; combined sensory and motor neglect; and conceptual neglect, in which the patients’ internal representations of their own bodies or of the external world exhibit contralateral hemineglect. Many tasks used to test for hemineglect depend on more than one component of the neglect syndrome. For example, drawing the face of a clock from memory depends on all of the above components. Although it has been postulated that more posterior or anterior lesions may cause more sensory or motor neglect, respectively, this has not been consistently demonstrated, and the subdivision of different aspects of the hemineglect syndrome is still under active investigation.

In the subsections that follow, we will describe several useful tests for evaluating different aspects of the hemineglect syndrome.

Testing for Sensory Neglect

Hemineglect can be present in just one or in more than one sensory modality. Tactile hemineglect is most common, but visual hemineglect is fairly common as well, with auditory hemineglect detected less frequently. As described in Chapter 3, visual, tactile, or auditory extinction on double simultaneous stimulation are useful tests of sensory hemineglect (see neuroexam.com Videos 27, 42, 77). For the results of extinction testing to be valid, it is important first to establish normal primary sensation by testing each side alone. Next, unilateral and bilateral presentations of stimuli should be randomly intermixed and the patient asked to report whether the stimulus was on the right, left, or both sides (eyes should be closed for tactile and auditory testing). With subtle neglect, extinction may be inconsistent. In addition, to bring out subtle tactile neglect, a proximal stimulus on the normal side (touching the left cheek) may produce extinction of a distal stimulus on the neglected side (touching the right hand), whereas when the sides are reversely, both stimuli may be reported (see neuroexam.com Video 77).

Patients with hemineglect commonly exhibit alliteration, in which they erroneously report the location of a stimulus given to the right side of the body as being on the left. The extent of sensory neglect may vary depending on the relative position of the stimulus to the patient’s eyes, head, or body. The frame of reference that is most important varies from patient to patient. For example, some patients may completely ignore both sides of a visual stimulus when it is placed to the left of their bodies, while ignoring only the left hand of the stimulus when it is placed directly in front of them. Therefore, it is usually best to examine patients with the eyes, head, and body aligned straight ahead, and to present the stimuli symmetrically. This may be difficult with patients who have a marked unilateral gaze preference (see the next subsection).

Testing for Motor-Intentional Neglect

Patients should be observed for akinesia or decreased spontaneous movements of unilateral limbs or trunk, or eye movements. A marked ipsilateral gaze preference (toward the lesion) is common, especially in acute frontal or parietal lesions (see Figure 13.15A). Patients may exhibit motor impersistence (see KCC 19.4), especially of the contralateral limbs. They may have apparently decreased motor power on the neglected side, yet normal power may be demonstrated with increased effort, increased motivation, and active redirection of the patient’s attention to the neglected side. The examiner can demonstrate motor extinction with the patient’s eye closed by randomly intermixing commands to raise the right arm, left arm, or both. Allolokinesia may also be present, in which the patient inappropriately moves the normal limb when asked to move the neglected limb.

A useful test of hemineglect in patients who are encephalopathic (see KCC 19.14, 19.15) or have difficulty following commands is the tactile response test. Patients are instructed to raise whichever limb is touched, observing the need for them to attend to and interpret the commands “right,” “left,” or “both.” Once they understand the task, more subtle deficits can be detected during this test if they are asked to close their eyes. Note that the tactile response test is sensitive to both sensory and motor neglect (see the next subsection).

To test motor neglect in isolation, a variant of the tactile response test, called the crossed response test, can be used. In this test the patient is asked to move the limb opposite the one touched. Some patients may have difficulty understanding this task. Other tests of motor neglect, or of directional motor bias, include asking the patient to close their eyes and then point to a spot directly opposite their sternum, or asking them to collect coins from a table while blindfolded. Some patients exhibit spatial akinesia, in which movements of the limbs are worse when they are located in the neglected hemisphere. The examiner can demonstrate this deficit by asking patients to cross their arms during testing.

Combined Testing for Sensory and Motor Neglect

Many tests of neglect combine sensory and motor modalities, as well as conceptual or representational functions described in the next section. One simple example of combined sensory and motor neglect testing is the tactile response test that was described in the previous section. Other useful tests that combine sensory and motor function often involve the use of pen and paper. Several of these tests are demonstrated on neuroexam.com Video 16. In administering pen-and-paper tests, it is essential to ensure that the patient is
centered and that the test objects are centered in front of the patient and immobile if possible, to prevent patients from moving the entire stimulus into their non-neglected field. In addition, the stimuli should be large enough that they extend into both fields, again to prevent patients from easily capturing the entire stimulus within their normal hemifield.

In the line bisection task, the patient is instructed to cross a horizontally oriented line right in the middle. The line should appear on a blank piece of paper without other cues and should be about 10 inches long. Normal individuals bisect the line right in the middle, or up to about 1 cm to the left of center, whereas patients with hemineglect often bisect the line far to the right of midline (Figures 19.9A, 19.10A). Other, more difficult cancellation tasks are useful in detecting and quantifying more subtle neglect. Such tasks include presenting patients with a page filled with numerous small lines for them to cross out, or harder still, a page full of mixed letters or other objects among which they must cancel only certain targets (e.g., the letter A, or all star shapes) while ignoring the distractors (see Figure 19.9B,C). Patients with neglect tend to miss the targets on the left side of the page.

Drawing is a useful test, and famous examples exist of artists who drew only half of objects or faces after developing hemineglect. A standard test is to ask the patient to draw a clock face, taking up as much of the page as possible, and then fill in the numbers (see Figure 19.10B). Patients can also be asked to draw other objects, such as a flower or a house, and to copy simple or complex figures (see neuroexam.com Video 17). In addition to testing for neglect, drawing tests constructional abilities (see KCC 19.10). These visual-spatial functions are often impaired in patients with lesions of the nondominant hemisphere, even when significant hemineglect is not present.

Reading a newspaper or magazine can be helpful in testing for hemineglect. Patients often read only the right few letters or the right few words of headlines. They may also ignore the left half of a picture when asked to describe it. In addition, while writing, patients with hemineglect tend to crowd their words onto one side of the page.

Conceptual Neglect

One of the more striking features of hemineglect syndrome is the common occurrence of anosognosia, meaning lack of awareness of the illness. Patients with hemiplegia, hemianopia, and hemisensory loss caused by right hemisphere lesions are often perplexed as to why they are in the hospital and may ask to be discharged. Anosognosia is not unique to right hemisphere lesions; it can be seen in other disorders as well. For example, anosognosia is also seen in patients with Wernicke's aphasia (see KCC 19.5), frontal lobe disorders (see Figure 19.9C, showing the letters correctly written).
TABLE 19.8 Some Functions of the Frontal Lobes

<table>
<thead>
<tr>
<th>RESTRAINT</th>
<th>INITIATIVE</th>
<th>ORDER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Judgment</td>
<td>Curiosity</td>
<td>Abstract reasoning</td>
</tr>
<tr>
<td>Insight</td>
<td>Spontaneity</td>
<td>Working memory</td>
</tr>
<tr>
<td>Perseverance</td>
<td>Motivation</td>
<td>Perspective taking</td>
</tr>
<tr>
<td>Diligence</td>
<td>Drive</td>
<td>Planning</td>
</tr>
<tr>
<td>Inhibiting socially inappropriate responses</td>
<td>Creativity</td>
<td>Insight</td>
</tr>
<tr>
<td>Shifting cognitive set</td>
<td>Organisation</td>
<td></td>
</tr>
<tr>
<td>Self-governance</td>
<td>Mental flexibility</td>
<td>Sequencing</td>
</tr>
<tr>
<td>Concentration</td>
<td>Personality</td>
<td>Temporal order</td>
</tr>
</tbody>
</table>

The Frontal Lobes: Anatomy and Functions of an Enigmatic Brain Region

More than any other part of the brain, the frontal lobes enable us to function as effective and socially appropriate human beings. It should perhaps be no surprise, therefore, that the frontal lobes are also among the most enigmatic, contradictory, and difficult to study brain regions. The importance of the frontal lobes has been debated over the years, with some earlier researchers believing that the frontal lobes are generally superfluous, and others feeling that they are the most important part of the brain. These different opinions arose because patients with frontal lobe lesions often have no deficits that can be detected on routine testing, yet they are completely unable to function normally in the "laboratory" of the real world. Additional complexity is evident in the wide variety of functions ascribed to the frontal lobes, some of which are listed in Table 19.8. Similarly, lesions of the frontal lobes produce highly variable behavioral syndromes, many of which seem contradictory even within a single patient (Table 19.9).

It should be clear from this discussion that there is no single frontal lobe syndrome. Frontal lobe function is probably best viewed as comprising several different realms, which we will present in this section, in somewhat simplified fashion, as clustering around the following three domains: restraint, initiative, and order (see Table 19.8). First, however, we will review the regional anatomy of the frontal lobes and some of the more important connections of frontal lobe cortex.

Regional Anatomy of the Frontal Lobes

The frontal lobes are the largest region of the brain, comprising nearly one-third of the cerebral cortex. Recent evidence suggests that the frontal lobes are comprised of several distinct sections, each with its own unique functional properties. The frontal lobes are divided into three main areas: the orbital, the medial, and the lateral frontal lobes. Each of these areas is further subdivided into several smaller regions. The orbital frontal lobes are involved in social behavior, decision making, and emotional regulation. The medial frontal lobes are involved in the regulation of movement and the expression of emotions. The lateral frontal lobes are involved in cognitive control, planning, and problem solving.

TABLE 19.9 Apparently Contradictory Behavior Seen in Frontal Lobe Syndromes

<table>
<thead>
<tr>
<th>Aphathic indifference</th>
<th>Explosive emotional liability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abulia</td>
<td>Environmental dependency</td>
</tr>
<tr>
<td>Akinesis</td>
<td>Distractibility</td>
</tr>
<tr>
<td>Perserverance</td>
<td>Impulsiveness</td>
</tr>
<tr>
<td>Mutism</td>
<td>Confabulation</td>
</tr>
<tr>
<td>Depression</td>
<td>Marital</td>
</tr>
<tr>
<td>Hypersociality</td>
<td>Hypersociality</td>
</tr>
</tbody>
</table>

KCC 19.11, among others, may be seen in Wernicke-Korsakoff syndrome (see KCC 19.1), and cortical blindness (see KCC 19.12).

Aside from anosognosia, some patients with right hemisphere lesions may exhibit anosodiaphoria, in which they are aware that they have severe deficits, yet show no emotional concern or distress about it. An even more bizarre manifestation of heminegligence is hemiasomatognosia, in which patients deny that the left half of their body belongs to them. A patient may become distressed because "someone left an arm in my bed." When asked about their left extremities, the patient may claim that they belong to someone else, or that they are not even limbs at all.

Other aspects of what we have called conceptual neglect include abnormal mental representations or memories of imagined scenes or experiences. For example, Bisiach and Luzzatti described a patient who was asked to recall various landmarks from a square in Milan while facing the cathedral. Patients with left heminegligence could recall details on only the right side of the square. When they were then asked to imagine themselves facing away from the cathedral, the patients were able to describe details on the opposite side of the square.
lobes have three surfaces: lateral, medial, and orbital (see Figure 19.11A, B, and C, respectively). Let’s study these three surfaces and briefly review the regions of frontal cortex discussed in previous chapters. On the lateral surface, the primary motor cortex lies in the precentral gyrus (see Figure 19.11A). The primary motor cortex consists medially in the anterior portion of the precentral lobe. Just in front of the primary motor cortex, on the lateral surface, lies the premotor cortex and, in the dominant hemisphere, Broca’s area. In front of the primary motor cortex on the medial surface is the supplementary motor area (see Figure 19.11B). The motor, premotor, and supplementary motor cortices were discussed in Chapters 6, 15, and 16. The frontal eye fields are located in the premotor cortex on the lateral convexity of the frontal lobes (see Figure 19.11C). The supplemental motor cortex and prefrontal regions of the orbital frontal cortex are important limbic areas that lie in the frontal lobes (see Figure 19.11B), and the ventral frontal lobes contain the orbital frontal area (see Figure 19.11C).

The discussion in this section will focus on the frontal cortex lying anterior to the motor, premotor, and limbic areas, which is called the prefrontal cortex (see Figure 19.11). The prefrontal cortex is the largest part of the frontal lobes and consists of higher-order heteromodal association cortex. It is the prefrontal cortex that is usually referred to when disorders of the frontal lobe are discussed.

Connections of the Prefrontal Cortex

The prefrontal cortex has numerous cortical and subcortical connections, which have been studied most extensively in nonhuman primates. Most of these connections are bidirectional. The anatomical configuration of frontal lobe connections is consistent with the role of this lobe in higher-order processes that require integration of multimodal sensory, motor, and limbic information. Cortical connections are mainly with the association cortex of the parietal, occipital, and temporal lobes, including unimodal sensory association cortex and heteromodal association cortex. In addition, there are connections with motor association cortex in the frontal lobes. Important connections of the prefrontal cortex are with the limbic cortex existing all way, especially with the anterior cingulate gyrus and the orbitofrontal cortex.

Subcortical connections are numerous as well. The amygdala is connected with the orbital and medial regions of the frontal lobes by the uncinate fasciculus (see Figure 18.4), C). The frontal lobes are connected to neostriatal temporal cortex by the cingulate gyrus and parahippocampal gyrus (see Figure 18.9).

The most important thalamic nucleus that relays information to and receives projections from the prefrontal cortex is the mediodorsal nucleus, although connections with the medial pulvinar and intralaminar nuclei are present as well (see Figure 7.8). The prefrontal cortex projects to the basal ganglia mainly via the head of the caudate nucleus (see Figure 16.8, Table 16.2). Other important subcortical connections exist with the hypothalamus, septal region, subthalamic region, cerebellum, and midbrain. Finally, like all other cortical areas, the frontal lobes receive projections from multiple subcortical and brainstem modulatory neurotransmitter systems, including dopamine, acetylcholine, serotonin, norepinephrine, and histamine.

Functions of the Frontal Lobes

As mentioned already, frontal lobe functions are quite diverse and apparently contradictory at times (see Tables 19.8, 19.9). The frontal lobes are crucial for the sophisticated decisions we make, and for the subtle social interactions we continually engage in as normal humans. The vast range of human peculiarities have been classified into three categories by philosophers and scientists from Plato to Freud, and we will follow this traditional simplification in describing the functions of the frontal lobes. These can be classified as functions important for (1) restraint (inhibition of inappropriate behavior), (2) initiative (motivation to pursue positive or productive activities), and (3) order (the capacity to correctly perform sequencing tasks and a variety of other cognitive operations) (mnemonic RIO). The functions listed in Table 19.8 are arranged according to this scheme. Note, however, that this is only a simplification, and that some frontal lobe functions do not fit easily into any one of these categories.

You will get a better sense for frontal lobe functions when we review frontal lobe disorders in KCC 19.11. Here we will discuss only briefly a few frontal lobe functions that have been studied extensively in the research setting. Working memory (see Table 18.6) is the ability to hold a limited amount of information in an immediately available store while a variety of cognitive operations are performed. An example is the carrying function in arithmetic. Both studies in animals and functional imaging in humans have shown the importance of the dorsolateral prefrontal cortex in working memory.

Recent functional imaging studies have also shown that the dorsolateral prefrontal cortex may function together with the medial temporal lobes in learning new material. In these studies, the left frontal lobe and medial temporal lobes showed activation during learning of visual or verbal information that was later successfully recalled. Similarly, the right frontal lobe and medial temporal lobes showed activation during learning of new visual or verbal information that was later successfully recalled.

Activation of the dorsolateral frontal cortices has also been shown during tasks that require shifting cognitive set. An example is the Wisconsin Card
Sorting Test, in which subjects must have the mental flexibility to infer that the rules for the sorting task are being performed change repeatedly. Interestingly, the frontal lobes are also activated during tasks that require selective attention—e.g., for example, listening to words while visual or tactile stimuli are presented simultaneously. Another important area of research has been the role of the frontal lobes in integrating information from limbic and heteromodal association cortex in decision making. This emotional weighting of abstract decision making is thought to enable subtle emotional and motivational factors to participate in human judgment so that more efficient, or “intuitive,” decisions can be made when limited information and time are available.

As shown in Table 19.9, the effects of frontal lobe lesions are often perplexing, with apparently contradictory features seen in different patients, or even within a single patient. Several explanations have been offered for this observation. First, the frontal lobes are large, encompassing many differently functional areas. Frontal lobe deficits are often subtle at first, and lesions may reach a large size and involve several different functional areas before becoming clinically apparent. Similarly, bilateral lesions usually produce more clinically obvious deficits than unilateral lesions, and behavioral and complex disorders result from bilateral lesions. Finally, the functions of the frontal lobes are themselves complex and therefore difficult to study, especially in the formal examination setting.

On the basis of studies of animals and humans with frontal lobe lesions, a distinction is sometimes made between lesions of the dorsolateral convexity and lesions of the orbitofrontal cortex. According to this scheme, dorsolateral convexity lesions tend to produce an apathetic, lethargic, and hypotonic behavior, while orbitofrontal lesions lead to impulsive, disinhibited behavior and poor judgment. In clinical practice, numerous exceptions to this dichotomy exist. In addition, many frontal lesions affect both dorsolateral and orbitofrontal regions, making the usefulness of this classification somewhat limited. Another distinction has been made, between left frontal lesions, which on the whole are more commonly associated with depression-like symptoms, and right frontal lesions, which are more commonly associated with behavioral disturbances resembling mania. Again, numerous exceptions exist.

