Neurologic diseases are common and costly. According to recent estimates by the World Health Organization, neurologic disorders affect over 1 billion people worldwide (Table 1-1), constitute 6.3% of the global burden of disease, and cause 12% of global deaths. Most patients with neurologic symptoms seek care from internists and other generalists rather than from neurologists. Because therapies now exist for many neurologic disorders, a skillful approach to diagnosis is essential. Errors commonly result from an overreliance on costly neuroimaging procedures and laboratory tests, which, while useful, do not substitute for an adequate history and examination. The proper approach to the patient with a neurologic illness begins with the patient and focuses the clinical problem fi rst in anatomic and then in pathophysiologic terms; only then should a specifi c diagnosis be entertained. This method ensures that technology is judiciously applied, a correct diagnosis is established in an effi cient manner, and treatment is promptly initiated. APPROACH TO THE PATIENT WITH NEUROLOGIC DISEASE CHAPTER 1 TABLE 1-1 PREVALENCE OF NEUROLOGIC AND PSYCHIATRIC DISEASES WORLDWIDE DISORDER PATIENTS, MILLIONS Nutritional disorders and neuropathies 352 Migraine 326 Trauma 170 Cerebrovascular diseases 61 Epilepsy 50 Dementia 24 Neurologic infections 18 Source: World Health Organization estimates, 2002–2005. THE NEUROLOGIC METHOD LOCATE THE LESION(S) The fi rst priority is to identify the region of the nervous system that is likely to be responsible for the symptoms. Can the disorder be mapped to one specifi c location, is it multifocal, or is a diffuse process present? Are the symptoms restricted to the nervous system, or do they arise in the context of a systemic illness? Is the problem in the central nervous system (CNS), the peripheral nervous system (PNS), or both? If in the CNS, is the cerebral cortex, basal ganglia, brainstem, cerebellum, or spinal cord responsible? Are the pain-sensitive meninges involved? If in the PNS, could the disorder be located in peripheral nerves and, if so, are motor or sensory nerves primarily affected, or is a lesion in the neuromuscular junction or muscle more likely? The fi rst clues to defi ning the anatomic area of involvement appear in the history, and the examination is then directed to confi rm or rule out these impressions and to clarify uncertainties. A more detailed examination of a particular region of the CNS or PNS is often indicated. For example, the examination of a patient who presents with a history of ascending paresthesias and weakness should be directed toward deciding, among other things, if the location of the lesion is in the spinal cord or peripheral nerves. Focal back pain, a spinal cord sensory level, and incontinence suggest a spinal cord origin, whereas a stocking-glove pattern of sensory loss suggests peripheral nerve disease; arefl exia usually indicates peripheral neuropathy but may also be present with spinal shock in acute spinal cord disorders. Deciding “where the lesion is” accomplishes the task of limiting the possible etiologies to a manageable, fi nite number. In addition, this strategy safeguards against making serious errors. Symptoms of recurrent vertigo, CHAPTER 1 3Approach to the Patient with Neurologic Disease diplopia, and nystagmus should not trigger “multiple sclerosis” as an answer (etiology) but “brainstem” or “pons” (location); then a diagnosis of brainstem arteriovenous malformation will not be missed for lack of consideration. Similarly, the combination of optic neuritis and spastic ataxic paraparesis should initially suggest optic nerve and spinal cord disease; multiple sclerosis (MS), CNS syphilis, and vitamin B12 deficiency are treatable disorders that can produce this syndrome. Once the question, “Where is the lesion?” is answered, then the question, “What is the lesion?” can be addressed. DEFINE THE PATHOPHYSIOLOGY Clues to the pathophysiology of the disease process may also be present in the history. Primary neuronal (gray matter) disorders may present as early cognitive disturbances, movement disorders, or seizures, whereas white matter involvement produces predominantly “long tract” disorders of motor, sensory, visual,

and cerebellar pathways. Progressive and symmetric symptoms often have a metabolic or degenerative origin; in such cases lesions are usually not sharply circumscribed. Thus, a patient with paraparesis and a clear spinal cord sensory level is unlikely to have vitamin B12 deficiency as the explanation. A Lhermitte symptom (electric shock–like sensations evoked by neck flexion) is due to ectopic impulse generation in white matter pathways and occurs with demyelination in the cervical spinal cord; among many possible causes, this symptom may indicate MS in a young adult or compressive cervical spondylosis in an older person. Symptoms that worsen after exposure to heat or exercise may indicate conduction block in demyelinated axons, as occurs in MS. A patient with recurrent episodes of diplopia and dysarthria associated with exercise or fatigue may have a disorder of neuromuscular transmission such as myasthenia gravis. Slowly advancing visual scotoma with luminous edges, termed fortification spectra, indicates spreading cortical depression, typically with migraine. THE NEUROLOGIC HISTORY Attention to the description of the symptoms experienced by the patient and substantiated by family members and others often permits an accurate localization and determination of the probable cause of the complaints, even before the neurologic examination is performed. The history also helps to bring a focus to the neurologic examination that follows. Each complaint should be pursued as far as possible to elucidate the location of the lesion, the likely underlying pathophysiology, and potential etiologies. For example, a patient complains of weakness of the right arm. What are the associated features? Does the patient have difficulty with brushing hair or reaching upward (proximal) or buttoning buttons or opening a twist-top bottle (distal)? Negative associations may also be crucial. A patient with a right hemiparesis without a language deficit likely has a lesion (internal capsule, brainstem, or spinal cord) different from that of a patient with a right hemiparesis and aphasia (left hemisphere). Other pertinent features of the history include the following: 1. Temporal course of the illness. It is important to determine the precise time of appearance and rate of progression of the symptoms experienced by the patient. The rapid onset of a neurologic complaint, occurring within seconds or minutes, usually indicates a vascular event, a seizure, or migraine. The onset of sensory symptoms located in one extremity that spread over a few seconds to adjacent portions of that extremity and then to the other regions of the body suggests a seizure. A more gradual onset and less well-localized symptoms point to the possibility of a transient ischemic attack (TIA). A similar but slower temporal march of symptoms accompanied by headache, nausea, or visual disturbance suggests migraine. The presence of “positive” sensory symptoms (e.g., tingling or sensations that are difficult to describe) or involuntary motor movements suggests a seizure; in contrast, transient loss of function (negative symptoms) suggests a TIA. A stuttering onset where symptoms appear, stabilize, and then progress over hours or days also suggests cerebrovascular disease; an additional history of transient remission or regression indicates that the process is more likely due to ischemia rather than hemorrhage. A gradual evolution of symptoms over hours or days suggests a toxic, metabolic, infectious, or inflammatory process. Progressing symptoms associated with the systemic manifestations of fever, stiff neck, and altered level of consciousness imply an infectious process. Relapsing and remitting symptoms involving different levels of the nervous system suggest MS or other inflammatory processes. Slowly progressive symptoms without remissions are characteristic of neurodegenerative disorders, chronic infections, gradual intoxications, and neoplasms. 2. Patients’ descriptions of the complaint. The same words often mean different things to different patients. “Dizziness” may imply impending syncope, a sense of disequilibrium, or true spinning vertigo. “Numbness” may mean a complete loss of feeling, a positive sensation such as tingling, or even weakness. “Blurred vision” may be

used to describe unilateral visual loss, as in transient monocular blindness, or diplopia. The interpretation of the true meaning of the words used by patients to describe symptoms SECTION I Introduction to Neurology 4 obviously becomes even more complex when there are differences in primary languages and cultures. 3. Corroboration of the history by others. It is almost always helpful to obtain additional information from family, friends, or other observers to corroborate or expand the patient's description. Memory loss, aphasia, loss of insight, intoxication, and other factors may impair the patient's capacity to communicate normally with the examiner or prevent openness about factors that have contributed to the illness. Episodes of loss of consciousness necessitate that details be sought from observers to ascertain precisely what has happened during the event. 4. Family history. Many neurologic disorders have an underlying genetic component. The presence of a Mendelian disorder, such as Huntington's disease or Charcot-Marie-Tooth neuropathy, is often obvious if family data are available. More detailed questions about family history are often necessary in polygenic disorders such as MS, migraine, and many types of epilepsy. It is important to elicit family history about all illnesses, in addition to neurologic and psychiatric disorders. A familial propensity to hypertension or heart disease is relevant in a patient who presents with a stroke. There are numerous inherited neurologic diseases that are associated with multisystem manifestations that may provide clues to the correct diagnosis (e.g., neurofibromatosis, Wilson's disease, neuro-ophthalmic syndromes). 5. Medical illnesses. Many neurologic diseases occur in the context of systemic disorders. Diabetes mellitus, hypertension, and abnormalities of blood lipids predispose to cerebrovascular disease. A solitary mass lesion in the brain may be an abscess in a patient with valvular heart disease, a primary hemorrhage in a patient with a coagulopathy, a lymphoma or toxoplasmosis in a patient with AIDS, or a metastasis in a patient with underlying cancer. Patients with malignancy may also present with a neurologic paraneoplastic syndrome (Chap. 44) or complications from chemotherapy or radiotherapy. Marfan's syndrome and related collagen disorders predispose to dissection of the cranial arteries and aneurysmal subarachnoid hemorrhage; the latter may also occur with polycystic kidney disease. Various neurologic disorders occur with dysthyroid states or other endocrinopathies. It is especially important to look for the presence of systemic diseases in patients with peripheral neuropathy. Most patients with coma in a hospital setting have a metabolic, toxic, or infectious cause. 6. Drug use and abuse and toxin exposure. It is essential to inquire about the history of drug use, both prescribed and illicit. Sedatives, antidepressants, and other psychoactive medications are frequently associated with acute confusional states in the elderly. Aminoglycoside antibiotics may exacerbate symptoms of weakness in patients with disorders of neuromuscular transmission, such as myasthenia gravis, and may cause dizziness secondary to ototoxicity. Vincristine and other antineoplastic drugs can cause peripheral neuropathy, and immunosuppressive agents such as cyclosporine can produce encephalopathy. Excessive vitamin ingestion can lead to disease; for example vitamin A and pseudotumor cerebri, or pyridoxine and peripheral neuropathy. Many patients are unaware that overthe-counter sleeping pills, cold preparations, and diet pills are actually drugs. Alcohol, the most prevalent neurotoxin, is often not recognized as such by patients, and other drugs of abuse such as cocaine and heroin can cause a wide range of neurologic abnormalities. A history of environmental or industrial exposure to neurotoxins may provide an essential clue; consultation with the patient's coworkers or employer may be required. 7. Formulating an impression of the patient. Use the opportunity while taking the history to form an impression of the patient. Is the information forthcoming, or does it take a circuitous course? Is there evidence of anxiety, depression, or hypochondriasis? Are there any clues to

defects in language, memory, insight, or inappropriate behavior? The neurologic assessment begins as soon as the patient comes into the room and the first introduction is made. THE NEUROLOGIC EXAMINATION The neurologic examination is challenging and complex; it has many components and includes a number of skills that can be mastered only through repeated use of the same techniques on a large number of individuals with and without neurologic disease. Mastery of the complete neurologic examination is usually important only for physicians in neurology and associated specialties. However, knowledge of the basics of the examination, especially those components that are effective in screening for neurologic dysfunction, is essential for all clinicians, especially generalists. There is no single, universally accepted sequence of the examination that must be followed, but most clinicians begin with assessment of mental status followed by the cranial nerves, motor system, sensory system, coordination, and gait. Whether the examination is basic or comprehensive, it is essential that it be performed in an orderly and systematic fashion to avoid errors and serious omissions. Thus, the best way to learn and gain expertise in the examination is to choose one's own approach and practice it frequently and do it in the same exact sequence each time. The detailed description of the neurologic examination that follows describes the more commonly used CHAPTER 1 5Approach to the Patient with Neurologic Disease parts of the examination, with a particular emphasis on the components that are considered most helpful for the assessment of common neurologic problems. Each section also includes a brief description of the minimal examination necessary for adequate screening for abnormalities in a patient who has no symptoms suggesting neurologic dysfunction. A screening examination done in this way can be completed in 3–5 min. Several additional points about the examination are worth noting. First, in recording observations, it is important to describe what is found rather than to apply a poorly defined medical term (e.g., "patient groans to sternal rub" rather than "obtunded"). Second, subtle CNS abnormalities are best detected by carefully comparing a patient's performance on tasks that require simultaneous activation of both cerebral hemispheres (e.g., eliciting a pronator drift of an outstretched arm with the eyes closed; extinction on one side of bilaterally applied light touch, also with eyes closed; or decreased arm swing or a slight asymmetry when walking). Third, if the patient's complaint is brought on by some activity, reproduce the activity in the office. If the complaint is of dizziness when the head is turned in one direction, have the patient do this and also look for associated signs on examination (e.g., nystagmus or dysmetria). If pain occurs after walking two blocks, have the patient leave the office and walk this distance and immediately return, and repeat the relevant parts of the examination. Finally, the use of tests that are individually tailored to the patient's problem can be of value in assessing changes over time. Tests of walking a 7.5-m (25-ft) distance (normal, 5–6 s; note assistance, if any), repetitive finger or toe tapping (normal, 20–25 taps in 5 s), or handwriting are examples. MENTAL STATUS EXAMINATION • The bare minimum: During the interview, look for difficulties with communication and determine whether the patient has recall and insight into recent and past events. The mental status examination is underway as soon as the physician begins observing and talking with the patient. If the history raises any concern for abnormalities of higher cortical function or if cognitive problems are observed during the interview, then detailed testing of the mental status is indicated. The patient's ability to understand the language used for the examination, cultural background, educational experience, sensory or motor problems, or comorbid conditions need to be factored into the applicability of the tests and interpretation of results. The Folstein mini-mental status examination (MMSE) (Table 29-5) is a standardized screening examination of cognitive function that is extremely easy to administer and takes <10 min to

complete. Using age-adjusted values for defining normal performance, the test is ~85% sensitive and 85% specific for making the diagnosis of dementia that is moderate or severe, especially in educated patients. When there is sufficient time available, the MMSE is one of the best methods for documenting the current mental status of the patient, and this is especially useful as a baseline assessment to which future scores of the MMSE can be compared. Individual elements of the mental status examination can be subdivided into level of consciousness, orientation, speech and language, memory, fund of information, insight and judgment, abstract thought, and calculations. Level of consciousness is the patient's relative state of awareness of the self and the environment, and ranges from fully awake to comatose. When the patient is not fully awake, the examiner should describe the responses to the minimum stimulus necessary to elicit a reaction, ranging from verbal commands to a brief, painful stimulus such as a squeeze of the trapezius muscle. Responses that are directed toward the stimulus and signify some degree of intact cerebral function (e.g., opening the eyes and looking at the examiner or reaching to push away a painful stimulus) must be distinguished from reflex responses of a spinal origin (e.g., triple flexion response—flexion at the ankle, knee, and hip in response to a painful stimulus to the foot). Orientation is tested by asking the person to state his or her name, location, and time (day of the week and date); time is usually the first to be affected in a