Despite these contradictions and uncertainties, certain characteristic features revealed during evaluation of a patient can suggest frontal lobe dysfunction. Familiarity with these features is important for recognizing patients with probable frontal lobe dysfunction, so we will now discuss them in detail.

**Evaluating Patients with Suspected Frontal Lobe Dysfunction**

The basic steps of clinical assessment for patients with suspected frontal lobe dysfunction are summarized in Table 19.10. The most important information in the evaluation of patients with suspected frontal lobe dysfunction is often obtained during the formal neuropsychologic exam. Clinical evidence of frontal lobe dysfunction may be obtained from the patient's history and through discussions with family and other contacts who have witnessed the patient's abnormal functioning in the real world. In addition, careful observations should be made for certain behavioral abnormalities that may be seen in patients with frontal lobe dysfunction (see Table 19.10).

Abulia patients are passive, exhibiting little spontaneous activity, markedly delayed responses, and a tendency to speak briefly or softly. In the extreme, they may be totally immobile, akinetic, and mute but will continue to appear awake, sitting with their eyes open. In contrast, disinhibition may also be seen, including sly behavior, crass jokes, and aggressive outbursts. Some patients exhibit inappropriate joviality (witzelsucht), seeming unconcerned about potentially serious matters. Patients may have limited insight into their condition and may not accommodate. Patients who display utilization behavior or environmental dependency tend to respond to whatever stimulus is at hand, even when not appropriate. For example, they may put on glasses that are not theirs. Perseveration, impersistence, and frontal release signs are tested during the formal neuropsychologic exam, but they may also be observed spontaneously, especially in more minimally affected patients. Patients with severe perseveration may repeatedly answer the same question even when the examiner is trying to move on. Incontinence is sometimes seen in frontal lobe disorders, especially those affecting the medial frontal regions. Patients are characteristically unconcerned about their incontinence.

During the mental status portion of the neuropsychologic exam, important clues can be obtained about possible frontal lobe dysfunction. Note that many of these tests do not test frontal lobe function alone, but depend on intact functioning of numerous other systems, which should be assessed during the remainder of the exam. The tests listed here were selected for their clinical usefulness in detecting subtle frontal lobe abnormalities.

In patients with frontal lobe dysfunction, attention may be impaired; such impairment can be evaluated with digit span and other type tests (see KCC 19.14; Table 19.10). Subtle perseveration may be detected by use of one of the Luria sequencing tasks (see neurorum.com Videos 19-20). For example, when a patient was asked to copy the sequence in Figure 3.1 and continue it to the end of the paragraph, they clearly perseverated. Figure 3.1 also demonstrates the closing-in phenomenon with this test, in which some patients' drawing gradu.

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**TABLE 19.10 Evaluating Frontal Lobe Function**

<table>
<thead>
<tr>
<th>Test</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Digit span forward and backward</td>
<td></td>
</tr>
<tr>
<td>2. Digit span forward and backward</td>
<td></td>
</tr>
<tr>
<td>3. Perseveration and set-ability ability</td>
<td></td>
</tr>
<tr>
<td>4. Bedside Luria alternating sequencing tasks (written, manual)</td>
<td></td>
</tr>
<tr>
<td>5. Formal testing: Trails B, Wisconsin Card Sorting Test</td>
<td></td>
</tr>
<tr>
<td>6. Ability to suppress inappropriate response</td>
<td></td>
</tr>
<tr>
<td>7. Bedside auditory or visual go-no-go tasks</td>
<td></td>
</tr>
<tr>
<td>8. Formal testing: Stroop test</td>
<td></td>
</tr>
<tr>
<td>9. Word generation, figure generation</td>
<td></td>
</tr>
<tr>
<td>10. FAS test or other word generation tasks</td>
<td></td>
</tr>
<tr>
<td>11. Figure generation</td>
<td></td>
</tr>
<tr>
<td>12. Abstract reasoning</td>
<td></td>
</tr>
<tr>
<td>13. Similarities</td>
<td></td>
</tr>
<tr>
<td>14. Verbal interpretation</td>
<td></td>
</tr>
<tr>
<td>15. Logic problems</td>
<td></td>
</tr>
<tr>
<td>16. Judgment, influence of future consequences on current behavior</td>
<td></td>
</tr>
<tr>
<td>17. Difficult to test; questions about situations (e.g., fire in theater) are artificial and test mainly general knowledge and reasoning ability</td>
<td></td>
</tr>
<tr>
<td>18. Gambling task</td>
<td></td>
</tr>
<tr>
<td>19. Language testing</td>
<td></td>
</tr>
<tr>
<td>20. Testing for hemineglect</td>
<td></td>
</tr>
<tr>
<td>21. Other exam findings</td>
<td></td>
</tr>
<tr>
<td>A. Skull shape (hypertension may signify a frontal meningioma)</td>
<td></td>
</tr>
<tr>
<td>B. Olfaction (anosmia may signify an orbitofrontal tumor)</td>
<td></td>
</tr>
<tr>
<td>C. Optokinetic nystagmus test (impaired saccades occur away from side of lesion)</td>
<td></td>
</tr>
<tr>
<td>D. Hemiparesis or upper motor neuron signs</td>
<td></td>
</tr>
<tr>
<td>E. Motor incoherence (stick tongue out or hold up arms for 20 seconds)</td>
<td></td>
</tr>
<tr>
<td>F. Coganian (parasthesia)</td>
<td></td>
</tr>
<tr>
<td>G. Primitive reflexes, or &quot;frontal release signs&quot; (grasp, suck, snout)</td>
<td></td>
</tr>
<tr>
<td>H. Frontal &quot;magnetic&quot; gag disturbance</td>
<td></td>
</tr>
</tbody>
</table>

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ally approaches that of the examiner, possibly exhibiting a form of environ
mentally testable perseveration, in which the patient is asked to tap their
with a closed
and then plant the palm of their hand, and then with the side of their open
hand, repeatedly. Some formal neuropsychological tests of perseveration
and set-shifting ability are also listed in Table 19.10.
A useful bedside test of a patient’s inability to suppress inappropriate re-
spose is the go-no-go task (see neuroexam.com Video 21). This task is
similar to (but easier than) the children’s game “Simon Says.” In the audi-
tory go-no-go task, the patient is first taught to respond to one
and to the other to response to two taps. The examiner
then produces a random sequence of one or two tapping sounds. In the vi-
sual form of the task, the examiner randomly shows one or two fingers.
More formal testing can be accomplished with the Stroop test. In the Stroop
test, patients are given a list of colors names such as “red,” “yellow,” “green,”
and so on, which are printed in colored ink, but the colors do not match
the meanings of the words (e.g., the word “yellow” might be printed in
ink). Patients are then instructed to list the ink colors of the words without
reading the words.
The ability to spontaneously generate lists of related words or values
is often impaired in patients with frontal lobe lesions. Word generation
tasks can be used to detect subtle decreases in verbal fluency and are a sen-
sitive measure of dominant frontal dysfunction. A useful standardized test
of this kind is the FAS test, in which the patient is given 60 seconds to pro-
duce as many words as possible starting with the letter F, then 60 seconds
to produce words starting with the letter A, and then with the letter S. Proper
names of persons or places are not allowed. Normal individuals produce 12
or more words for each letter. Similarly, normal individuals can name at
least 15 animals in 60 seconds. For detecting nondominant frontal lobe dys-
fuction, similar tasks based on the generation of simple drawings can be used
(referred to as tests of figural fluency).
Frontal dysfunction often interferes with abstract reasoning ability. Two
common tools for testing this are proverb and similarities. (See neuro-
exam.com Video 22). Responses are rated as either normal or concrete. It is
important to use proverb and similarities ranging from easy to difficult
(Table 19.11) to gauge the patient’s level of functioning. A variety of logical
problems can also be used to test abstract reasoning. Judgment is very
difficult to test in any normal, smooth, and normal individuals produce 12
or more words for each letter. Similarly, normal individuals can name at
least 15 animals in 60 seconds. For detecting nondominant frontal lobe dys-
fuction, similar tasks based on the generation of simple drawings can be used
(referred to as tests of figural fluency).

<table>
<thead>
<tr>
<th>TABLE 19.11 Examples of Proverbs and Similarities Used for Testing Abstraction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Proverbs:</strong> “What does it mean if I say...”</td>
</tr>
<tr>
<td>Don’t cry over spilled milk.</td>
</tr>
<tr>
<td>People who live in glass houses should not throw stones.</td>
</tr>
<tr>
<td>The tongue is the mirror of the heart.</td>
</tr>
<tr>
<td>One swallow does not a summer make.</td>
</tr>
<tr>
<td>You never cross the same stream twice.</td>
</tr>
<tr>
<td><strong>Similarities:</strong> “How are a ______ and a ______ alike?”</td>
</tr>
<tr>
<td>Hammer</td>
</tr>
<tr>
<td>Screwdriver</td>
</tr>
<tr>
<td>Orange</td>
</tr>
<tr>
<td>Apple</td>
</tr>
<tr>
<td>Table</td>
</tr>
<tr>
<td>Couch</td>
</tr>
<tr>
<td>Train</td>
</tr>
<tr>
<td>Airplane</td>
</tr>
<tr>
<td>Poem</td>
</tr>
<tr>
<td>Sculpture</td>
</tr>
<tr>
<td>Math</td>
</tr>
<tr>
<td>True</td>
</tr>
<tr>
<td><strong>Easiest</strong></td>
</tr>
<tr>
<td><strong>Most difficult</strong></td>
</tr>
</tbody>
</table>

In addition, so-called frontal release signs, or primitive reflexes, nor-
mally seen in infants may return in adults with frontal lesions. The most
useful of these is the grasp reflex, which the examiner can elicit by stroking
the patient’s palm (see neuroexam.com Video 18). When the grasp reflex is
severe, the patient cannot release their grasp even when explicitly told to
grasp the examiner’s hand. A more subtle grasp reflex may be elicitable only
if the examiner elicits the patient—for example, by engaging the patient in
conversation. If asked why they are grasping the examiner’s hand, pa-
nents usually respond that they do not know.

Other, less specific reflexes are the suck, elicited by touching the patient’s
lip with a cotton swab; snout, elicited by tapping the patient’s lips; and
root, elicited by stroking the patient’s cheek or holding an object near
their mouth. The palmarogenual reflex, in which stroking the thenar
emc changes the ipsilateral chin muscles to contract, is not generally useful
because it is seen in many normal individuals. Myerson’s glabellar sign is
associated with movement disorders such as Parkinson’s disease (see KCC
15.1). Frontal lobe lesions can cause characteristic frontal gait abnormali-
ties (see KCC 6.5; Table 6.6), with a shuffling, unsteady, magnetic gait,
in which the patient’s feet barely leave the floor.
Differential Diagnosis of Frontal Lobe Disorders

Disorders that commonly affect the frontal lobes are listed in part I of Table 19.12. Often patients with clinical syndromes that closely resemble frontal lobe lesions turn out to have disorders that affect the brain diffusely (Table 19.12, part II). One reason for this may be that the frontal lobes make up a large proportion of the brain, and therefore multifocal disorders have a greater chance of affecting the frontal lobes before other brain regions. In the case of hydrocephalus, it has been proposed that the dilated ventricles compress frontal subcortical white matter pathways, or possibly the anterior cerebral arteries. Other disorders, some of which have lesions located remotely from the frontal lobes, may also mimic frontal lobe pathology (see Table 19.12, part III). This is likely because, as already discussed, the frontal lobes form part of a network of widespread cortical and subcortical connections. In addition, abnormalities of certain neurotransmitter systems, especially dopaminergic, can lead to frontal lobe dysfunction. These numerous other conditions listed in Table 19.12, which can mimic frontal lobe disorders are discussed in more detail elsewhere (see KCC 5.7, 6.5, 6.6, 14.2, 15.2, 16.2, 18.3, 19.5, 19.16).

Visual Association Cortex: Higher-Order Visual Processing

As we discussed in Chapter 11, after arrival at the primary visual cortex, visual information is processed in two streams of association cortex (Figure 19.12). The dorsal pathways project to parieto-occipital association cortex. These pathways answer the question “What?” by analyzing motion and spatial relationships between objects, and between the body and visual stimuli. The ventral pathways project to occipitotemporal association cortex. These pathways answer the question “Where?” by analyzing form and color.


One important area of research is the question of how information from different cortical areas, both visual and nonvisual, is combined to form the unified perceptions that we experience. For example, our experience of someone speaking to us is not fragmented into a perception of sounds, verbal comprehension, facial recognition, facial color, location of the face in space, and emotional impact of the words spoken, even though these functions occur in a different cortical area. The question of how unified perceptions are formed in the brain is called the binding problem. Much research and hypothesis development is taking place to investigate the binding problem, especially in the visual system; however, no conclusive mechanism has yet been found.

A second area of research is visual mental imagery—that is, our ability to imagine a scene even when it is not present. This process appears to utilize the same visual areas that perceive external visual stimuli; however, there is some controversy over the extent to which primary visual cortex is involved.

A third research area is the phenomenon of blindsight, in which some individuals with lesions of the primary visual cortex are able to perform tasks such as inserting an envelope correctly in a slot, despite having no conscious visual perception of the slot. Blindsight apparently depends on information transmitted to association cortex by extrageniculate visual pathways (see Figure 11.6), bypassing the lateral geniculate nucleus and primary visual cortex. Some studies have also demonstrated small islands of preserved vision in the blind hemifield measuring only a few minutes of degree that are not able to support conscious vision but may influence behavior.

Visual hallucinations, illusions, and other visual phenomena were introduced in Chapter 11; review this material before reading further (see KCC 11.1). In this section we will build on this background and describe several syndromes of abnormal visual processing associated with specific localization to the primary visual cortex, inferior occipitotemporal cortex (“what” pathways), or dorsal lateral parieto-occipital cortex (“where” pathways).

Syndromes of Primary Visual Cortex

Visual hallucinations, seizures, and migraine-related phenomena associated with the primary visual cortex were discussed in KCC 11.1, and alexia without agraphia associated with color anomia was discussed in KCC 19.7. Another well-known syndrome is cortical blindness, or Anton’s syndrome, caused by bilateral lesions of the primary visual cortex. In Anton’s syndrome, patients have complete visual loss on confrontation testing, yet they have anomognosia and are completely unaware of the deficit. Other exam findings include loss of blind to threat, loss of eye closure in response to bright lights, and loss of optokinetic nystagmus (OKN). Some patients may have blindsight (see the previous section). Anomognosia for visual loss can also be seen in other situations that are not, strictly speaking, Anton’s syndrome: a combined occipital and frontal lesions (resulting in confabulation) or combined occipital and right parietal lesions (resulting in neglect).
Syndromes of the Inferior Occipitotemporal Cortex

The inferior occipitotemporal cortex lies in the "what" stream of visual analysis and processes color and visual form involved in object identification. Specialized regions that are involved in recognizing colors, forms, and letter strings (see Figure 19.13) have been described. Lesions of the inferior occipitotemporal cortex can therefore cause deficits in the recognition of colors, faces, and other objects, as well as other visual phenomena related to color and form. Complex visual hallucinations resulting from seizures of the inferior occipitotemporal visual association cortex were described in KCC 11.1 and KCC 18.2.

In prosopagnosia, patients are unable to recognize people by looking at their faces. The usual lesion location in prosopagnosia is the bilateral inferior occipitotemporal cortex, also known as the fusiform gyrus (see Figure 19.13; see also Figure 2.11C). Some evidence suggests that the right hemisphere is more important in face recognition, but in most reported cases of prosopagnosia with an enduring deficit, the lesions are bilateral. Recall that agnosia is defined as normal perception stripped of its meaning. In prosopagnosia, for example, patients can describe or name even the different parts of a face and can identify a face as being a face, and they may even be able to match faces on the basis of similar features, but they cannot recognize a face as belonging to a particular individual, even if it is someone they know very well. This "pure" form of agnosia without perceptual deficits is also known as associative agnosia, which should be distinguished from perceptual (appreceptive) agnosia, in which impairments of the primary sensory modality may contribute to difficulties with recognition. One way to remember the definition of agnosia is to think of it as a higher-order deficit, in contrast to simple impairments of perception.

Patients with prosopagnosia cannot recognize people by their faces, but they can identify people by their clothes, voices, or other cues. Interestingly, the recognition deficit in prosopagnosia is not restricted to human faces. Famers with prosopagnosia have been reported to have difficulty recognizing their cows, and bird-watchers have been reported to have difficulty recognizing specific birds. One formulation is that prosopagnosia results in "perception recognition"—for example, the ability to recognize felines—but impaired "specific recognition"—for example, the ability to recognize leopards, tigers, lions, and so on. Prosopagnosia is often associated with achronmatopsia (see the next paragraph). In addition, it is sometimes associated with alesia and with upper-quadrant or bilateral upper visual field defects (see Figures 11.15, 11.17B).

Achronmatopsia is a central disorder of color perception. It can be thought of as cortical color blindness and should be contrasted with color agnosia, in which color perception is intact (see the next paragraph). Patients with achromatopsia cannot name, point to, or match colors presented visually. They can, however, name the appropriate color for an object described verbally. Usually patients with achromatopsia are aware of the deficit and describe connected vision as appearing in shades of gray. Achronmatopsia may occur in a quadrant, a hemifield, or the entire visual field. When the whole field is involved, the deficit is usually associated with prosopagnosia and is caused by lesions in bilateral inferior occipitotemporal cortex (see Figure 19.13). Hemifield achromatopsia is caused by lesions in the contralateral inferior occipitotemporal cortex. Other deficits that are sometimes associated with achronmatopsia include alesia and upper-quadrant or bilateral upper visual field defects.

Although color anoma, more correctly referred to as color nemeosis, is not caused by lesions of the inferior occipitotemporal cortex, we discuss it briefly here to contrast it with achronmatopsia. Color agnosia is caused by lesions of the primary visual cortex of the dominant hemisphere extending into the corpus callosum, and it is associated with alesia without agraphia and right hemianopia (see KCC 19.7; Figure 19.5). Patients cannot name or point to colors presented visually. However, perception of colors is preserved as demonstrated by patients' ability to name colors presented verbally. This is not a true anoma or language disorder because patients can name the appropriate color for an object described verbally, and it should be distinguished from amnesic anoma.

Other visual agnosias are more controversial. For example, investigators have described several category-specific visual agnosias for living things, human-made tools, or other specific categories. Large bilateral lesions of the inferior occipitotemporal region may cause a generalized visual-object agnosia applying to both generic and specific recognition of all visual objects, including those just described. This may be considered a perceptual agnosia because vision is often described as appearing hazy. Interestingly, some patients with lesions of this kind have a so-called visual static agnosia, in which they are able to recognize an object only when it moves.

Other illusory phenomena can occur with lesions of the inferior occipitotemporal cortex that are less specifically localized to this region. In microopsia, objects appear unusually small; in macropsia, objects appear unusually big; and either disorder can sometimes occur in only part of the visual field. Metamorphopsia is a more general term describing a condition in which objects have distorted shape and size. These disorders are sometimes referred to as "Alice in Wonderland" syndrome and can occur in migraine, infarct, hemorrhage, tumors, or other disorders of the inferior or lateral visual association cortex. They can also occasionally be seen in retinal pathology or toxic or metabolic disturbances.

In visual reorientation, the environment appears tilted or inverted to the patient. This condition has been associated with vestibular or lateral medullary dysfunction. In palinopsia, lesions of the visual association cortex cause a previously seen object to reappear periodically. For example, one patient looked at a plant, and then a few minutes later the plant reappeared and seemed to be growing out of her omelet. Another patient saw an aide entering her hospital room, and then later that evening she saw the image of the aide entering her room over and over again. Palinopsia can occasionally be caused by medications such as trazadone.

In cerebral diplopia or polyopsia, patients see two or more images, respectively, of an object. Diplopia caused by disconjugate gaze was discussed in KCC 13.1. The appearance of more than two images, as well as monocular diplopia, is sometimes psychiatric in origin. However, monocular or binocular double vision, triple vision, and so on can also occasionally be seen with occipital lesions, cornet lesions, or catactas. Another visual illusion occasionally seen with cortical lesions is erythropsia, which is characterized by gold, red, purple, or other unnatural coloring of the visual field. Disturbances of color vision can also be seen with certain drugs, such as digoxin toxicity, in which objects may appear to have a yellowish halo.

Syndromes of the Dorsolateral Parieto-Occipital Cortex

The dorsolateral parieto-occipital cortex lies in the "where" stream of visual analysis and processes motion and spatial localization and integration (see Figure 19.12). Lesions of the dorsolateral parieto-occipital cortex can therefore cause deficits in these aspects of visual processing. Constructional impairments and other deficits of visual-spatial analysis occurring especially in lesions of the parietal lobes and more commonly in the nondominant hemisphere were mentioned earlier in this chapter (see KCC 19.10).
In Balint's syndrome, caused by bilateral lesions of the dorsolateral parieto-occipital association cortex, there is a clinical triad consisting of (1) simultanagnosia, (2) optic ataxia, and (3) ocular apraxia. Simultanagnosia is the core abnormality of Balint's syndrome and consists of impaired ability to perceive parts of a visual scene as a whole. Patients with simultanagnosia are a relatively common cause that perceives only one small region of the visual field at a time. This region shifts around unpredictably, often causing patients to lose track of what they were looking at. Patients have particular difficulty scanning a complex visual scene or identifying objects that are nearby. A deficit in the primary auditory cortex can cause simple auditory agnosia, described earlier. When confronted with a large complex visual stimulus, patients tend to describe small, isolated parts seemingly at random and have no awareness of the overall unified object or scene. Simultanagnosia can be thought of as a deficit in visual-spatial binding.

Optic ataxia is the impaired ability to reach for or point to objects in space under visual guidance. This condition can be distinguished from cerebellar ataxia because in optic ataxia the ability to point using proprioceptive or auditory cues is intact, and once an object has been touched, a patient with optic ataxia can perform smooth movements back and forth to it even with the eyes closed. Ocular apraxia is difficult voluntarily directing one's gaze toward objects in the peripheral vision through saccades. Some patients need to move their heads to initiate a voluntary redirection of gaze. This condition again may be related to the defect in visual perception of stimuli other than in a small region of the visual field.

Patients with Balint's syndrome may be diagnosed incorrectly with visual agnosia or alexia, which can be shown not to be present when care is taken to ensure that the visual stimulus is in a region the patient can see. Because Balint's syndrome is caused by lesions in the dorsolateral parieto-occipital association cortex, associated deficits may include inferior-quadrant visual field cuts (see Figure 11.15), aphasia, or hemineglect. Most often these bilateral lesions of dorsolateral parieto-occipital cortex are caused by MCA-PCA watershed infarcts (see Figure 19.3B, also Figure 10.10A), although bilateral hemispheric tumors, or other lesions can also produce this syndrome.

Related features of Balint's syndrome may occur in some patients with bilateral parieto-occipital lesions who do not exhibit the full syndrome. For example, some patients may exhibit optic ataxia (a false localization of objects in visual space) or cerebellar akinetopsia (an inability to perceive moving objects).

**KEY CLINICAL CONCEPT**

**AUDITORY HALLUCINATIONS**

**Disorders of higher-order auditory processing involving the auditory cortex and adjacent association cortex** (see Figure 19.1) are just one cause of auditory hallucinations and other positive auditory phenomena. Tinmanitis is a common disorder consisting of a persistent ringing tone or buzzing in one or both ears, usually caused by peripheral auditory disorders affecting the tympanic membrane, middle ear ossicles, cochlea, or eighth cranial nerve (see KCC 12.5). Self auditory bruits are pulsatile "whooshing" sounds that can be associated with turbulent flow in arteriovenous malformations, carotid dissection, or the extracranial-to-intracranial pressure gradient that is produced by elevated intracranial pressure. Some positive auditory phenomena are analogous to similar disturbances of the visual system (see KCC 11.1.19.12). For example, elderly patients with sensorimotor deafness can develop elaborate auditory hallucinations (music, voices, etc.), which may be a reason phenomenon analogous to Bonnet syndrome (visual hallucinations in not possible caused by visual loss). Lesions or ischemia of the pontine tegmentum involving the trapezoid body, superior olivary nucleus, and other auditory cl
related processes that maintain (1) alertness; (2) attention; and (3) awareness of self and environment (mnemonic AAA). We introduced these concepts in Chapter 14, along with the networks that regulate the level of consciousness. Recall that these networks include the brainstem-diencephalic activating systems, basal forebrain, and cortex. We will now continue our exploration of consciousness by moving from functions that prevent coma (and promote alertness), first to a discussion of attention, and later to the more controversial topic of awareness.

Attention can be described in many different ways and has a variety of different functional components. A coherent, physiologically or anatomically based taxonomy of attention has not yet emerged, so we will simply list several different attentional functions that have been described. Selective attention, or directed attention, implies attention to certain objects, stimuli, or concepts to the exclusion of others. Selectivity is an essential component of attention and has been studied extensively. In selective attention, attention is directed at specific components of the "substrate," or content of consciousness, described in the previous paragraph. Examples of selective attention are quite diverse; they include:

- Attention to a visual, tactile, or auditory stimulus in a particular location in space (discussed earlier in this chapter)
- Attention to inputs of a specific sensory modality
- Attention to a specific higher-order aspect of a stimulus (e.g., color versus shape)
- Attention to a particular object, including inputs from various modalities
- Attention to an object, emotion, plan, or concept that is not physically present but is either remembered or imagined

Functional MRI and evoked-potential studies in humans, and recordings from animal models, suggest that these examples of directed attention are reflected in the activation of specific brain regions, following known anatomical principles. For example, attention to a somatosensory stimulus on the body activates the corresponding somatotopic region of the somatosensory cortex, attention to a visual stimulus in a particular location activates the corresponding retinotopic region of the visual cortex, and so on. In humans, specific areas of the hippocampus and association cortex are involved in aspects of higher-order processing.

Sustained attention (concentration, vigilance, nondistractibility) is a second major set of attentional functions. Sustained attention can be directed at a specific task, object, or modality, or it can involve a more generalized increased level of vigilance—for example, while one is awaiting an anticipated stimulus.

As illustration of different types of attentional mechanisms, imagine a student trying to study for a final exam while sitting in the middle of a rowdy fraternity party. The student demonstrates directed (selective) attention by looking at her book and reading, attending to the visual, linguistic, and conceptual aspects of its content while ignoring the loud noises, flashing lights, and scents of the room around her. She demonstrates sustained attention and concentration by continuing to read even if she finds the subject slightly boring, and she exhibits nondistractibility by ignoring other students' pleas for her to join in the dancing. Finally, she demonstrates vigilance by being prepared to duck quickly out of harm's way when flying objects occasionally enter her peripheral vision.

It should be evident from this discussion that both selective and sustained attention may involve enhanced activity in stimulus-relevant regions of the brain ("signal") and/or decreased activity in stimulus-irrelevant brain regions ("noise"). The relative importance of signal enhancement versus noise suppression in attention is still under active investigation. Similarly, attention must be able to shift from one target to the next, which may involve mechanisms that both engage the relevant stimuli and disengage the irrelevant (or no longer relevant) stimulus. Other, harder questions still under active investigation include the mechanisms through which directed attention has a limited capacity in the spatial, temporal, modality-specific, and other domains, and the mechanisms through which attended targets from disparate brain regions are unified into a single coherent concept (the binding problem).

Anatomy of Attention

Networks involved in attention are distributed through many cortical and subcortical structures. Systems involved in attention include (1) widespread projection systems (discussed in Chapter 14); (2) frontal and parietal association cortex; (3) anterior cingulate cortex and limbic pathways; (4) tegument, pretectal area, and pulvinar; and (5) other structures, such as the cerebellum and basal ganglia. Interestingly, networks involved in generalized alertness and attention also participate in mechanisms of directed attention. Recall that attentional networks are asymmetrical and that the nondominant (usually right) hemisphere plays a more important role (see KCC 19.9). Let's review each of the anatomical systems involved in generalized and directed attention in more detail.

Widespread Projection Systems

A prerequisite for attention is an awake, alert state. Mechanisms of arousal were discussed in Chapter 14; they include widespread projection systems of the upper brainstem, thalamus, hypothalamus, and basal forebrain. In addition to aiding in generalized arousal, many of the same systems may contribute to directed and sustained attention. We will therefore briefly review these systems (see Table 14.2 and Figures 14.7–14.13) again here. Upper brainstem projection systems include cholinergic (pedunculopontine and laterodorsal tegmental nuclei) and noncholinergic (porrothoracic reticular formation, possibly glutamatergic) projections to thalamus, hypothalamus, and basal forebrain systems, which in turn have widespread cortical projections. In addition, noradrenergic (locus coeruleus and lateral tegmental area) and serotoninergic (dorsal and medial raphe) systems project widely to the cortex and other structures, while dopaminergic (substantia nigra pars reticulata, ventral tegmental area) systems project to striatum, limbic cortex, and prefrontal cortex.

Thalamic Systems involved in arousal include the intralaminar, midline, ventral, and possibly other thalamic nuclei that transfer inputs from the upper brainstem reticular formation and cholinergic nuclei to widespread areas of cerebral cortex. In addition, the thalamic reticular nucleus has been postulated to play a role in gating information transfer through the thalamus because it receives inputs from cortex, thalamus, and brainstem systems and sends inhibitory (GABAergic) projections to the thalamus (and possibly back to the thalamus as well).

Hypothalamic Systems important to arousal include the posterior lateral hypothalamic histaminergic neurons (tuberoinfundibular nucleus), which receive inputs from basal forebrain, anterior hypothalamus, and brainstem and project widely to cortex and hypothalamus.

Finally, basal forebrain systems involved in arousal include the nucleus basalis, diagonal band, and medial septal cholinergic and GABAergic neurons, which receive inputs from the brainstem and project to the entire cortex and thalamus.
FRONTAL AND PARITIAL ASSOCIATION CORTEX. The frontal and parietal association cortices (see Figure 19.1) communicate with each other via strong reciprocal connections and play an important role in attentional mechanisms. The lateral parietal cortex and adjacent temporal and occipital association cortices lie at the nexus of auditory, visual, and somatosensory unimodal association cortex (see Figure 19.1). This region is thus ideally situated for heteromodal integration in attention. As we discussed earlier in this chapter, the parietal association cortex plays an important role in heteromodal spatial representations, encoding the location of attended objects in space. Lesions of the parietal cortex, especially in the nondominant hemisphere, are the best-known cause of deficits in contralateral directed attention, or hemineglect (see KCC 19.9).

The frontal heteromodal association cortex (prefrontal cortex; see Figure 19.1), also discussed earlier, plays important roles in both directed and sustained attentional mechanisms. In particular, the region of the frontal eye fields is important in directed attention to the contralateral side and in the initiation of eye movements toward attended targets. In addition, the prefrontal cortex may play an important role in motor-intentional aspects of attention toward the contralateral side. The ability to initiate spontaneous movements of the contralateral limbs or toward the contralateral hemispace may depend on prefrontal cortex and on ascending dopaminergic modulation of the prefrontal cortex and striatum. Finally, on the basis of both function imaging studies and the effects of lesions, the prefrontal cortex is crucial to sustaining attention and reducing distractibility.

ANTERIOR CINGULATE CORTEX AND LIMBIC PATHWAYS. The anterior cingulate cortex (see Figure 19.1B) is important in motivational aspects of attention. It forms a network together with the amygdala, medial orbitofrontal cortex, thalamic medialdorsal nucleus, and other limbic structures (see Chapter 18) that may play an important role in motivating directed and sustained attention toward a relevant or interesting stimulus. The importance of motivational factors in attention is illustrated by the example in which a patient performs poorly when asked to remove objects such as pieces of paper from a table but then shows a dramatic improvement when the objects are replaced with dollar bills.

TECTUM, PRETECTAL AREA, AND PULVINAR. The superior colliculi, precollicular area, and pulvinar participate together with the parieto-temporo-occipital cortex and frontal eye fields in directing visual attention toward relevant visual stimuli for saccadic eye movements (see Figures 11.6, 13.14). Directed attention for other modalities, such as audition, may also be processed by these pathways.

OTHER STRUCTURES. There is accumulating evidence that certain parts of the basal ganglia and cerebellum also participate in mechanisms of directed attention.

Awareness of Self and Environment. One of the great remaining mysteries of modern science is the mechanism for our subjective and personal experience of awareness. As we have discussed in this chapter, consciousness certainly includes a "substrate" or content, represented by sensorimotor systems, memory systems, and limbic systems, as well as mechanisms for controlling the level of consciousness, including the level of alertness, attention, and awareness. So far, we have discussed alertness and attention, but what are the mechanisms of awareness? Philosophers may debate whether a biological explanation for the awareness aspects of consciousness, sometimes referred to as qualia, is even possible. As this debate continues, and although the final answers are not in yet, exciting new developments in neuroscience have begun to shed light on at least some systems that may participate in generating our subjective personal experience of awareness.

Like other functions of the nervous system, awareness most likely is mediated by a network involving both specialized regions of local processing and widespread regions of distributed processing. We saw in Chapter 18 that memory functions are segregated anatomically into declarative memory, which involves conscious awareness and is processed by medial temporal and diencephalic regions, and nondeclarative memory, which does not involve conscious awareness and is processed by other brain regions (see KCC 18.1). Further investigation of the neural circuits underlying declarative memory may ultimately help us understand what is "special" about conscious versus nonconscious memories.

We have discussed the hemineglect syndrome, in which inattention causes circumscribed loss of awareness of both the self and the environment (see KCC 19.9). This syndrome suggests that the same mechanisms that are involved in attention play an important role in awareness as well, and some investigators even debate whether a distinction between attention and awareness is valid. One aspect of awareness that is difficult to explain in terms of current theories of attention is the binding of sensory, motor, emotional, and mnemonic information from disparate brain regions into what we perceive as a single unified experience. Where or how is this synthesis of multiple forms of information perceived? Some investigators have contended that binding is a distributed process occurring over widespread networks. Theories for binding, on a cellular level have included widespread horizontal connections between certain cortical layers, and synchronization of coherent gamma-frequency (about 40 hertz) oscillations in neuronal activity occurring between regions involved in binding. Others have proposed that specific regions of high-order association cortex, such as the frontal or parietal lobes, may be critical for binding. From a clinical perspective, Balint's syndrome (see KCC 19.12) provides an interesting example of how focal lesions of the parieto-occipital cortex can cause a profound deficit in the ability to bind various individual parts of a visual scene into a single integrated whole.