variety of conditions. Speech is assessed by observing articulation, rate, rhythm, and prosody (i.e., the changes in pitch and accentuation of syllable and words). Language is assessed by observing the content of the patient's verbal and written output, response to spoken commands, and ability to read. A typical testing sequence is to ask the patient to name successively more detailed components of clothing, a watch, or a pen; repeat the phrase "No ifs, ands, or buts"; follow a three-step, verbal command; write a sentence; and read and respond to a written command. Memory should be analyzed according to three main time scales: (1) immediate memory is assessed by saying a list of three items and having the patient repeat the list immediately, (2) short-term memory is tested by asking the patient to recall the same three items 5 and 15 min later, and (3) long-term memory is evaluated by determining how well the patient is able to provide a coherent chronologic history of his or her illness or personal events. Fund of information is assessed by asking questions about major historic or current events, with special attention to educational level and life experiences. SECTION I Introduction to Neurology 6 Abnormalities of insight and judgment are usually detected during the patient interview; a more detailed assessment can be elicited by asking the patient to describe how he or she would respond to situations having a variety of potential outcomes (e.g., "What would you do if you found a wallet on the sidewalk?"). Abstract thought can be tested by asking the patient to describe similarities between various objects or concepts (e.g., apple and orange, desk and chair, poetry and sculpture) or to list items having the same attributes (e.g., a list of four-legged animals). Calculation ability is assessed by having the patient carry out a computation that is appropriate to the patient's age and education (e.g., serial subtraction of 7 from 100 or 3 from 20; or word problems involving simple arithmetic). CRANIAL NERVE EXAMINATION • The bare minimum: Check the fundi, visual fields, pupil size and reactivity, extraocular movements, and facial movements. The cranial nerves (CN) are best examined in numerical order, except for grouping together CN III, IV, and VI because of their similar function. CN I (olfactory) Testing is usually omitted unless there is suspicion for inferior frontal lobe disease (e.g., meningioma). With eyes closed, ask the patient to sniff a mild stimulus such as toothpaste or coffee and identify the odorant. CN II (optic) Check visual acuity (with eyeglasses or contact lens correction) using a Snellen chart or similar tool. Test the visual fields by confrontation, i.e., by comparing the patient's visual

fields to your own. As a screening test, it is usually sufficient to examine the visual fields of both eyes simultaneously; individual eye fields should be tested if there is any reason to suspect a problem of vision by the history or other elements of the examination, or if the screening test reveals an abnormality. Face the patient at a distance of approximately 0.6–1.0 m (2–3 ft) and place your hands at the periphery of your visual fields in the plane that is equidistant between you and the patient. Instruct the patient to look directly at the center of your face and to indicate when and where he or she sees one of your fingers moving. Beginning with the two inferior quadrants and then the two superior quadrants, move your index finger of the right hand, left hand, or both hands simultaneously and observe whether the patient detects the movements. A single small-amplitude movement of the finger is sufficient for a normal response. Focal perimetry and tangent screen examinations should be used to map out visual field defects fully or to search for subtle abnormalities. Optic fundi should be examined with an ophthalmoscope, and the color, size, and degree of swelling or elevation of the optic disc noted, as well as the color and texture of the retina. The retinal vessels should be checked for size, regularity, arterial-venous nicking at crossing points, hemorrhage, exudates, etc. CN III, IV, VI (oculomotor, trochlear, abducens) Describe the size and shape of pupils and reaction to light and accommodation (i.e., as the eyes converge while following your finger as it moves toward the bridge of the nose). To check extraocular movements, ask the patient to keep his or her head still while tracking the movement of the tip of your finger. Move the target slowly in the horizontal and vertical planes; observe any paresis, nystagmus, or abnormalities of smooth pursuit (saccades, oculomotor ataxia, etc.). If necessary, the relative position of the two eyes, both in primary and multidirectional gaze, can be assessed by comparing the reflections of a bright light off both pupils. However, in practice it is typically more useful to determine whether the patient describes diplopia in any direction of gaze; true diplopia should almost always resolve with one eye closed. Horizontal nystagmus is best assessed at 45° and not at extreme lateral gaze (which is uncomfortable for the patient); the target must often be held at the lateral position for at least a few seconds to detect an abnormality. CN V (trigeminal) Examine sensation within the three territories of the branches of the trigeminal nerve (ophthalmic, maxillary, and mandibular) on each side of the face. As with other parts of the sensory examination, testing of two sensory modalities derived from different anatomic pathways (e.g., light touch and temperature) is sufficient for a screening examination. Testing of other modalities, the corneal reflex, and the motor component of CN V (jaw clench—masseter muscle) is indicated when suggested by the history. CN VII (facial) Look for facial asymmetry at rest and with spontaneous movements. Test eyebrow elevation, forehead wrinkling, eye closure, smiling, and cheek puff. Look in particular for differences in the lower versus upper facial muscles; weakness of the lower two-thirds of the face with preservation of the upper third suggests an upper motor neuron lesion, whereas weakness of an entire side suggests a lower motor neuron lesion.

STORAGE AND TRANSMISSION OF GENETIC INFORMATION NUCLEIC ACIDS The genetic material of all known organisms is nucleic acid: deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). Nucleic acids act as an information storehouse. They also actively

participate in the reading and transmission of stored information within the cell and from one cell generation to the next. The usual flow of genetic information is from DNA to RNA to protein. The transition from DNA to RNA is called transcription, and the transition from RNA to protein is called translation. The direction of flow from DNA to RNA to protein was considered the “central dogma” in biologic sciences because most organisms exhibit this directionality in the expression of genetic information. However, it was found that some viruses, including retroviruses and the virus that causes autoimmune deficiency syndrome, transmit information from RNA to DNA using an enzyme called reverse transcriptase. Nucleic acids are polymers comprised of nucleotides (generally four different types) chemically linked together in chains that can be many millions of units long. The number of possible nucleic acid combinations n units long is thus 4n . A nucleic acid only 10 units in length therefore has 4 10 possible sequences. Each nucleotide in the chain contains a nitrogenous base, a five-carbon sugar, and a phosphate group. The sequence of bases is the form in which the genetic information is coded. There are two types of bases: pyrimidines and purines. Pyrimidines are six-membered rings and include cytosine (C), thymine (T), and uracil (U). Purines are fused five- and six-membered rings and include adenine (A) and guanine (G). The chemical structures of the bases is shown in Figure 1-1. Bases C, A, and G are found in both DNA and RNA. T is specific to DNA, and U is specific to RNA. FIGURE 1-1. Purines and pyrimidines. Nucleosides are constituted by a nitrogenous base linked to a five-carbon sugar (pentose). The linkage is from the N1 position of the pyrimidines or from the N9 position of the purines to the carbon at position 1 on the pentose. DNA and RNA use different pentose sugars. The sugar in DNA is deoxyribose, and the pentose in RNA is ribose. The difference in the two sugars is a hydroxyl group at the 2' position on the sugar. Nucleotides are nucleoside phosphates. A nucleotide is formed when a phosphate group is added to the 5' position on the pentose. The nucleotides that form the nucleic acid chain are connected in a very specific way: The 5' position of one pentose ring is connected to the 3' position of the next pentose ring by a phosphate group. The connection is called a phosphodiester bond. DNA The DNA backbone is made up of bonded sugar and phosphate groups in which a phosphate group connects the 5' carbon of one sugar to the 3' carbon of the next sugar in the chain by a phosphodiester bond. As shown in Figure 1-2, the beginning of the DNA chain has a phosphate group attached to the 5' carbon of deoxyribose, whereas the end of the chain has an OH group on the 3' carbon of deoxyribose. FIGURE 1-2. The backbone of DNA is made of bonded sugar and phosphate groups in which a phosphate group connects the 5' carbon of one sugar to the 3' carbon of the next sugar in the chain. The beginning of the chain has a phosphate group attached to the 5' carbon of deoxyribose. DNA is a double helix. It is a double-stranded polymer. The bases of each chain face inward, with the restriction that a purine is always paired opposite to a pyrimidine; thus, a G on one strand is paired with a C on the other, and an A is paired with a T. The sugar phosphates are on the backbone of the helix. The resulting negative charge on the outside of the helix is neutralized in the chromosome by metal ions or positively charged proteins. The two polynucleotide chains in the double helix are connected by hydrogen bonds between the bases. As noted earlier, G hydrogen-bonds specifically with a C, whereas an A can only hydrogen-bond with a T. The resulting base pairs are said to be complementary. As shown in Figure 1-3, the GC base pair has three hydrogen bonds, and the AT base pair has only two hydrogen bonds. Each strand can serve as the template for the synthesis of the other, enabling faithful reproduction of the genetic code. FIGURE 1-3. Base pairs are formed by hydrogen bonds. T=A; GºC. The two polynucleotide chains of the DNA double helix run in opposite directions (antiparallel). Thus, as one strand runs in the 5' to the 3' direction, the

partner strand runs in the 3' to 5' direction, as in the following example: 5' P A G T C T G C C A OH 3' 3' HO T C A G A C G G T P 5' DNA can be methylated in the carbon-5 position of cytosine to form 5-methylcytosine. This occurs in animals in DNA locations where the cytosine is followed on the same strand by guanine. The pattern of methylation is passed on when the DNA replicates. RNA In RNA, the pyrimidine uracil replaces the DNA base thymine, and the pentose ribose is used instead of deoxyribose in DNA. During the synthesis of RNA from a DNA template, adenine in DNA is transcribed into uracil in RNA. Because the pentose ribose is used in RNA instead of deoxyribose, this produces a ribonucleotide having a 2' OH group on the sugar, whereas the 2' OH group is not present in DNA. The important consequence is that RNA is much less stable than DNA. RNA is highly base labile. Although RNA can have a complex secondary structure, it is single stranded, not double stranded like DNA. RNA is transcribed from a DNA template and is the first step by which the genetic information of DNA is converted into the synthesis of specific proteins. A single strand of RNA is generated that is identical in its sequence to one of the strands of the DNA. The DNA strand that has the same sequence (with T instead of U) as the messenger RNA (mRNA) is the coding, or positive, strand; the opposite antiparallel strand is the anticoding, or negative, strand. The RNA itself then becomes the template (mRNA) for translation into the sequence of amino acids that comprise the protein polypeptide. Three main types of RNA are present in the cell: mRNA, ribosomal RNA (rRNA), and transfer RNA (tRNA). mRNA encodes the sequence for all cellular