The role of the prefrontal cortex in working memory, or the ability to hold a certain amount of information in an active short-term store, is also likely to play an important role in any process that mediates awareness, as are the senses of chronological sequence and self-monitoring that are mediated by the frontal lobes. Similarly, studies of mental imagery have begun to demonstrate the involvement of certain regions of primary and association cortex in generating internal representations of both sensory and motor phenomena—important ingredients for any internal representation or engram of awareness.

Finally, although significant advances are being made in understanding limbic networks, the question of how neural activity gives rise to emotions remains as difficult for us to answer as the question of how neural activity gives rise to conscious thought. In summary, conscious awareness may yet be explained on the basis of an understanding of both distributed and specialized local network processing in the brain. However, this important and interesting quest for understanding is still very much under way and will undoubtedly continue to provide a rich vein for researchers.
Because attention depends on so many different systems, as described in the preceding sections, it is not surprising that deficits in attention can be produced by focal lesions in many locations, as well as by diffuse disorders affecting larger regions of the nervous system. In this section, we will discuss the assessment and diagnosis of patients with general disorders of sustained attention (see KCC 19.9 for the special case of unilateral deficits in directed attention). In the next two sections, we will discuss other disorders that tend to affect the nervous system in a widespread manner and which may also cause prominent deficits in global attention (see KCC 19.15, 19.16).

Like most other disorders of the nervous system, attentional disorders can range in severity from mild to severe. Mild inattention may cause patients to have difficulty regaining new information, and they may occasionally fail to complete tasks. Severe inattention, on the other hand, may cause patients to be completely unresponsive to outside stimuli. Of note, patients may be fully awake and yet profoundly inattentive.

### Testing Sustained Attention

Because attention is so important for performance on the mental status examination and can affect nearly all other tests, it is essential to evaluate and document the patient's level of attention toward the beginning of the examination. Clues that an attentional disorder is present can often be obtained from the history, and by observation of the patient's behavior during all parts of the examination. A very useful test and well-standardized measure of attention (and working memory) is digit span. In this test, a random series of numbers is recited to the patient, and the patient is asked to repeat the numbers back immediately to the examiner. Normal digit span is five to seven or more digits. Next, patients can again be given a series of numbers but then asked to repeat them backward. This task is slightly more difficult, and backward digit span is normally four or more digits, or two less than the patient's forward digit span.

A similar test that is easier to administer is to ask the patient to recite the months of the year forward and then backward (see neuroexam.com Video 4). This test is not standardized, with an increased risk for having the disorder. The examiner gets a sense of what is normal and what is abnormal. Normally, reciting the months backward should take less than twice as long as reciting them forward, and this task should be performed without errors. Other similar but perhaps useful tests include asking the patient to spell "world" backward, or to count backward by threes from 30, or by sevens from 100.

### Motor Impersistence

Motor impersistence is another useful bedside indication of impaired attention, which we discussed earlier in the evaluation of frontal lobe disorders (see KCC 19.11; Table 19.10). The patient is asked to stick out their tongue, or hold up their arms for 20 seconds, without subsequent prompting. If they fail to do so, they have motor impersistence, a form of inattention. Vigilance can also be tested at the bedside with the "A" random letter text, in which the examiner recites a random sequence of letters at a rate of about one per second, and the patient is instructed to tap the desk each time they hear the letter A.

Formal neuropsychological tests of attention exist as well, and can be useful for obtaining a more quantitative assessment. As already noted, patients with impaired attention may perform poorly on many other parts of the mental status exam. This type of overall performance can be assessed with the perseverative errors test, which gives the patient a task with no significant focal findings on examination, other than impaired cognitive abilities. The impairments of mental status are often relatively non-localizing as well, consisting of prominent inattention, confusion, and memory impairment.

### Differential Diagnosis of Disorders of Sustained Attention

Some common causes of impaired general attention are listed in Table 19.13. As already noted, impaired attention can be mild or quite severe. Encephalopathy is a nonspecific term that means simply diffuse brain dysfunction, which we will discuss further in KCC 19.15 and 19.16. Various forms of diffuse encephalopathy are the most common causes of impaired attention. Encephalopathy, especially when acute in onset, can also be associated with an impaired level of alertness ranging from mild lethargy to coma. Focal lesions can also cause impaired attention. This is particularly true of lesions in the frontal lobes, parietal lobes, or brainstem activating systems, although focal lesions in numerous other brain regions can also result in impaired attention.

### Attention-deficit hyperactivity disorder (ADHD)

ADHD is a fairly common condition affecting 1 to 5% of elementary school children. Onset is typically by age 3 years, although problems do not usually become severe until school is started. In some children the disorder of attention is predominant, while in others problems with impulsive and hyperkinetic behaviors are predominant. Most children with ADHD have normal neuroimaging studies and essentially normal neurologic evaluations, except for markedly impaired attention, impulsivity, and perhaps some "soft" findings on exam. The impaired attention in ADHD is somewhat different from the other disorders listed in Table 19.13. ADHD is more likely, for example, to cause problems with high-level executive functions, organizational skills, and time management abilities rather than simpler impairments of digit span. ADHD is occasionally seen in patients with other neurologic conditions, but in most cases the cause of ADHD is unknown. ADHD is three to five times more common in boys than girls, and siblings are at increased risk for having the disorder. The condition is treated with CNS stimulants such as methylphenidate (Ritalin), combined with individual and family psychotherapy. It is interesting that stimulants that enhance dopaminergic and noradrenergic neurotransmission are beneficial in this disorder. Long-term outcome is variable. Many individuals do well even reaching adolescence, but 15 to 20% of patients continue to have ADHD into adulthood.

### Psychiatric Disorders

Psychiatric disorders (see KCC 18.3) are a very important cause of impaired attention. Patients with depression, anxiety, mania, schizophrenia, or other milder conditions are often severely inattentive on examination. The remainder of the mental status examination in these patients should therefore be carefully interpreted in this context to avoid misdiagnosis of the patient as having a memory disorder or other focal dysfunction. Formal neuropsychological testing can often be helpful in distinguishing "pseudodementia" seen in psychiatric conditions from true dementia (see KCC 19.16).
TABLE 19.14 Causes of Acute or Subacute Mental Status Changes

<table>
<thead>
<tr>
<th>Toxic or metabolic encephalopathies</th>
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<tbody>
<tr>
<td>Drug or alcohol toxicity</td>
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<tr>
<td>Withdrawal from alcohol or other sedatives</td>
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<tr>
<td>Electrolyte abnormality (especially elevated sodium, calcium, or magnesium)</td>
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<tr>
<td>Hypopyonemia</td>
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<td>Diffuse amnesia</td>
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<tr>
<td>Hypothyroidism, hyperthyroidism</td>
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<tr>
<td>Hypoparathyroidism</td>
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<tr>
<td>Thiamine deficiency (Wernicke-Korsakoff encephalopathy)</td>
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<td>Hepatic failure</td>
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<tr>
<td>Pulmonary failure</td>
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<tr>
<td>Sepsis</td>
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<tr>
<td>Intraocular errors of metabolism</td>
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<tr>
<td>Pancreaticohepatic syndrome</td>
</tr>
<tr>
<td>Hereditary endogenous benzodiazepine production</td>
</tr>
</tbody>
</table>

Head trauma

Diffuse or focal cerebral ischemia or infarct

Intercranial hemorrhage

Migraine

Seizures or postictal state

Hydrocephalus

Elevated intracranial pressure

Diffuse cerebral edema

Menigitis, encephalitis, brain abscess

Vasculitis, diffuse subcortical demyelination (e.g., multiple sclerosis)

Intracranial neoplasm

Paraneoplastic syndrome

Mild insult (e.g., urinary infection or change in environment) in setting of underlying impaired mental status

Psychiatric disorders (e.g., depression, mania, schizophrenia, etc.)

Sleep deprivation

Visual deprivation or more generalized sensory deprivation

Hypotension

Hypertensive crisis

States are inattentive, the level of alertness may be normal in mild cases and can range from agitation to near coma in more severe cases. Dementia is a common form of acute confusional state in which agitation and hallucinations (auditory, visual, and tactile) are often prominent. The most common causes of acute confusional states are toxic or metabolic disorders, followed by infection, head trauma, and seizures (see Table 19.1). Patients should therefore be evaluated promptly by assessment of vital signs, respiratory status (including arterial blood gas), and other appropriate blood tests, including blood glucose, electrolytes, blood urea nitrogen, creatinine, liver function tests, ammonia level, complete blood count, thyroid function tests, and toxicology screen. The patient's medications should be reviewed for those known central nervous system side effects (e.g., anticholinergic, sedative-hypnotic, narcotic). When the diagnosis remains uncertain, the patient should immediately undergo neuroimaging and a lumbar puncture. If these are negative, an EEG should be performed promptly to rule out subtle ongoing seizure activity. An EEG is also helpful because in most forms of encephalopathy listed in Table 19.1, diffuse slowing of the EEG should be present, with the exception of psychiatric disorders, sleep deprivation, and sensory deprivation. In elderly patients or patients with previous neurologic disorders, acute confusional states can be provoked by seemingly minor causes, such as a urinary tract infection, or even by a change from home to the hospital setting. Patients in intensive care units prone to acute confusional states from the combination of sedative use, immobilization, and sleep and sensory deprivation, although they should be evaluated for treatable causes as described above.

Chronic mental status changes, as we will discuss in the next section, can also have numerous causes and are more typically gradually progressive, as in Alzheimer's disease, or static, as in acrodynia damage (see KCC 19.16). Dementia is a broad term, meaning literally "decrease in mental function," however, it is usually applied more specifically to gradually progressive disorders such as Alzheimer's disease. Although both acute and chronic mental status changes can be treatable, acute mental status changes usually carry a better prognosis. Therefore, an important goal is often to distinguish delirium versus dementia.

To summarize, acute confusional states such as delirium typically develop over the course of days to months, have prominent attentional disturbances, tend to wax and wane over the course of hours, often have marked slowing on the EEG, and are most often caused by toxic or metabolic disorders, head trauma, infection, and seizures. Chronic mental status changes, typified by Alzheimer's disease and other gradually progressive degenerative diseases (see KCC 19.16), usually develop over months to years, do not tend to fluctuate as rapidly (although exacerbations of function can occur in certain settings), and early in their course tend to have less prominent disturbances in attention and a relatively normal EEG. Note that there are many exceptions to these general principles. For example, patients with acute mental status changes do not always show wanning and waning function, and many patients with chronic mental status changes (Huntington's disease, for example) show prominent deficits in attention in the early course of the disorder.

The vast majority of cases of encephalopathy and global confusional states are caused by conditions that affect the brain in a diffuse manner bilaterally. However, unilateral lesions, particularly in the right parietal, right frontal, or right temporal-occipital regions, can occasionally produce global states of impaired alertness and attention that mimic diffuse encephalopathy.
As we approach the end of this book, it is appropriate to discuss a group of disorders that may await many of us in the future, so that we may be motivated to pursue greater understanding of these disorders and ultimately to discover more effective treatments for them. Dementia is defined as a decline in memory and other cognitive abilities from a previously higher level of function to impaired functional status. Although this definition includes patients in which the decline is sudden or nonprogressive (e.g., the result of a single head injury or other insult), the term “dementia” is medically used when there is gradually progressive deterioration over the course of months to years.

Patients with dementia typically show a decline in memory and other general cognitive abilities, although patients with focal decline, such as in primary progressive aphasia, are often included in the definition of dementia as well. Dementia is not restricted to the elderly; however, disorders causing dementia are much more common in the later years of life. Dementia should be distinguished from the apparently “normal” mild deterioration of memory function that occurs with age and that is referred to as benign forgetfulness of senescence. Patients with dementia exhibit deterioration of cognitive skills beyond statistical norms for age-matched controls.

Aside from dementia, several other terms for chronic mental status changes are sometimes used. Static encephalopathy is a term that refers to persistent or nonprogressive brain damage, as a result of head injury, anoxia, or congenital abnormalities of brain development, for example. Mental retardation is defined as impaired general intellectual and social adaptive function originating during development that is approximately two or more standard deviations below average.

Cortical dementias, with prominent disturbances in language, praxis, visual-spatial functions, and other typically cortical functions, are sometimes distinguished from subcortical dementias (such as Huntington’s disease or progressive supranuclear palsy), in which these features are not present, although the usefulness of this distinction has been questioned. Dementia can also be subdivided into primary dementia, typically associated with neurodegenerative conditions for which definitive treatments are usually unavailable, and secondary dementia, caused by other conditions that may, in some cases, be reversible. In the sections that follow we will discuss the different causes of dementia and other chronic mental status changes, and the general approach to evaluating patients with these disorders, before focusing on Alzheimer’s disease in greater detail.

Causes and Evaluation of Dementia

Fifty years ago, senile dementia was thought to be caused mainly by cerebrovascular disease, known colloquially as “hardening of the arteries,” and Alzheimer’s disease was considered relatively rare. With increased knowledge and understanding of Alzheimer’s disease, it is now recognized that over 50% of the cases of senile dementia are caused by Alzheimer’s disease, making it the most common cause by far. We will discuss Alzheimer’s disease in more detail in the sections that follow; here we focus on the other causes of chronic mental status changes (Table 19.15). Many of the causes of chronic mental status changes listed in Table 19.15 are the same as for acute mental status changes (see Table 19.14), but are the result of long-standing treatable disorders such as chronic hypothyroidism or chronic hydrocephalus, or of the outcome of permanent brain injury such as previous head trauma or encephalitis. Note that because Alzheimer’s disease is relatively common, many elderly patients will have Alzheimer’s disease coexisting with one of the other disorders listed in Table 19.15.

Because there are so many possible causes of dementia, evaluation of patients with dementia should focus on and target treatable disorders, with the recognition that a treatable cause is found in only about 10% of cases. Patients should be evaluated with a thorough history, including an assessment of activities of daily living, family history, and description of any previous premonitory symptoms. As in the evaluation of patients with acute mental status changes (see KCC 19.15), it is crucial to review the patient’s medical history for any that may cause central nervous system side effects. A careful general and neurologic exam should then be performed.

Normal neuropsychological testing can be useful in distinguishing dementia from “pseudo-dementia” caused by depression or other treatable psychiatric conditions. Testing batteries that can be administered easily at the bedside and that are especially useful in following patients during serial evaluations over time include the Blessed Dementia Scale (Table 19.16), the Folstein Mini-Mental State Examination, and the Activities of Daily Living Rating Scale. Blood tests should include routine chemistries, as well as thyroid function tests, B12 and folate levels, serum cortisol test, and other blood tests (see Table 19.15), depending on the patient’s age and the clinical situation. Neuroimaging should ideally include an MRI scan of the brain. If the patient is unusually young (e.g., dementia before age 50), has headaches, or any other atypical features suggesting chronic meningitis, a lumbar puncture should be performed. In selected cases, an EEG can be helpful (for example, to detect periodic sharp waves in Creutzfeldt-Jakob disease, or triphasic waves in hepatic encephalopathy), and occasionally a brain biopsy is indicated, when the results may guide treatment (e.g., suspected CNS vasculitis).

The distinction between acute and chronic mental status changes is not obvious, as discussed in KCC 19.15. In addition, patients may have a combination of acute mental status changes superimposed on an underlying chronic mental status disorder, such as the “sundowning” seen in demented patients, especially when in unfamiliar surroundings, or the delirium caused by a minor infection or the outcome of permanent brain injury such as previous head trauma or encephalitis. Note that because Alzheimer’s disease is relatively common, many elderly patients will have Alzheimer’s disease coexisting with one of the other disorders listed in Table 19.15.