proteins; however, most initial transcripts of mRNA contain large pieces of intervening sequences, or introns, that must be spliced out to leave the coding sequences, or exons. At the 3' end of most mRNA molecules is a poly(A) tail of 150 to 250 adenine nucleotides. The mRNA also has an untranslated leader and tailer sequence at both ends. rRNA does not code for protein. Instead, it comprises part of the machinery that decodes the information in the mRNA. tRNA also does not code for protein. It reads off the mRNA triplet code and matches it with the correct amino acid. tRNA contains specific bases not found in other RNAs: inosine, pseudouridine, and dihydrouridine. At the end of each tRNA is an acceptor arm whose free end is aminoacetylated, or carries the specific amino acid. Another arm on the tRNA contains the anticodon, which recognizes the complementary mRNA codon. Thus, mRNA functions as a transportable copy of the blueprint for the synthesis of protein, and tRNA functions as part of the protein synthetic assembly line. NUCLEASES AND POLYMERASES Endonucleases are enzymes that cleave bonds within a nucleic acid chain. They may be specific for RNA, DNA, or hybrids of RNA-DNA or DNA-DNA. Restriction enzymes are a special class of endonucleases that recognize specific short sequences of DNA and cleave the DNA at or next to the recognition sequence. These enzymes are isolated from bacteria and are named after the genus (first letter) and species (second two letters) of the bacteria they are derived from. Because a bacteria can make more than one restriction enzyme, the specific member is designated by a roman numeral (e.g., EcoRI: Escherichia coli, strain R, first enzyme from that strain). Restriction enzymes cut DNA at palindromes. The palindrome is a sequence of DNA that is the same when one strand is read left to right (5' to 3') or the other is read right to left (still 5' to 3' because of the antiparallel rule). An example for EcoRI is 5' GAATTC 3' 3' CTTAAG 5' Restriction endonucleases are now standard tools in molecular biology and permit the cutting of large stretches of DNA at very precise points. They allow fragments of DNA to be “fingerprinted” by the size of the cleaved fragments. Moreover, a restriction enzyme can cleave the DNA so as to leave blunt ends, or staggered “sticky” ends with 5' or 3' overhangs. Because of this property, restriction enzymes are powerful tools to analyze DNA sequences and to create cleaved pieces of DNA that can be shuffled, recombined, and reannealed in the process of

DNA cloning. Polymerases are enzymes that synthesize nucleic acid chains. RNA polymerases synthesize RNA, and DNA polymerases synthesize DNA. All polymerases require a template (nucleic acid strand to be synthesized), which is complementary to the strand being synthesized. They also need a primer, which is a short sequence (oligonucleotide) that is complementary to the 3' end of the template. This provides a free 3' OH end at which the polymerase starts to build a new chain. Reverse transcriptase is a special polymerase that has, as its primary function, the ability to use RNA as a template to generate a copy in the form of DNA. It is an important enzyme in the life cycle of the human immunodeficiency viruses that cause autoimmune deficiency syndrome and other disorders, and as such, is a prime target for anti–human immunodeficiency virus therapeutics. Reverse transcriptase is also a unique reagent that can be used to create complementary DNA (copy) from mRNA extracted from cells, and therefore it is used in complementary DNA cloning. The genetic code is a series of three mRNA nucleotides; each is a codon that encodes one amino acid (Fig. 1-4). Three codons are nonsense or termination codons. The genetic code is degenerate, with more than one codon for most amino acids. FIGURE 1-4. Genetic code. The first base of each codon is presented vertically outside the left margin. The second base of each codon is presented horizontally above and below the chart. The third (wobble) position of each codon is presented just within the left margin. GENES AND THEIR EXPRESSION A gene is a unit of inheritance that carries the information representing a polypeptide or a structural RNA molecule. Genes are stable information packets transmitted from one generation to the next. A gene includes “control” regions that precede and follow a central coding region and that include the sequences encoding the protein product. The coding region is preceded by a leader sequence and followed by a trailer. The leader and trailer are not translated into protein and represent the 5' and 3' untranslated regions of the mRNA that often function in regulating the half-life of the mRNA or in controlling translation. The coding region is divided into alternating exons and introns. The exons, which are represented in the mature spliced RNA product, are interrupted or intervened by the introns. The introns are spliced out and do not encode amino acids. The reason for the introns is not obvious, but it is a hallmark of all higher order species in evolution. A gene family is a set of genes whose exons are related. A gene cluster is a group of genes related to each other that are adjacent. Transcription is the process by which a single-stranded RNA is generated that is identical in sequence with the coding strand of the DNA. A transcription unit is a sequence of DNA that can be transcribed by RNA polymerase into a single RNA, beginning at an initiation start point and ending at a terminator. Three types of genes are found in eukaryotes that are differentiated from each other by the type of RNA polymerase that transcribes the gene: RNA polymerase I, II, and III. RNA polymerase II produces heterogeneous nuclear RNA, which becomes mRNA after processing and splicing. Proteins are encoded by mRNA. In the vast majority of cases, therefore, it is the protein product of a polymerase II gene that finally determines gene activity. The genetic code that transfers nucleotide sequences into amino acid sequences is organized as triplets of nucleotides forming a codon. Each codon is recognized by the translational machinery as representing an amino acid. Some codons are used as traffic signals that tell the machinery to start and stop translation (therefore their designation as start and stop codons). Mutations in important tumor suppressor genes, such as the breast cancer gene BRCA1 and the colon cancer gene APC, are frequently mutations that convert a codon that normally encodes an amino acid to a stop codon. This results in a prematurely truncated and, therefore, inactive protein. A series of potential points for control of gene expression and functional protein production exist. These include activation of the gene chromatin complex, initiation of transcription, processing and capping of the RNA