### TABLE 19.15 Causes of Chronic Mental Status Changes

<table>
<thead>
<tr>
<th>Primary neurodegenerative disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer’s disease</td>
<td></td>
</tr>
<tr>
<td>Frontotemporal dementia (including Pick’s disease)</td>
<td></td>
</tr>
<tr>
<td>Dementia with Lewy bodies</td>
<td></td>
</tr>
<tr>
<td>Parkinson’s disease with dementia</td>
<td></td>
</tr>
<tr>
<td>Huntington’s disease</td>
<td></td>
</tr>
<tr>
<td>Progressive supranuclear palsy</td>
<td></td>
</tr>
<tr>
<td>Corticobasal atrophy</td>
<td></td>
</tr>
<tr>
<td>Cortical basal ganglionic degeneration</td>
<td></td>
</tr>
<tr>
<td>Primary progressive aphasia</td>
<td></td>
</tr>
<tr>
<td>Dementia with prominent impairment of daily living and activities</td>
<td></td>
</tr>
<tr>
<td>Other disorders</td>
<td></td>
</tr>
<tr>
<td>Vascular dementia</td>
<td></td>
</tr>
<tr>
<td>Multi-infarct dementia</td>
<td></td>
</tr>
<tr>
<td>Biowranger’s disease</td>
<td></td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td></td>
</tr>
<tr>
<td>Cerebral amyloid angiopathy</td>
<td></td>
</tr>
<tr>
<td>Psychiatric pseudodementia (especially depression, schizophrenia, and conversion disorder)</td>
<td></td>
</tr>
<tr>
<td>Thiamine deficiency (Wernicke-Korsakoff encephalopathy) and other alcohol-related causes</td>
<td></td>
</tr>
<tr>
<td>Intracranial neoplasms, and parenchymal syndromes</td>
<td></td>
</tr>
<tr>
<td>Normal-pressure hydrocephalus and noncommunicating hydrocephalus</td>
<td></td>
</tr>
<tr>
<td>Head trauma, including chronic subdural hematomata and dementia pseudodementia</td>
<td></td>
</tr>
<tr>
<td>AIDS dementia complex and other infections including meningitis, encephalitis, neurosyphilis, Lyme disease, Creutzfeldt-Jakob disease, other prion diseases, and CNS Whipple’s disease</td>
<td></td>
</tr>
<tr>
<td>Diffuse encephalitis</td>
<td></td>
</tr>
<tr>
<td>Prolonged status epilepticus</td>
<td></td>
</tr>
<tr>
<td>Chronically elevated intracranial pressure</td>
<td></td>
</tr>
<tr>
<td>Multiple sclerosis and other demyelinating disorders</td>
<td></td>
</tr>
<tr>
<td>Vasculitis</td>
<td></td>
</tr>
<tr>
<td>Chronic electrolyte abnormalities or hepatic, renal, or polynuclear failure</td>
<td></td>
</tr>
<tr>
<td>Heavy-metal toxicity (lead, arsenic, gold, bismuth, manganese, mercury)</td>
<td></td>
</tr>
<tr>
<td>Hypothyroidism, hyperthyroidism</td>
<td></td>
</tr>
<tr>
<td>Vitamin B12 deficiency, pellagra</td>
<td></td>
</tr>
<tr>
<td>Inborn errors of metabolism</td>
<td></td>
</tr>
<tr>
<td>Wilson’s disease</td>
<td></td>
</tr>
<tr>
<td>Congenital or developmental disorders</td>
<td></td>
</tr>
</tbody>
</table>
TABLE 19.16 Blessed Dementia Scale* 

<table>
<thead>
<tr>
<th>A. CHANGES IN PERFORMANCE OF EVERYDAY ACTIVITIES</th>
<th>E. INFORMATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inability to perform household tasks</td>
<td>Name</td>
</tr>
<tr>
<td>Inability to cope with small sums of money</td>
<td>Age</td>
</tr>
<tr>
<td>Inability to remember short lists of items</td>
<td>Time (hour)</td>
</tr>
<tr>
<td>Inability to find way about inside</td>
<td>Time of day</td>
</tr>
<tr>
<td>Inability to find way about familiar streets</td>
<td>Day of week</td>
</tr>
<tr>
<td>Inability to interpret surroundings (e.g., to recognize whether in hospital or at home)</td>
<td>Date</td>
</tr>
<tr>
<td>Inability to recall recent events (e.g., recent outings, relatives’ or friends’ visits, etc.)</td>
<td>Month</td>
</tr>
<tr>
<td>Tendency to dwell in the past</td>
<td>Season</td>
</tr>
<tr>
<td></td>
<td>Year</td>
</tr>
<tr>
<td></td>
<td>Place: Name</td>
</tr>
<tr>
<td></td>
<td>Street:</td>
</tr>
<tr>
<td></td>
<td>Town:</td>
</tr>
<tr>
<td></td>
<td>Type of place (home, hospital, etc.)</td>
</tr>
<tr>
<td></td>
<td>Recognition of persons (any 2 available.)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B. CHANGES IN HABIT</th>
<th>F. PERSONAL MEMORY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eating:</td>
<td>Date of birth</td>
</tr>
<tr>
<td>Mesally with spoon</td>
<td>Place of birth</td>
</tr>
<tr>
<td>Simple solids (no utensils)</td>
<td>School attended</td>
</tr>
<tr>
<td>Has to be fed</td>
<td>Occupation</td>
</tr>
<tr>
<td></td>
<td>Name of sibling or spouse</td>
</tr>
<tr>
<td></td>
<td>Name of any town where patient worked</td>
</tr>
<tr>
<td></td>
<td>Name of employer</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>C. CHANGES IN PERSONALITY</th>
<th>G. NONPERSONAL MEMORY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased rigidity</td>
<td>Date of WWI (1914-1918)</td>
</tr>
<tr>
<td>Increased egocentricity</td>
<td>Date of WWI (1939-1945)</td>
</tr>
<tr>
<td>Impairment of speech</td>
<td>President</td>
</tr>
<tr>
<td>Coarsening</td>
<td>Vice-President</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>D. CHANGES IN INTERESTS AND DRIVES</th>
<th>H. 5-MINUTE RECALL</th>
<th>I. CONCENTRATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hobbliness aloquated</td>
<td>(Mr.) John Brown</td>
<td>Months backwards</td>
</tr>
<tr>
<td>Diminished initiative or growing apathy</td>
<td>42 West (Street)</td>
<td></td>
</tr>
<tr>
<td>Purposeless hyperactivity</td>
<td>Cambridge, (MA)</td>
<td>1-20</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20-1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>LEFT SCORE</th>
<th>RIGHT SCORE</th>
<th>TOTAL SCORE</th>
</tr>
</thead>
</table>


Aside from Alzheimer’s disease, numerous other primary neurodegenerative disorders can lead to dementia, some of which are listed in Table 19.15. Many (such as dementia with Lewy bodies, Parkinson’s disease, and others) are associated with movement disorders and are described in Chapters 15 and 16 (see KCC 15.3, 16.1-16.5). Briefly, recall that dementia with Lewy bodies typically begins with fluctuating dementia, parkinsonism, and visual hallucinations. Pathologically, there are intraneuronal inclusions called Lewy bodies in the substantia nigra (as in Parkinson’s disease) as well as in more widespread cortical and subcortical structures, often coexisting with the pathologic changes of Alzheimer’s disease. After Alzheimer’s disease and dementia with Lewy bodies the next most common group of primary degenerative dementias consists of the frontotemporal dementias. These patients develop lobar atrophy, usually involving the anterior frontal and temporal lobes out of proportion to other structures. The atrophy may be asymmetrical in some patients. Onset is often accompanied by behavioral changes suggestive of frontal lobe dysfunction, such as personality changes, abulia, and disinhibition (see KCC 19.11).

One relatively common type of frontotemporal dementia is Pick’s disease, in which pathological changes include neuronal loss, especially in cortical layers 1 to 3, and argyrophilic inclusion bodies in the cytoplasm of neurons called Pick’s bodies, that stain with anti-ubiquitin and anti-tau antibodies. Other frontotemporal dementias involve frontotemporal atrophy without these characteristic pathologic changes, referred to as dementia lacking specific histopathology (DLBD). In some forms, motor neuron disease resembling ALS (amyotrophic lateral sclerosis; see KCC 6.7) occurs as well. One interesting form of frontotemporal dementia having autosomal dominant inheritance has been localized to chromosome 17.

In cortical-basal ganglionic degeneration (corticobasal degeneration), there is asymmetrical onset of a movement disorder such as dystonia, accompanied by cortical features most often consisting of a marked apraxia. Primary progressive aphasia is likely a family of degenerative conditions in which apraxia may be prominent at the outset. Pathology in these patients shows changes similar to Alzheimer’s disease, Pick’s disease, DLBD, or Creutzfeldt-Jakob disease, often more severe in the language areas of the dominant hemisphere.

Although Alzheimer’s disease is now recognized as being the most common cause, vascular dementia remains the second most common single cause, representing 10 to 15% of all cases of dementia. In multi-infarct dementia, several cortical or subcortical infarcts cause a stepwise decline in cognitive function. Diffuse subcortical infarcts, often associated with chronic hypertension, cause a form of subcortical dementia termedBinswanger’s disease. With the advent of CT and MRI scans, however, nonspecific diffuse white matter changes termed leukoaraiosis are often seen in older patients but are not always associated with dementia. When diffuse and severe white matter degeneration of any cause are present, a clinical picture emerges consisting of dementia, pseudobulbar affect, and frontal lobe-like features such as shuffling, gait, and gogalhen (see KCC 19.11). Cerebral amyloid angiopathy, often familial, can cause dementia through multifocal recurrent hemorrhages, as well as through white matter ischemic diseases. Patients who recover from severe intracranial hemorrhage of any cause may remain with astatic encephalopathy.

Psychiatric pseudodementia resulting from depression or conversion disorder can sometimes be mistaken for dementia. The diagnosis of depression, especially in the elderly, is often overlooked. It is critical to recognize the presence of so-called masked depression in these cases because
depression is usually much more treatable than dementia, can have at least as significant an impact on function, and may be life-threatening because of suicide risk. In cases of uncertainty, neuropsychology testing can be helpful in making the distinction. A clinical rule of thumb with many exceptions is that depressed patients often complain about having memory problems, while demented patients usually do not. Schizophrenia can also occasionally mimic dementia, but in addition to its typically younger age of onset, in schizophrenia delusions and hallucinations are more prominent than in the milder forms of dementia. In schizophrenia, attention is often profoundly impaired, making examination of cognition difficult. When patients are able to attend, however, they usually are oriented and have intact recent memory, unlike patients with dementia.

Alcoholism is another major cause of dementia. Dementia in such patients is likely multifactorial, with possible causes including thiamine deficiency, other nutritional deficiencies, multiple head injuries, and seizures. Whether alcohol itself causes permanent cortical neuronal injury remains controversial, although it is likely to cause cerebellar degeneration.

Intracranial neoplasms, which were discussed in KCC 5.8 can cause cognitive decline through local cerebral injury or through elevated intracranial pressure. It is important to perform a neuroimaging study as part of the evaluation of dementia because sometimes treatable tumors such as meningiomas can present with no significant neurologic findings other than slowly progressive cognitive decline over months to years. Similarly, imaging studies can elucidate other treatable causes, such as normal-pressure hydrocephalus or chronic subdural hematoma (see KCC 5.6, 5.7). In the elderly, chronic subdural hematoma can occur with little or no significant history of head injury.

The relationship of head injury to dementia is complicated because some epidemiologic studies suggest an increased risk of Alzheimer’s disease in patients who have had head injuries with loss of consciousness. Dementia pugilistica is another form of head trauma–related dementia, seen mainly in boxers who suffer recurrent head injuries. The AIDS dementia complex is common in advanced AIDS, but it can also occur early in the course of the illness. HIV encephalopathy, and other CNS infections (see KCC 5.9). Prion diseases, such as Creutzfeldt-Jakob disease, are unfortunately untreatable at present, and they lead to a relatively rapid cognitive decline (see KCC 5.9).

We will now briefly touch on a few of the other secondary causes of chronic mental status changes listed in Table 19.15, particularly those that are treatable. Electrolyte abnormalities, especially of calcium, magnesium, or sodium, or hepatic, renal, or pulmonary failure can cause reversible cognitive impairment. Either hypothyroidism or hyperthyroidism can impair cognition. Particularly in the elderly, cognitive impairments may occur without obvious manifestations of thyroid dysfunction. Vitamin B₁₂ deficiency causes megaloblastic anemia, along with subacute combined degeneration of the spinal cord (posterior columns more than corticospinal tracts). Subacute combined degeneration can also involve the central white matter, resulting in dementia. The degree of reversibility depends on how quickly vitamin B₁₂ deficiency is treated. In psychosis, nicotinic deficiency can cause dementia, delirium, and diabetes (membranous nephrosis three Ds).

Treatable infectious disorders (see KCC 5.9) such as chronic meningitis, particularly caused by Cryptococcus, can occasionally present as dementia (most often seen in elderly patients or patients with HIV). Neurosyphilis was formerly common and has returned somewhat in recent decades, possibly in association with the rise of HIV. Lyme disease is a spirochetal illness that sometimes causes impaired cognition (see KCC 5.9).

Wilson’s disease is an important treatable cause of dementia, often presenting in adolescence with hepatic dysfunction, dystarthis, movement disorders, or psychiatric manifestations (see KCC 16.1). Heavy-metal toxicity can result in cognitive impairment, often with other neurologic signs, such as peripheral neuropathy. Dementia is now referred to as Wilson’s disease because aluminum was once removed from dextran solutions.

Pathophysiology of Alzheimer’s Disease

In Alzheimer’s disease, the distribution of pathologic changes parallels the typical clinical features of this disorder (Figure 19.14). The major pathologic changes are cerebral atrophy, neuronal loss, amyloid plaques, and neurofibrillary tangles. These changes typically occur initially and are most severe in the following regions (see Figure 19.14), in decreasing order: (1) medial temporal lobes, including the amygdala, hippocampal formation (especially CA1), and entorhinal cortex; (2) basal temporal cortex extending over the lateral posterior temporal cortex, parieto-occipital cortex, and posterior cingulate gyrus; (3) frontal lobe. Of note, the primary motor, somatosensory, visual, and auditory cortices are relatively spared (see Figure 19.14). Cell loss and neurofibrillary tangles are also prominent in the nucleus basalis, septal nuclei, and nucleus of the diagonal band, where cholinergic projections arise (see Figure 19.5B), and to a lesser extent in the locus ceruleus (norepinephrine), and raphe nuclei (serotonin).

The cause of neuronal loss and the other pathologic changes of Alzheimer’s disease is still under investigation, although much progress has been made in recent years. Senile plaques are composed of insoluble protein core containing β-amyloid, along with apolipoprotein E, surrounded by a rim of abnormal axons and dendrites (see dystrophic neurites). Neurofibrillary tangles are intracellular accumulations of hyperphosphorylated microtubule-associated proteins or paired helical filaments known as tau proteins. Amyloid is a general term for insoluble protein deposits that can occur in various organ systems in different forms of amyloidosis. β-Amyloid is a specific insoluble protein associated with Alzheimer’s disease, derived from proteolytic cleavage of a transmembrane protein of unknown function called amyloid precursor protein (APP). Cleavage of APP can occur at several
eral different sites, but clearance at an intramembranous location by a protein called -secretase is thought to promote the formation of insoluble forms of -amyloid, increasing plaque formation.

Investigations of the genetic basis of Alzheimer’s disease have also begun to shed some light on pathogenesis. Most cases of Alzheimer’s disease are sporadic and occur after the age of 60 years. However, two genetic loci have been found so far that affect the risk of developing Alzheimer’s disease late in life. The first, located on chromosome 19, encodes apolipoprotein E (apo E) and has several different alleles. The e2 allele reduces the risk of developing Alzheimer’s disease, while the e4 allele increases the risk of developing Alzheimer’s disease. Because apo E is a component of the amyloid plaques, these different forms of apo E have been postulated to play a role in modulating plaque formation and clearance. The second locus that may affect susceptibility to late-onset Alzheimer’s is located on chromosome 12 and encodes D1-macroglubulin. Two alleles have been found that increase susceptibility, and this protein has also been postulated to play a role in amyloid deposition.

In addition, Alzheimer’s disease can rarely be inherited as an autosomal dominant disorder in some families with early onset, as early as the third or fourth decade of life. In these families, mutations have been found in three different locations that can cause early-onset disease: (1) the APP gene located on chromosome 21, (2) the presenilin 1 gene on chromosome 14, and (3) the presenilin 2 gene on chromosome 1. These findings are very interesting because APP is the precursor for -amyloid, while the presenilins appear to be involved in APP cleavage. Additional genetic evidence suggests the importance of abnormal APP processing in the pathogenesis of Alzheimer’s disease comes from Down’s syndrome. In Down’s syndrome, there is an extra copy of chromosome 21, which contains the APP gene. Patients with Down’s syndrome develop early pathologic and clinical features of Alzheimer’s disease after the age of 30 years.

Clinical Features of Alzheimer’s Disease

Alzheimer’s disease is a common disorder affecting a large proportion of the elderly population. The prevalence of Alzheimer’s disease increases rapidly with age, from 1% below the age of 65 to 40% over the age of 85 years. Aside from age, the strongest risk factor is positive family history. Another possible risk factor is a history of head trauma causing loss of consciousness. Estrogen and nonsteroidal anti-inflammatory drug use may be protective.

The clinical course of Alzheimer’s disease is variable; however, a description of the typical evolution is instructive and parallels the anatomical distribution of pathologic changes (see Figure 19.14). Obtaining the history from patients with Alzheimer’s disease may be difficult because patients often, but not always, have anosognosia and are unaware of their deficits. Family members may be helpful, although some will also deny deficits in loved ones, so the best data comes from either previous mental tests or assessments (when available) or objective descriptions of functional status at specific times, such as ability to balance a checkbook, pay the bills, shop unaccompanied, and so on.

The earliest clinical feature, often appreciated only in retrospect, is typically subtle loss of interest, or memory loss, particularly for recent memories, with a relative sparing of re-

mote memories. Patients may have difficulty remembering recent events, where they left their keys, or what they were planning on buying in a store. Although remote memories are less severely impaired, there is often some memory loss for less recent events as well. These early changes in memory function parallel the prominent pathologic involvement of the medial temporal lobe structures in Alzheimer’s disease (see Figure 19.14; see also KCC 18.3).

Next, patients often develop word-finding difficulty, or an anomic aphasia (see KCC 19.6), along with other features of posterior temporoparieto-occipital dysfunction, including apraxia and visual-spatial deficits (see KCC 19.7, 19.10). At some point in the course of the illness, patients develop various behavioral abnormalities that become very difficult for caregivers. Typically, behavioral abnormalities occur later in this illness than in the frontotemporal dementias, but eventually they occur in Alzheimer’s disease as well. Patients may wander and become lost in the neighborhood; leave the house unclothed; become paranoid or accusatory, sexually inappropriate, agitated, or aggressive; fall to recognize family members; or perform unusual activities, such as placing food in the oven without turning it on or, even worse, turning on all the stove’s burners and then leaving the house. One woman cut holes in her pillows, poured orange juice into them, and then explained that she was “feeding the babies.” Later in the course of the disease, patients develop more severe frontal lobe dysfunction, with gait impairment, aphasia, and incontinence.

Of note, motor disturbances are not usually present early in the course, and if abnormal gait is present early on, other diagnoses should be considered. Similarly, while hallucinations may occur in Alzheimer’s disease, they are not usually an early feature, and they are more common in dementia with Lewy bodies. In late Alzheimer’s disease, patients eventually become akinetic, mute, unresponsive, and bedridden, ultimately succumbing to infection or other illnesses. The median time of survival from onset is approximately 8 years.

The evaluation of patients with suspected Alzheimer’s disease is similar to that of other patients with dementia, as described earlier.

Treatment of Alzheimer’s Disease

Although a definitive treatment for Alzheimer’s disease has not yet been developed, a combination of symptomatic treatment and counseling of the patient and family members can substantially improve quality of life. Several cholinesterase inhibitors, including donepezil, rivastigmine, and galantamine have been shown to produce a modest delay in cognitive decline in patients with Alzheimer’s disease. The occurrence of depression, psychosis, or agitation should be treated carefully with medications, with care being taken to avoid worsening functional status with medication side effects.

Investigations are ongoing for a new agents that may slow the progression of Alzheimer’s disease. Several other anti-inflammatory and antioxidant agents are being investigated, and most recently the possibility of beta-amyloid protein immunization therapy is being explored. It is hoped that with further research, a cure for this common and debilitating disorder will be developed in the near future.
**CASE 19.1 ACUTE SEVERE APHASIA, WITH IMPROVEMENT**

**CHIEF COMPLAINT**
A 74-year-old right-handed woman was brought to the emergency room because of sudden inability to speak and right-sided weakness.

**HISTORY**
One month prior to admission, the patient was diagnosed with atrial fibrillation associated with hyperthyroidism. Her medications included Coumadin anticoagulation, but she may have been noncompliant. During dinner on the evening of admission, she suddenly stopped speaking and was noted by her family to have right-sided weakness. By the time they brought her to the emergency room, the right-sided weakness had mostly resolved, but her speech remained very abnormal.

**PHYSICAL EXAMINATION (HOSPITAL DAY 1)**
- **Vitals:** T = 99.1°F, P = 100, BP = 138/84, R = 20.
- **Neck:** Supple with no bruits; thyroid slightly enlarged.
- **Lungs:** A few crackles at the bases bilaterally.
- **Heart:** Irregular rate; tachycardic; 2/6 systolic murmur heard at apex.
- **Abdomen:** Nontender, no mass detected. Extremities: No edema.

**Neurologic exam:**
- **Mental Status:** Alert.
  1. **Speech:** Marked paucity of spontaneous speech; said only single words and rare rote phrases, such as "No" (inappropriately), "I can't", or "I don't know." Gave normal responses to questions appropriately and followed one-step commands. Repetition, naming, and writing were still very poor or nonexistent.

**FOLLOW-UP EXAM (HOSPITAL DAY 3)**
- Spontaneous speech was markedly nonfluent, with brief agrammatical phrases and occasional paraphasias. For example, when asked to describe what she saw in a complex scene that included water overflowing a sink, she said, "Water over here." She appeared frustrated and discouraged by her limitations. Comprehension continued to improve, and she was able to answer simple questions related to herself with 70% accuracy, and to point to objects with 75% accuracy, with occasional perseverations. When asked to name a pen, she said "pencil," and she could not name a watch. She wrote "Thank you" instead of her name, and she could not read it back.

**LOCALIZATION AND DIFFERENTIAL DIAGNOSIS:**
- Summarize the findings on day 1. What kind of aphasia did the patient have that day, and what is the localization? What is the most likely cause? Summarize the findings on days 3 and 5. What kind of aphasia did the patient have, and what is the localization?

**Discussion**
1. The key symptoms and signs in this case on day 1 are:
   - **Poor fluency**
   - **Poor comprehension**
   - **Poor repetition**
   - **Paraphasias, anomia, alexia, agaphria, frustration**
   - **Dysarthria, with right face and hand weakness**

2. Severely impaired fluency, comprehension, and repetition together are classified as global aphasia (see Figure 19.4; KCC 19.6), a diagnosis that is compatible with the other language abnormalities seen in this patient. Persistent global aphasia is usually caused by large lesions involving the anterior and posterior language areas, or by large subcortical lesions (KCC 19.6). However, global aphasia can also occur acutely in new-onset lesions confined to the anterior or posterior language areas. Combined anterior-posterior language area lesions or large subcortical lesions usually result in contralateral hemiplegia, whereas this patient had relatively mild arm weakness and no leg weakness.

3. The pattern of weakness in this patient is compatible with a lesion occurring in the left lenticulostriate artery and head and arm areas (see Figures 6.2, 6.14D), suggesting that she has acute global aphasia resulting from a lesion in the left frontal lobe cortex, including the anterior language areas. Given her vascular risk factors of atrial fibrillation and possible noncompliance with anticoagulation therapy, as well as the sudden onset of her deficits, the most likely diagnosis is embolic infarction in the territory of the left middle cerebral artery superior division (see Figure 19.3A). Another possibility is a hemorrhage in the left frontal lobe, especially because she is taking Coumadin. Focal seizures or migraine are also possible, but much less likely (see also Table 19.5).

4. The key symptoms and signs in this case on days 3 and 5 are:
   - **Poor fluency**
   - **Poor repetition**
   - **Comprehension relatively spared**
   - **Poor naming, reading, and writing, with paraphasias and frustration**
   - **Mild right arm weakness**

5. By days 3-5 the patient's global aphasia had improved to a typical Broca's aphasia (see KCC 19.4). This pattern of evolution is often seen in acute lesions of the left frontal lobe. The next most common cause would be left MCA superior division infarct.

**Clinical Course and Neuroimaging**
Initial head CT was normal. The patient's admission INR (International Normalized Ratio), a measure of the amount of anticoagulation, was subtherapeutic at 1.1 (target 2.0-3.0), and levels of her heart medication were also low, supporting medication noncompliance as the cause of a presumed embolic infarction in the territory of the left MCA superior division. She was admitted and placed on intravenous heparin anticoagulation while her Coumadin was readjusted. Two days after admission, a brain MRI (Figure 19.15) revealed a medium-sized infarct in the left frontal operculum involving Broca's area, just in front of the precentral gyrus face and arm areas.

As already noted, the patient's global aphasia rapidly evolved into a Broca's aphasia, and this condition continued to improve, as did her trace right-sided weakness. She was seen in follow-up 2 months later, at which time she was able to speak in sentences with occasional pauses to find words, and occasional paraphasias. Comprehension, repetition, reading, and writing were relatively good (although not perfect), and her main difficulties were with naming and finding words. Thus, as is commonly seen in cases with good recovery, her residual deficit was predominantly a dysphasic aphasia.
CASE 19.1 ACUTE SEVERE APHASIA, WITH IMPROVEMENT

Figure 19.15 Left MCA Superior Division Infarct MRI scans. (A) Axial T2-weighted image showing bright region compatible with infarct in the left frontal operculum including Broca's area. (B) Sagittal T1-weighted image showing hypointense region compatible with infarct.

MINICASE

An 81-year-old right-handed woman with a history of hypertension was brought to the emergency room by her family one morning when she was suddenly "unable to communicate properly," speaking with words and sentences that did not make any sense. On exam, she had an irregular pulse, and spontaneous speech was fluent with normal prosody and grammatical constructs; however, most of what she said was meaningless and did not fit the context, showing frequent paraphasic errors and repetition. She followed no commands, except to close her eyes. When asked to raise her arms, she said, "What do you want?" She could not repeat even single words. On testing of naming, she called a pen "red rains," a watch "round thing," a tie "po, do, bi, fisio," and a pen (second presentation) "like when you want to write down something." Writing sample: "the word youw wogw whaweta." She could not read what she wrote. When asked to read, "The dog ran down the road," she read, "The roth ran ra a goth." She had a pleasant, unconcerned affect and seemed oblivious to any deficits. Blink to threat was decreased on the right side. The remainder of her exam was normal.

LOCALIZATION AND DIFFERENTIAL DIAGNOSIS
1. What kind of aphasia does this patient have?
   - Where is her lesion?
2. What is the most likely cause, and what are some other possibilities?

Discussion
The key symptoms and signs in this case are:
- Fluent, meaningless speech
- Poor comprehension
- Poor repetition
- Poor naming, reading, and writing; frequent paraphasias
- Lack of concern about and obliviousness to deficits
- Right visual field defect

1. This patient has typical findings of Wernicke's aphasia (see KCC 19.5). The localization therefore is most likely to the left posterior superior temporal and left inferior parietal region. A lesion in this location would also explain the patient's right visual field cut because it could interrupt the left optic radiations (see Figure 11.8).
2. The left temporoparietal region lies in the territory of the left MCA inferior division. The most likely diagnosis, especially given the patient's age, history of hypertension, and acute onset, is an infarct in this territory (see Figure 19.3A). Hemorrhage in this location is also possible, with focal seizure or migraine again possible but unlikely (see also Table 19.5).

Clinical Course and Neuroimaging

A head CT on the day of admission showed an infarct in the left temporoparietal region, in the territory of the left MCA inferior division. This was confirmed 4 days later by an MRI scan (Figure 19.16). Note that the infarct included Wernicke's area along with the adjacent temporoparietal cortex, as well as the left optic radiation where it passes just lateral to the atrium of the lateral ventricle. The MRI also demonstrated moderate cortical atrophy as an incidental finding in this patient. Admission electrocardiogram showed new onset of atrial fibrillation. Other embolic workup (see KCC 10.4) was negative. The patient was treated with intravenous heparin, changed over to oral anticoagulation with Coumadin, and discharged home in the care of her family after 1 week. Further follow-up was not available.

Additional Basic Aphasia Cases

For additional cases illustrating basic types of aphasia, see Chapter 10 (Cases 10.5, 10.6, and 10.8).
CASE 19.2 NONSENSICAL SPEECH

Figure 19.16 Left MCA Inferior Division Infarct: Axial T2-weighted images. A, B: Progress from inferior to superior. The infarct includes Wernicke's area.

CASE 19.3 APHASIA WITH PRESERVED REPETITION

MINICASE

A 63-year-old right-handed woman with a history of breast cancer in remission was talking on the phone with her sister one evening and suddenly began to have difficulty getting the words out, and she could not answer simple questions. She was taken to the hospital, and on exam she was alert and able to state her name, the month, and the year, but not the date, and she correctly chose her location by multiple choice.

Her language exam was as follows:

1. SPONTANEOUS SPEECH: Halting, labored, telegraphic, with decreased use of function words (verbs and prepositions). She frequently used fillers such as "um," "ahh," and "you know" and had many paraphasic errors and neologisms. She did better once started by the examiner on automatic tasks such as naming the days of the week. On word generation tasks, she could name only six animals in 1 minute, and she came up with no words starting with the letter "s" in 1 minute.

2. COMPREHENSION: Followed three-step verbal commands. Was able to rapidly identify body parts, objects, shapes, and letters by pointing. Correctly answered 6 of 8 questions on verbally presented paragraphs. Had difficulty following only lengthy, complex commands.

3. REPERT: Repeated words and sentences with 100% accuracy (much better than spontaneous speech). With low-probability sentences, she made occasional paraphasic errors.

4. NAMING: Could name only 1/6 objects and no shapes. Naming was improved when she was given the first sound of the word as a hint.

5. READING: Reading aloud was not tested.

6. WRITING: Wrote the following sentence spontaneously: "I this a mighty foynam 97." The remainder of her exam was normal.

LOCALIZATION AND DIFFERENTIAL DIAGNOSIS

1. What kind of aphasia was present in this patient? Where was her lesion?
2. What are some possible causes in this patient?

Discussion

The key symptoms and signs in this case are:

- Poor fluency
- Repetition and comprehension relatively spared
- Poor naming and writing; paraphasias

1. This patient had a transcortical motor aphasia (see Figure 19.4). This can be produced by lesions located in the lateral frontal cortex in the dominant hemisphere that spare the arcuate fasciculus, the other peri-Sylvian conducting pathways, and Broca's area (see Figure 19.3B), or occasionally by subcortical lesions of the dominant hemisphere sparing the same regions.

2. Possible causes of a lesion in these locations resulting in sudden onset of deficits include watershed infarct in the ACA-MCA territory (see Figure 19.3B) or hemorrhage (see KCC 5.6). Given the patient's history of breast cancer, a metastasis should also be considered, possibly resulting in hemorrhage. Of note, sudden onset of deficits in brain tumors can sometimes occur even without hemorrhage, although this is relatively uncommon.

Clinical Course and Neuroimaging

Head CT (Figure 19.17A) showed a hemorrhage in the left frontal lobe, sparing the peri-Sylvian cortex and sparing Broca's area, but lying just dorsal to it. This hemorrhage would be expected to disconnect Broca's area from other structures in the left frontal lobe needed for language formulation, producing the transcortical motor aphasia (impaired fluency, preserved repetition) seen in this patient. An MRI scan (see Figure 19.17B) done with gadolinium was negative for brain metastases, but again showed a hemorrhage in this location. The exam and neuroimaging findings in this patient should be contrasted against those for the patient with Broca's aphasia in Case 19.1.
Follow-up MRI scans at 1, 4, and 9 months after the hemorrhage showed no evidence of metastases or vascular malformation. The patient did not undergo an angiogram, but MRAs were unremarkable. Her language gradually improved, and 1 year later her fluency was nearly normal. She remained in active speech therapy, and her main residual problems were some word-finding difficulties and circumlocution.

CASE 19.4 IMPAIRED REPETITION

MINICASE

A 67-year-old right-handed woman was in a motor vehicle accident with brief loss of consciousness and mild confusion at the scene. Past history was significant for a mechanical mitral valve and coronary artery disease, treated with aspirin and Coumadin anticoagulation. After the accident she complained of left frontal headache, neck pain, nausea, and vomiting. She was brought to the emergency room, where cervical spine X-rays were normal and initial neurologic exam was described as normal except for amnesia for the accident and uncertainty about the exact date, although she knew the correct month and the year. Two days later her headache worsened, and she was noted to have some new speech difficulties. A neurology consult was called. Exam showed some nuchal rigidity, a systolic murmur, fluent speech, intact comprehension following three-step commands, but difficulties with repetition (unable to repeat "no ifs, ands, or buts" or other similar short phrases), a slight right pronator drift, and an upgoing toe on the right side.

LOCALIZATION AND DIFFERENTIAL DIAGNOSIS

1. What kind of aphasia did this patient have on exam, and what is the localization of her aphasia and associated mild motor abnormalities?
2. What diagnosis is suggested by the patient’s history and her initial symptoms?

Discussion

The key symptoms and signs in this case are:
- Poor repetition
- Relatively preserved fluency and comprehension
- Mild right pronator drift and right Babinski’s sign
- Brief loss of consciousness, amnesia, left frontal headache, nausea, vomiting, and nuchal rigidity

1. This patient had conduction aphasia (see Figure 19.4), which can be caused by subcortical lesions involving the arcuate fasciculus or by cortical lesions of the peri-Sylvian region in the dominant hemisphere (see Figure 19.2A). The mild right corticospinal findings also suggest a lesion in the left hemisphere causing mild impairment on the nearby corticospinal tract (see Figure 6.104). The brief loss of consciousness and confusion suggest a possible head injury during the motor vehicle accident. The headache, nausea, vomiting, and nuchal rigidity are signs of meningeal irritation (see Table 5.3) which, together with the patient’s use of oral anticoagulation and aspirin, suggest intracranial hemorrhage (see KCC 5.6) located in the peri-Sylvian region of the dominant (left) hemisphere. Other less likely possibilities include infarct, neoplasm, or infection in this location.

Clinical Course and Neuroimaging

Head CT (Figure 19.18) demonstrated a traumatic intracranial hemorrhage (see KCC 5.5, 5.6) in the left Sylvian fissure. This included layering of subarachnoid blood in the sulci, as well as a more confluent parenchymal hematoma. The hemorrhage involved the peri-Sylvian region, including the region of the arcuate fasciculus, and could thus disconnect the anterior and posterior language areas (see Figure 19.2A). A small subdural hematoma was present as well.

adjacent to the right fals cerebri (not shown on Figure 19.18), likely unrelated to the patient’s findings.

The patient’s aspirin was discontinued and her Coumadin temporarily stopped. She was also given a few units of fresh frozen plasma to partly reverse her anticoagulation. She remained stable over the next few days and was carefully treated with low-dose heparin before resuming her Coumadin. Nine days after admission, her repetition had improved, but she also practiced the commonly used phrases, and would greet the neurology team on morning rounds with “Good morning. No ifs, ands, or buts. I was here. She would be there. . . . How was that?” She continued to have some mild difficulties, especially when repeating new sentences that she had not heard before.

CASE 19.5 INABILITY TO READ, WITH PRESERVED WRITING SKILLS

MINICASE

A 64-year-old right-handed woman had 1 week of progressive troubles with her vision and reading. Of note, she had a 3-year history of colon cancer with metastases to the liver. Exam was normal, except for inability to read written words, some difficulties with short-term verbal memory, and a right homonymous hemianopia. She was able to write normally, writing “Today is a nice day” and “It is a sunny day in Boston,” but when shown her own writing a few minutes later, she was unable to read it. She also had a subtle dysnomia, naming a watch, ring, finger, elbow, and lips, but unable to name knuckle, nail, vein, or hand. Color naming was not tested.