transcript, splicing of the RNA, polyadenylation of the RNA transcript, transport of the RNA to the cytoplasm, degradation of the RNA, translation of the mRNA into protein, correct folding and posttranslational modifications of the protein, transport and secretion of the protein, cleavage of the protein, or combination with inhibitors or activators. In the nucleus, DNA exists in a complex with proteins to form chromatin. Structural changes occur to the chromatin to activate the regions of the DNA and unwind regions of the DNA. The eukaryotic chromatin is made from nucleosomes. A nucleosome contains approximately 200 base pairs (bp) of DNA that is wrapped around an octomer of histone proteins. In between the nucleosomes are linker regions that can be digested by DNAases. Transcribable active DNA is particularly sensitive to DNAases. Between 2% and 7% of cytosines in animal DNA are modified by methylation, most often in sites where a C is followed by a G (CpG doublets). Methylation most often appears in genes that are not being expressed. DNA that is actively transcribed is often undermethylated. CpG-rich islands are often found upstream of constitutively transcribed genes near or at the promoters. This fact has been used by molecular geneticists to identify potential transcription units in large stretches of sequenced genomic DNA. TRANSCRIPTION CONTROL: PROMOTERS AND ENHANCERS A promoter is a region of DNA that is involved in binding of RNA polymerase (and associated factors) to initiate transcription and are therefore cis-acting sites. Promoters for polymerase I and II are usually located upstream of the transcription unit (initiation start point). Promoters for polymerase III are located downstream. Transcription factors are trans-acting elements that recognize specific cis-acting sites in the promoter. Cis-acting sites can be spread over regions of DNA that are greater than 100 bp. In general, they can be tentatively identified by footprinting experiments that localize sequences covered by transcription factors. In this type of experiment, a putative promoter DNA binding sequence is allowed to bind to the transcription factor. The DNA is radioactively labeled, digested with nucleases, and then electrophoresed on a sequencing gel. In the region of the binding site, access to nuclease digestion is blocked because of the “footprint” of the transcription factor. Once a candidate promoter sequence is mapped, it is possible to directly test its ability to regulate expression of a reporter gene that is positioned downstream. Promoters are characterized by short consensus sequences called boxes. The TATA box is usually located approximately 25 bp upstream from the start point of transcription. This consensus sequence of AT base pairs (e.g., TATAAA) is important in the correct positioning of the RNA polymerase II (in concert with a series of transcription factors) at the beginning of the initiation site. The CAAT box (often GGCCAATCT) is located approximately 80 bp upstream of the transcription start point. A large number of different transacting factors recognize the CAAT box. Its role is to determine the strength (frequency or rate of initiation events) of the promoter. The GC box comprises the sequence GGGCGG. It is found in multiple copies in either orientation. The GC box, usually upstream of the TATA box, is the binding site for the Sp1 transcription factor, which regulates the strength of the promoter. Enhancers are sequences that enhance initiation but may be located at a considerable distance from the start point upstream or downstream. Some enhancers have even been found within introns. Some transcription factors can bind to both promoters and enhancers. In retroviruses, enhancers are located in the viral long terminal repeats and are important for pathogenesis. Papillomaviruses contain enhancer elements that are specific for keratinocytes and thereby contribute to the specific tropism of the virus to these cells. Another example is the immunoglobulin cellular enhancer, which stimulates transcription in specific immune cell types. Response elements are consensus sequences that allow specific transcription factors to coordinate the transcription of a whole group of genes that all have the consensus sequences. Examples are the heat

shock response element, which responds to heat; the glucocorticoid response element, which responds to glucocorticoids; the metal response element; and the tumor promoting element (TRE). The TRE is a response element to TPA the carcinogenic promoting agent. It has the sequence TGACTCA. In response to TPA or phorbol ester, AP-1 transcription factors (a plurifunctional family including Jun and Fos) bind to the TRE. PROCESSING OF THE RNA TRANSCRIPT A cap is a complex methylated structure at the 5' end of mRNA that is essential for translation. The first base of a gene that is transcribed into an mRNA molecule is usually a purine (A or G). Almost immediately after transcription starts, a nuclear enzyme guanylyl transferase catalyzes the addition of a 5' G to the first transcribed base of the mRNA. This step is followed by a series of methylation events. The final cap structure maintains the stability of the mRNA transcript as it is forming. Processing of RNA includes termination and polyadenylation. All eukaryotic mRNAs (except histone genes) contain a poly(A) tail at their 3' end, which is added by poly(A) polymerase. A consensus sequence called the polyadenylation signal AAUAAA is located 10 to 30 bases upstream of the poly(A) tail. The polymerase transcribes through the polyadenylation signal, and after termination, an endonuclease cleaves the