LOCALIZATION AND DIFFERENTIAL DIAGNOSIS

1. What is the name for the syndrome that includes the inability to read and preserved writing seen in this patient, and where is it localized?
2. Given the gradual onset of deficits and the patient’s history, what are some possible causes of a lesion in this location?

Discussion

The key symptoms and signs in this case are:
- Ability to write normally, but inability to read
- Right homonymous hemianopia
- Some difficulties with short-term verbal memory
- Mild dysnomia

1. This patient has the classic findings of alexia without agraphia, which is caused by lesions of the left medial occipital visual cortex extending to the posterior corpus callosum (see KCC 15.7; Figure 19.5). Given the gradual onset over the course of a week, and the history of colon cancer, brain metastases should be considered in this patient. Other possibilities include a slowly evolving infarct in the left ICA territory, extending intracranial hemorrhage, other intracranial neoplasm, or abscess.

Clinical Course and Neuroimaging

A head CT with intravenous contrast (Figure 19.19) revealed a large, cystic enhancing lesion in the left medial occipital lobe with edema and mass effect extending into the posterior corpus callosum. The patient was admitted and treated with steroids to reduce edema. By means of a stereotactic approach (see KCC 16.4), fluid was drained from the cyst with a needle, leading to a partial improvement in her hemianopia and reading difficulties. In addition, a stereotactic biopsy revealed metastatic adenocarcinoma. She was then treated with stereotactic proton beam radiosurgery (see KCC 16.4) directed at the lesion, and she remained stable at last available follow-up, 3 months after presentation.
**CASE 19.3 APHASIA WITH PRESERVED REPETITION**

Figure 19.17 Left Frontal Hemorrhage The hemorrhage lies just dorsal to Broca’s area, and spares the peri-Sylvian region. (A) Axial CT scan image. (B) Coronal T1-weighted MRI with intravenous gadolinium.

(A)

(B)

**CASE 19.4 IMPAIRED REPETITION**

Figure 19.18 Left Peri-Sylvian Intraparenchymal Hemorrhage in Region of Arcuate Fasciculus Axial CT images. A-D progress from inferior to superior.

(A)

(B)
CASE 19.4 (CONTINUED)

**Figure 19.19** Metastasis of Colon Adenocarcinoma to the Left Medial Occipital and Posterior Callosal Region - Axial CT images with intravenous contrast enhancement.

(A) B progress from inferior to superior.

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**CASE 19.5 INABILITY TO READ, WITH PRESERVED WRITING SKILLS**

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CASE 19.6 LEFT HEMINEGLIGENCE

MINICASE

A 67-year-old left-handed security guard with a history of cigarette smoking had an episode of left hand tingling lasting less than an hour that was reported to medical staff by a friend. The next day he was at the grocery store buying a lottery ticket and reportedly slumped briefly to the floor. He denied that anything was wrong but said, "They called an ambulance because they said I had a stroke."

On examination, he was unaware of having any deficits and was quite impish and grously, wanting to go home. He had profound left visual neglect, describing only the curtains to the far right in a picture of a complex visual scene (Figure 19.20) and reading only the right two words on each line of a magazine article. When asked to write or draw a clock, he moved the pen in the air off to the right of the page. He then handed the pen back, saying, "I'm finished," apparently thinking he had completed the task. He had no blink to threat on the left, a marked right gaze preference, and mildly decreased left nasolabial fold. Spontaneous movements were decreased on the left side, but with provocation he was able to achieve 4/5 strength in the left arm and leg. He was able to feel touch on the left side but had extinction on the left to double simultaneous tactile stimulation. Reflexes were slightly brisker on the left.

LOCALIZATION AND DIFFERENTIAL DIAGNOSIS

1. Summarize the different types of neglect demonstrated by this patient (see Table 19.7).
2. On the basis of the symptoms and signs shown in bold above, what is the most likely location of the lesion in this patient?
3. What is the most likely diagnosis?

Discussion

The key symptoms and signs in this case are:
- Anosognosia
- Left visual neglect
- Extinction on the left to double simultaneous tactile stimulation
- Movement of the hand off to the right of the page when asked to draw, and decreased spontaneous movements on the left side, but ability to achieve 4/5 strength when pressed
- Impairment and irritability
- Right gaze preference
- No blink to threat on the left

Note: This patient was also presented as Case 20.10.

- Mildly decreased left nasolabial fold, 4/5 strength in the left arm and leg, and slightly brisker reflexes on the left side
- Transient episode of left hand tingling

Clincial Course and Neuroimaging

Head CT on the day of admission showed a mild hypodensity in the right temporoparietal area. Follow-up head CT 2 months later (Figure 19.21) confirmed right MCA infarct involving the temporal and parietal cortex and optic radiation.

Carotid Dopplers and an MRA suggested occlusion versus critical stenosis of the right carotid artery (see KCC 10.5), so a conventional cerebral angiogram was done showing occlusion of the right common carotid artery (see Figure 10.22). This result suggests that he had an embolus to the right MCA infarct division that broke off the thrombotic occlusion of the internal carotid. The patient was treated with intravenous and, later, oral anticoagulation in an attempt to reduce the risk of further emboli. By 3 days after admission, he was able to walk volitionally to the left, strength was normal on the left side when he was motivated, and reflexes were symmetrical. He still had decreased blink to threat on the left and occasional (one-third of trials) left extinction on double simultaneous tactile stimulation. Coumadin was eventually stopped, and in follow-up 1 year later, he had a normal exam except for a left visual field cut (not precisely mapped out by the examiner).

Interestingly, as is often the case, this patient had profound left heminegluct from a right hemisphere lesion, even though he was left-handed. Other examples of left heminegluct were shown earlier, in Figures 19.9 and 19.10, as well as in Cases 10.9 and 10.11.
**Related Case.** Figure 19.22 shows a head CT from an interesting patient who developed severe right hemineglect. She was a 52-year-old woman who had a left hemispherectomy (see KCC 18.2) in childhood because of early-onset severe refractory seizures arising from the left hemisphere. Despite this drastic surgery, she was highly functional as an adult, working as a librarian. Over the course of 6 months, however, she developed communicating hydrocephalus (see KCC 5.7), a known delayed complication of hemispherectomy (Figure 19.22A,C). In addition to signs of hydrocephalus such as impaired gait and lethargy, her exam was notable for right hemineglect (Figure 19.23A). This may be explained by "bilateral" lesions (see Figure 19.7D), consisting of left hemispherectomy together with depression of the right hemisphere by hydrocephalus. After ventriculoperitoneal shunting (see KCC 5.7), the patient's hydrocephalus improved (see Figure 19.22B,D) and she no longer had right hemineglect (see Figure 19.23B).

**CASE 19.7 ABULIA**

**CHIEF COMPLAINT**
A 27-year-old woman was brought to the hospital with increasing lethargy, slowdown, and incoherence.

**HISTORY**
Five years previously the patient had developed speech difficulties and was diagnosed with a left frontal oligodendroglioma. She was treated with resection, radiation therapy, and chemotherapy and did well, returning to work as a receptionist. Six months prior to admission, she underwent a personality change, becoming progressively slower and more withdrawn. As her slowness worsened, her voice became very muted, and she rarely initiated movements. This condition had become particularly severe over the most recent 2 to 3 weeks, and she had developed urinary incontinence, inability to walk without assistance, and falling to the left, and she had to be fed by her mother.

**PHYSICAL EXAMINATION**
Vital signs: T = 98.6°F, P = 80, BP = 120/70.
Neck: Soft.
Lungs: Clear.
Heart: Regular rate with no murmur, gallops, or rubs.
Abdomen: Normal bowel sounds; soft.
Extremities: Normal.
Neurologic exam:
- Mental status: Awake but lethargic, responding to questions or commands very slowly, often after a long delay. Sometimes she did not respond at all. Her voice was very soft, but she could speak louder when asked. She stated the correct month, date, year, and location. She named the past two presidents after a long delay, and then stopped. She was able to repeat correctly, and she named 5/5 objects. She recalled 0/3 objects after 4 minutes, even with prompting and with a second trial. She did not respond at all when asked a simple arithmetic question or when asked to spell "world."
- Cranial nerves: Normal, except for slight left facial droop and decreased shoulder shrug on the left.
- Sensorial: No deficit. Normal bulk and tone. Pover difficulty to test because of motor incoordination; exerted only a brief nonsustained submaximal effort during tests of each muscle group. However, she appeared to have 4/5 grip on the left, 4/5 grip on the right, and otherwise 4/5 approximately symmetrical strength throughout.
- Reflexes: Prominent grasp reflexes were present bilaterally. There was no snout or suck reflex.

**COORDINATION:** Slow but atactic on finger-to-nose and heel-to-shin testing.

**SAID:** Very slow, shuffling, not picking feet up off floor, requiring support to avoid falling to left.

**SENSATIONS:** Intact light touch, pinprick, and vibration sensation. No extinction.

**LOCALIZATION AND DIFFERENTIAL DIAGNOSIS**
1. Summarize the clinical features seen in this patient. Dysfunction of what region of the brain usually produces this syndrome? Is the lesion unilateral or bilateral?
2. Why does this patient have impaired memory testing?
3. What is the most likely diagnosis causing this patient's decline?

**Discussion**

1. The key symptoms and signs in this case are:
   - Abulia (awake but slow, withdrawn, responding after long delay)
   - Hypokinesia (rarely initiating movements)
   - Hypophonia
   - Impaired short-term memory
   - Motor incoordination
   - Bilateral grasp reflexes
   - Urinary incontinence
   - Unsteady, slow, shuffling "magnetic" gate, falling to the left
   - Slight left face and arm weakness, left Babinski's sign, right ankle clonus, brisk reflexes throughout
CASE 19.6 RELATED CASE

Figure 19.22 Head CT Scans from a Patient with Left Hemispherectomy and Hydrocephalus. Axial CT scan images. (A, C) Before shunting. (B, D) After ventriculoperitoneal shunt placement. (From Kalkanis SN, Blumenfeld H, Sherman JC, Krebs DE, Jr., Irazny MC, Parker SW, Cosgrove GR 1996. Delayed complications 36 years after hemispherectomy: a case report. Epilepsia 37(5): 758-762.)

Clinical Course and Neuroimaging

A head CT (Figure 19.24) demonstrated abnormal hypodensity involving virtually all of the prefrontal cortex bilaterally, probably representing edema and recurrent tumor. Glioblastomas of this kind, extending across the anterior corpus callosum to involve both frontal lobes, are sometimes referred to as butterfly gliomas. Note also that the sulci are fully effaced, suggesting that elevated intracranial pressure could also be contributing to the patient’s decreased alertness (see KCC 5.3).

The patient was admitted to the hospital and treated with increased steroids and a brief course of mannitol without any significant improvement. A repeat biopsy confirmed recurrent tumor. She was given additional chemotherapy, including intra-arterial chemotherapy delivered by superselective catheterization of the supraclinoid right internal carotid artery; however, she continued to deteriorate gradually.

Related Cases. Figure 19.25 shows an MRI from a different patient, a 75-year-old woman who was brought to a memory disorders clinic because of 6 months of forgetfulness. Neurologic exam was entirely normal except that she exhibited some perseveration, tending to answer the same thing for several questions in a row regardless of the question, and mild difficulties with both recent and remote memory. This case illustrates how enormous lesions in the frontal lobes sometimes cause relatively subtle deficits, especially if the lesion is slow growing. The lesion was removed surgically, and pathology showed it to be a meningioma. The patient’s mental status improved after surgery, and she subsequently did very well. Another important lesson of this case is the importance of performing a neuroimaging study in the evaluation of patients with suspected dementia (see KCC 19.16) in an attempt to find reversible causes.

An abnormality commonly seen in patients with frontal lobe lesions is perseveration. This finding may be obvious, as it was in the patient just described and in Case 19.7. In other cases, more subtle perseveration can be detected by tests such as manual or written alternating sequencing tasks (see neuroexam.com Videos 19, 20). Figure 19.26 shows an example of a different patient who exhibited perseveration on a written alternating sequencing task. Interestingly, this patient had benzodiazepine toxicity but did not have a frontal lobe lesion, demonstrating that diffuse disorders can sometimes mimic lesions of the frontal lobes (see KCC 19.13).
CASE 19.7 RELATED CASES

Figure 19.25 Large Falcine Meningioma Compressing the Frontal Lobes
Axial T2-weighted MRI.

Figure 19.26 Written Alternating Sequencing Task
Patient was instructed to copy a pattern drawn by the examiner and continue it to the end of the page. Persistance and "clinging in" are evident in this patient with benzodiazepine toxicity. This is an example of apparently focal deficits that can be seen in patients with diffuse encephalopathy (see KCC 19 H5).

CASE 19.8 BLINDNESS WITHOUT AWARENESS OF DEFICIT

Figure 19.27 Bilateral Infarcts of the Visual Cortex
Axial CT scan images.
A, B progress from inferior to superior.

(A)

(B)
CASE 19.9 SUDDEN INABILITY TO RECOGNIZE FACES

MINICASE

A 78-year-old right-handed man with a history of atrial fibrillation treated with Coumadin anticoagulation came to the emergency room because of unusual visual disturbances. He had a history of a cerebral infarct 6 years previously, resulting in a left homonymous hemianopia, which subsequently improved. On the day prior to admission, while driving his car, he suddenly saw “a translucent white curtain” obscuring the upper part of his vision and making it hard to see traffic. He felt that his motion perception was off because he nearly hit a truck that was stopped in front of him. By the morning of admission, he no longer saw a curtain, but instead had the perception of “shimmering glass balls or water drops” dotting the upper areas of his vision with both eyes open at the same time. He did not have a friend on the street, who began walking next to him, but his friend looked unfamiliar. “His facial features were moving all around his face. I couldn’t put it together. I know this guy like I know my brother.” The patient said to the Friend, “Who are you?” and his friend answered, “What are you talking about? You’ve known me for years!” The patient then recognized him, but by his voice only.

On exam in the emergency room, the patient had normal mental status, including naming presidents back to Wilson and 3/3 memory at 5 minutes. He had normal visual fields, except for a homonymous scotoma in the left inferior quadrant, and he was able to see through the teardrop-like distortion in his upper visual fields. In addition, he had difficulty recognizing faces in a magazine. For example, when shown a picture of George Bush, he said, “I think I should know him.” When shown a picture of Bill Clinton, he said, “Get that thing away from me! (the patient was a staunch Republican). He was able to name objects other than faces well. Reading and writing abilities were normal, and he did not have achromatopsia. The remainder of his exam was normal.

LOCALIZATION AND DIFFERENTIAL DIAGNOSIS

1. What is the name for disorders in which perception and language are normal but recognition is impaired? Given the findings shown in boldface above, what is the most likely localization for this patient’s lesion(s)?
2. What is the most likely diagnosis?

Discussion

The key symptoms and signs are:
- Difficulty recognizing faces
- Visual obscuration of upper fields bilaterally
- Left inferior-quadrant scotoma

1. Impaired recognition in the absence of defects in primary perception or in naming ability is called agnosia (see KCC 19.12). This patient demonstrates impaired ability to recognize faces, with preserved ability to see, recognize, and name other objects. This syndrome is known as prosopagnosia and is usually caused by bilateral lesions of the face recognition areas in the visual association cortex of the inferior occipitotemporal ( fusiform ) gyrus (see Figure 19.13). Associated features can include upper visual field obscuration of the kind seen in this patient because of the proximity to the inferior calcarine regions (see Figure 11.15). This patient’s left inferior-quadrant scotoma is most likely related to his prior history of a cerebral infarct 6 years earlier that had caused a left homonymous hemianopia at the time, which subsequently improved.

2. Given his history of atrial fibrillation and treatment with Coumadin, the most likely diagnoses are bilateral inferior occipitotemporal infarcts or hemorraghes.

Clinical Course and Neuroimaging

A head CT (Figure 19.28) demonstrated an old right occipital infarct, along with a recent infarct of the left inferior occipitotemporal ( fusiform ) gyrus. The patient was admitted and briefly treated with intravenous heparin, in addition to the Coumadin that he was already taking for atrial fibrillation. On admission, his anticoagulation INR (International Normalized Ratio) was in the therapeutic range. An MRA showed no significant stenoses. His ability to recognize faces improved markedly within 2 days of admission, and the visual distortion in his upper fields resolved more gradually. He was discharged home on Coumadin.

CASE 19.10 MUSICAL HALLUCINATIONS

MINICASE

A 21-year-old right-handed man from El Salvador was brought to the emergency room after having a seizure. Beginning 3 years previously, he had developed frequent brief episodes in which he heard music playing and voices. These episodes were often followed by a generalized convolution. He was living in a rural area at the time, and the episodes stopped on their own after about 3 months without medical treatment. On the day of admission, while at work, the patient again suddenly heard music playing and voices. He then felt dizzy, saw spots, and lost consciousness. Witnesses reported that he had had a generalized tonic-clonic seizure lasting 2 to 3 minutes, followed by post-ictal lethargy and generalized headache, but no clear language deficit. He had a second identical episode upon arrival at the emergency room. Exam performed a few hours after the last seizure was entirely normal.

LOCALIZATION AND DIFFERENTIAL DIAGNOSIS

1. What anatomical structures could be involved sequentially during this patient’s seizures to produce the sequence of reported ictal phenomena? Which side of the brain and what location were likely involved in seizure onset (see KCC 18.7)?
2. What are some possible causes of seizures in this patient?

Discussion

The key symptoms and signs in this case are:
- Hearing music playing and voices
- Dizziness
- Seeing spots
- Loss of consciousness, and generalized convulsion
- No clear language deficit post-ictally

1. Although auditory hallucinations can be caused by lesions in many possible locations along the auditory pathways (see KCC 19.13), only lesions in the cortex would be expected to produce seizures. Therefore, this patient’s seizures probably began in the auditory cortex or auditory association cortex, spread to the ventral part of the parietal cortex, producing dizziness; then to the posterior-occipital cortex, producing visual spots; and finally to the entire brain, producing generalized tonic-clonic activity (see KCC 19.2). Musical abilities depend more on the right hemisphere than on the left in most individuals who are not trained musicians (see Table 19.5), and musical hallucinations are more often seen with right rather than left temporal seizures (see KCC 19.13). In addition, left hemisphere seizures are often associated with post-ictal aphasia, which was not present in this patient. Therefore, the most likely site of seizure onset is the right superior temporal gyrus, in the vicinity of Heschl’s gyrus (primary auditory cortex) or auditory association cortex (see Figure 19.1).

2. The most common cause of nontraumatic early-adult-onset seizures in patients from Central America is CNS tuberculosis (see KCC 5.9; see also Figure 5.30). Other possibilities include other CNS infections, a low-grade brain tumor, or a cortical developmental abnormality.

*Certain rat attains exhibit seizures triggered by brain stem auditory pathways, but a similar condition has not been reported in humans.
CASE 19.9 SUDDEN INABILITY TO RECOGNIZE FACES

A brain MRI revealed an enhancing cyst near the right superior gyrus and Hecht's gyrus (Figure 19.29). The patient underwent lumbar puncture and had blood serology sent to confirm the diagnosis of cysticercosis. He was treated with anticonvulsant medications and given a course of the antiperistaltic agent propranolol, together with a brief course of steroids to prevent swelling that can sometimes occur in response to treatment. He did well and was discharged home without further problems.

CASE 19.11 PROGRESSIVE DEMENTIA, BEGINNING WITH MEMORY PROBLEMS

CHIEF COMPLAINT
A 76-year-old right-handed woman was referred to a memory disorders clinic because of 4 years of worsening memory problems.

HISTORY
The patient had previously been in good health. Her memory problems began when she retired as a secretary at age 72, and had progressed slowly ever since. Her husband reported that she initially had difficulty making dinner recipes at home, as well as trouble recalling things she had been told in recent days or weeks. She seemed to recall events from the distant past somewhat better. Her memory gradually grew worse, and she began losing her keys and her passport book. She often repeated questions that she had asked a few minutes before. She occasionally had difficulty distinguishing the letter "O" from the number zero on the touch-tone phone. Most recently, her husband had been concerned that she was often lost or uncertain of her directions. She was often irritable and became angry over little things that would not have bothered her in the past.

For example, one morning she was very insistent on making her bed before going to church. She saw her physician, who ordered a head CT and routine blood tests, including thyroid function tests, VDRL (test for syphilis), B12 level, and erythrocyte sedimentation rate, all of which were normal.

PHYSICAL EXAMINATION
Vital signs: T = 98°F, BP = 140/82.
Neck: No bruits.
Lungs: Clear.
Heart: No murmurs.

Abdomen: Soft, nontender.
Extremities: No edema.
Neurologic exam:
Mental status: Alert. Named five objects easily, and had no apraxia. No delusions or hallucinations.
The Blessed Dementic Scale (BDS) showed significant memory impairment (see Table 19.16). She scored 3 on the left column and 11 on the right column, losing points mostly for questions on 5-minute recall, nonverbal memory, and orientation. Her Activities of Daily Living (ADL) score was 22%. (Higher scores on the BDS and ADL indicate more severe impairment.)
Cranial nerves: Normal.
Senses: No grasp, root, suck, or shout reflexes.

COGNITION: Normal on finger-to-nose testing.
Coordination: Normal.
LOCALIZATION AND DIFFERENTIAL DIAGNOSIS
Disfunction in what anatomical structures could explain the abnormalities shown in boldface above? What is the most likely diagnosis, and what are some other possibilities?

Discussion
The key symptoms and signs in this case are:
- Slowly progressive memory impairment, worse for recent memories
- Difficulty distinguishing the letter "O" from zero on a touch-tone phone
- Tendency to get lost
- Irritability

Impairment of recent memory can be caused by bilateral dysfunction of the medial temporal lobe or medial diencephalic memory systems (see KCC 18.3). This patient's geographic disorientation and her spatial disorientation with regard to O and zero on the telephone (or possibly reading difficulties) suggest possible posterior temporal dysfunction (see KCC 19.7, 19.10). Irritability and personality changes are nonspecific; but they can also be caused by dysfunction of limbic or association cortex. Overall, these findings and the slowly progressive time course fit both anatomically and clinically with early Alzheimer's disease.
(see Figure 19.14: KCC 19.16). In a patient over the age of 65 with progressive deficits in recent memory, mild temporal lobe dysfunction, no motor abnormalities on neurologic exam, and normal basic blood tests and neuroimaging, as in this patient, Alzheimer’s disease is by far the most likely diagnosis. Other possible causes of chronic mental status changes are listed in Tables 19.15.

**Clinical Course**
The patient had an MRI scan of the brain that was unremarkable except for mild atrophy. Follow-up in the months after her first visit was as follows:

- **7 months:** BDS left = 2.5, right = 11; ADL = 23%. The patient was still carrying out activities around the house, such as making the beds and doing the cooking, and she was doing volunteer work with her husband at a hospital.
- **11 months:** BDS right = 10; ADL = 36%. Still doing some volunteer work.
- **17 months:** BDS right = 16; ADL = 32%.
- **25 months:** BDS right = 15; ADL = 47%.
- **31 months:** BDS right = 21; ADL = 37%. No longer cooking, could not be left alone, and was enrolled in a day care program. No longer wanted to take regular baths, and instead took sponge baths. Neurologic exam and general health still normal, other than her dementia.
- **37 months:** BDS right = 25; ADL = 32%. Increased agitation, with daily episodes of incontinent screaming and swearing at her husband.
- **43 months:** BDS right = 26; ADL = 59%. Needed assistance in getting dressed. Continued occasional agitation. Husband attending support groups.
- **47 months:** BDS right = 23; ADL = 60%. Having occasional hallucinations. For the first time, her tandem gait and hopping were mildly unsteady on exam. General health remained good, and she was on no medications.
- **52 months:** She became angry and aggressive with increasing frequency and was placed in a nursing home.
- **70 months:** The patient died at age 82, about 10 years after her first symptoms.

**Pathology**
The patient’s family consented to a postmortem examination, which revealed typical changes of Alzheimer’s disease, including cortical atrophy, neuronal loss, and plaques and tangles in a widespread distribution but most prominent in the medial temporal lobes. A typical amyloid plaque and intracytoplasmic neurofibrillary tangle were seen on silver staining from the frontal polar cortex of this patient, as shown in Figure 19.30.

**Additional Cases**
Related cases can be found in other chapters for the following topics: acute mental status changes (Cases 5.5, 5.10, 7.1, 14.8); chronic mental status changes (Cases 5.1, 5.9, 13.3, 16.2); aphasia (Cases 7.1, 10.5, 10.6, 10.8); hemineglect (Cases 5.1, 10.2, 10.13); and limbic system disorders (18.1–18.5). Other relevant cases can be found using the CaseIndex.
CASE 19.11 PROGRESSIVE DEMENTIA, BEGINNING WITH MEMORY PROBLEMS

Figure 19.30 Plaque and Tangles. Pathology slide from the frontal cortex prepared with a silver stain demonstrating an amyloid plaque and neurofibrillary tangles typical of Alzheimer's disease.

Brief Anatomical Study Guide

1. In this chapter we discussed networks involved in higher-order cognitive functions, emphasizing the cerebral cortex. A majority of the cerebral cortical surface is composed of association cortex. Association cortex can be divided into unimodal (modality-specific) association cortex and heteromodal (higher-order) association cortex (see Figure 19.1; Table 19.2).

2. Although most structures and sensorimotor functions are distributed symmetrically in the brain, there are also marked asymmetries in brain function. The left hemisphere is typically dominant for skilled motor functions (handedness) and language, and the right hemisphere plays a greater role in attentional mechanisms and spatial analysis (see Table 19.3). The left hemisphere is dominant for language in over 95% of right-handers, and in over 60 to 70% of left-handers. Language is mediated by a network centered on structures in the dominant (usually left) hemisphere, but extending to the right hemisphere as well (see Figure 19.2).

3. Broca's area, located in the frontal lobe adjacent to the speech articulatory motor cortex, is important in language formulation. Wernicke's area, located in the temporal lobe adjacent to the primary auditory cortex, is important in associating meaning with words. Both Broca's and Wernicke's areas function through interactions between the posterior and anterior language areas via the arcuate fasciculus.

4. In Chapter 14 we described the activating systems of the brainstem pontomesencephalic region—the basal forebrain, thalamus, and cortex—essential for maintaining the normal awake state (see Figures 14.7, 14.8; Table 14.2). In this chapter we discussed mechanisms of attention, touching briefly on the more controversial topic of awareness. In discussing networks mediating attention, we reviewed the roles of widespread projection systems, frontal and parietal association cortex, anterior cingulate cortex and limbic pathways, tectal circuits, and other structures, such as the basal ganglia and cerebellum.

5. Although both hemispheres are involved, the right hemisphere is more important for attentional mechanisms in most individuals (see Figure 19.7). Lesions of the right hemisphere often cause prominent neglect of the contralateral side. In addition, the right hemisphere, particularly the right parietal region, is most important in visual-spatial analysis.

6. The frontal lobes are large in humans, constituting nearly one-third of the cerebral hemispheres. They have three surfaces: lateral, medial, and orbitofrontal (see Figure 19.11). In this chapter we focused on the frontal cortex lying anterior to the motor, premotor, and limbic areas, which is called the prefrontal cortex (see Figure 19.1) and consists of higher-order heteromodal association cortex. The prefrontal cortex has corticoconnections with heteromodal association cortex (parietal, occipital, and temporal lobes), motor association cortex (frontal lobes), and limbic cortex (anterior cingulate and posterior orbital frontal cortex). Subcortical connections include the amygdala (connected with the orbital and medial portions of the frontal lobes by the uncinate fasciculus; see Figure 18.46C), the hippocampal formation (via the cingulate gyrus and parahippocampal gyrus; see Figure 18.9), thalamus (mediodorsal nucleus, medial pulvinar, and intralaminal nuclei; see Figure 7.8), and the basal ganglia (mainly via the head of the caudate nucleus; see Table 16.2; Figure 16.8).

7. Frontal lobe functions are quite diverse and apparently contradictory at times (see Tables 18.8, 19.9). The frontal lobes are crucial for the sophisticated decisions we make, and for the subtle social interactions we continually engage in as normal humans. The functions of the frontal lobes can be classified as important for (1) restraint, or inhibition of inappropriate behaviors; (2) initiative, or motivation to pursue positive or productive activities; and (3) order, or the capacity to correctly perform sequencing tasks and a variety of other cognitive operations. As we discussed in Chapter 11, after arrival at the primary visual cortex, visual information is processed in two streams of association cortex (see Figure 19.12). The dorsal pathways project to parieto-occipital association cortex. These pathways answer the question "Where?" by analyzing motion, as well as spatial relationships between objects and between the body and visual.
Brief Anatomical Study Guide (continued)

stimuli. The ventral pathways project to occipitotemporal associa-
tion cortex. These pathways answer the question "What?" by ana-
lyzing form, with specific regions identifying colors, faces, letters, and other visual stimuli (see Figure 19.13). The functions of these
two streams of higher-order visual information processing are well
illustrated by clinical syndromes of the dorsal and ventral visual as-
ociation pathways (see KCC 19.12).

6. We concluded this chapter with a discussion of dementia because it
demonstrates the functional importance of multiple neuroanatom-
ical systems (see Figure 19.14; KCC 19.16), and because discovering
new treatments for dementia and other presently incurable neuro-
logic disorders may lie just over the horizon if we continue through
study and investigation to increase our understanding of the brain.

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Syndromes of Visual Association Cortices


Functions of Human Inferior Occipitaltemporal Cortex


Basil Forebrain and Dementia


Epilogue

A Simple Working Model of the Mind

Where is the mind, and what is the mind? These questions have taunted scientists and philosophers throughout human history. Although we cannot yet answer these questions with certainty, investigation of the nervous system allows at least tentative conjectures in this realm.

Basic Assumptions

Although some would argue otherwise, the burden of evidence currently available suggests that the mind is manifested through ordinary physical processes located within the body. Note that these first two fundamental conjectures about where the mind is (in the body) and what the mind is (normal physical processes) remain hypotheses, perhaps with growing evidence in their favor, yet remaining unproven nonetheless. Within the body, one can conjecture further, the mind appears to be manifested in the nervous system. Interactions with the rest of the body and with the external environment are clearly important, yet most evidence suggests that the main functions of the mind are carried out within the nervous system. Finally, there appears to be a gradation in the importance of different parts of the nervous system in what we consider to be the mind. For example, although the peripheral nervous system and spinal cord play a significant role in channeling (and even in modulating) inputs and outputs to the remainder of the nervous system, the brain is likely more important to the mind. It should be emphasized, however, that there is no sharp division between “mind” and “nonmind” parts of the nervous system. A gradient of relative importance to mind may exist within the nervous system, yet reciprocal interactions ensure that the tapering of the gradient extends to all parts and possibly even to structures outside the nervous system.

We will now briefly summarize some of the abundant evidence supporting these conjectures before moving on to a more specific model of the mind. As for the location and nature of the mind, we know that physical injuries to the brain cause changes in mind function. Furthermore, changes in mind function vary from mild disturbances in cognition, to profound abnormalities in thought, to brain death, and they are related to both the anatomical sites involved and the mechanisms of the injury. We have seen numerous examples of this kind in the patients discussed throughout this book, and an overwhelming number of other examples exist in the literature.

In addition to negative effects of lesions, positive evidence for the participation of specific regions of the nervous system in mind functions comes from a multitude of studies employing electrophysiological recordings, functional neuroimaging, brain stimulation, and other methods. Lesion studies and recordings of neural function come not just from humans, but from other animals as well. In this regard, another line of evidence supporting the dependence of mind on brain comes from the parallel evolutionary trends in the complexity of brain and mind. However, despite these and a mountain of other studies, some lingering doubts remain as to
whether the mind is truly an ordinary physical process manifested within the nervous system.

**Summary and Model of Mind Functions**

Perhaps the reason for these lingering doubts is that many processes of the mind, particularly certain aspects of consciousness and emotions, remain difficult to explain fully in neurophysiological terms. Plausible and testable hypotheses for the relationship between brain activity and conscious thought are still under development. However, as understanding of the brain increases, functions of the mind once thought beyond the ken of scientific investigation come more and more firmly into the arena of neuroscience. Examples include memory, language, planning, and attention, to name a few. With continued investigation, my opinion is that consciousness will eventually migrate as well into the domain of accepted neurophysiological phenomena. In the interim, and as a conclusion to this neuroanatomy text, it may be useful to consider an overall framework for summarizing the functions of the nervous system and the mind, encompassing both those mechanisms that are relatively well understood and those still under intense investigation.

The first task in this summary is to discuss inputs and outputs (see figure). In the earlier chapters of this book, we discussed numerous sensory and motor systems. Different sensory inputs include vision, somatic sensation, hearing, smell, taste, and vestibular sense, as well as various chemical, mechanical, and other signals arising from the body’s internal milieu. Similarly, numerous different effector pathways leave the nervous system, including motor outputs to skeletal muscle, autonomic outputs to smooth muscle and glands, and neuromodulator outputs. These sensory and motor pathways are organized in multiple parallel channels entering and leaving the nervous system and subserving different sensory and motor functions.

Information processing in sensory and motor systems is hierarchically organized (see figure). For example, primary somatosensory information is processed at the most rudimentary level by the receptor cell and primary somatosensory neuron entering the spinal cord. This information is refined further and integrated with inputs and influences from other neurons at successively higher-order levels of processing in the nervous system, including the brainstem, thalamus, primary somatosensory cortex, unimodal association cortex, and heteromodal association cortex. In motor systems, similar hierarchical processing occurs, but in reverse. For example, higher-order signals for motor planning that arise from heteromodal association cortex are conveyed to successively lower levels of processing in premotor cortex, primary motor cortex, and lower motor neurons in the spinal cord before traveling to the periphery.

Information flow in the hierarchically organized sensory and motor pathways is not strictly linear, however. Direct connections exist between sensory and motor systems beginning at the spinal cord and continuing throughout successively higher levels of processing. In addition, from the spinal cord and upward, chains of interneurons of varying complexity further process sensory and motor information at various levels and carry information between these systems. Numerous feed-forward and feedback loops occur between higher-level and lower-level sensory and motor systems, involving both local and long-range network interactions. The integrated action of these hierarchically organized sensory and motor systems is capable of fantastic feats of information processing, including visual recognition of abstract shapes, programming movements, reacting to changes in response to the environment, understanding and formulation of written and spoken language, and even generation of sensory-motor mental images.

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**A Working Model of the Mind**

Parallel interconnected and hierarchically organized sensory and motor systems receive inputs, generate outputs, and perform internal processing on multiple levels, from relatively simple to highly abstract. Three additional special functions—consciousness, emotions and drives, and memory—act on these systems in a widely distributed manner, especially at the highest levels of processing.
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by signs, symptoms, and diagnoses

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