transcribed RNA at a site 10 to 30 bases downstream of the polyadenylation signal. The site of this event involves small nuclear ribonuclear particles. Once the cleavage occurs, the poly(A) polymerase adds A residues one by one to the 3' free end of the RNA. The poly(A) tail added to the end of the cleaved mRNA may assist the mRNA export out of the nucleus and may also be involved in the stability and lifespan of the mRNA molecule. Processing of the transcribed RNA is required to remove the introns and produce a continuous linear sequence as a template for translation into the protein polypeptide. The coding region of a gene consists of exons and introns. Splicing is the mechanism by which the introns are removed from the precursor RNA to form a mature mRNA. Splicing mechanisms differ depending on the type of RNA being spliced. Splicing of heterogeneous nuclear RNA requires a cap structure and is not complete until a poly(A) tail is added. The ends of the intron conform to the GT-AG rule, meaning that each intron in the gene begins with GT and ends with AG. The left 5' site is the donor site, and the right 3' site is the acceptor site. Alternative splicing refers to the possibility that there are variations in which exons are spliced together. A large complicated gene with many exons and introns can use alternative splicing to encode different proteins that are generated by different combinations of exons. Cellular genes for structural proteins, such as collagen, fibronectin, and myelin basic proteins, use alternative splicing to produce different proteins with different biologic functions. In this manner, a single gene can produce a number of protein isoforms using sequences within its “start” and “stop” borders. Translation is the process by which the nucleotide sequence of mRNA is converted into a sequence of amino acids to make a protein. As mentioned, the genetic information of the RNA is organized into triplets of bases called codons. Translation requires ribosomal RNA that combines with ribosomal protein to form ribosomes. The ribosomes are docking sites for adaptor molecules, such as tRNA, that can recognize specific codons and the correct amino acid specified by that codon. Thus, the tRNA translates the base sequence of the mRNA into the different language of the amino acid sequence of the protein. REPAIR OF DNA Correction of DNA sequence errors is critical to survival. Environmental factors, including radiation, mutagenic chemicals, and thermal energy, can induce errors in the DNA sequence. In addition, errors are occasionally introduced by DNA polymerases during replication. A certain low level of random DNA errors may be required to generate genotype variation to fuel Darwinian evolution. Nevertheless, if most errors were left uncorrected, then both proliferating and nonproliferating cells would accumulate so much genetic damage that they would no longer be viable. Moreover,

damage of DNA in germ cells can prevent normal offspring from developing. Although a significant body of knowledge has been accumulated about DNA polymerase proofreading and excision repair in E coli, many of the enzymes required for repairing DNA damage in eukaryotic cells are now being characterized. DNA repair mechanisms have significant roles in carcinogenesis (see Chapter 2). READING THE GENETIC CODE AND PRODUCTION OF ENCODED PROTEINS GENETIC CODE The genetic code refers to triplets of DNA or RNA and the amino acids they specify. A triplet code specifies 4 3 words; thus, there are 43 codons. The code is redundant because more than one codon can specify the same amino acid. An open reading frame is a string of codons that are flanked on the 5' side by an initiation codon and on the 3' side by a termination codon. All proteins start with methionine. The codon AUG specifies methionine and is therefore the initiation codon. Termination or nonsense codons are stop signals for the end of a protein chain. They include the codons UAA, UAG, and UGA. Protein synthesis proceeds from the amino-terminus (N-terminus) to the carboxy-terminus (C-terminus). Because of the triplet codon, each stretch of mRNA contains three potential open reading frames. The reading frame can be shifted by moving the starting point one or two bases to the right or left. Mutations in which a base is deleted or inserted within an exon are called frameshift mutations, because they would alter the reading frame of the sequence. RIBOSOMES Ribosomes are the protein synthesizing machinery that brings together the mRNA template and the charged tRNAs. The ribosomes contain two subunits. The small subunit is 40s; it contains an 18s rRNA and 40 proteins and is responsible for binding the tRNAs and the mRNAs. The large subunit, which catalyzes peptide bonds between amino acids on the growing polypeptide chain, has three rRNAs of 28S, 5.8S and 5S, as well as 50 proteins. Every tRNA has two properties: It can covalently link to the amino acid it recognizes to form a charged aminoacyl-tRNA, and it contains an anticodon that is complementary to the codon recognizing its amino acid. The anticodon recognizes the codon by complementary base pairing. Some of the base pairs in the third position can be nonstandard or can wobble. This permits one tRNA to recognize more than one codon. PROTEIN SYNTHESIS: INITIATION, ELONGATION, AND TERMINATION There are three general steps of protein synthesis: initiation, elongation, and termination. Initiation is the recognition by a specific initiating tRNA for the small ribosome subunit, along with guanosine triphosphate (GTP), and the initiating codon of the mRNA. A special tRNA met binds to the small ribosome subunit, and a molecule of GTP correctly positions the initiating AUG codon of the mRNA on the ribosomal subunit. In concert with several initiating factors, the large ribosomal subunit now binds to the small subunit, met ferrying-tRNA met becomes localized to the ribosome at the P site (peptidyl-tRNA). Elongation is the extension of the amino acid chain by introducing a second aminoacyl-tRNA to the proper site on the ribosome called the A site. With the help of elongation factors, the growing polypeptide chain is attached to the tRNA that brought in the previous amino acid. A peptide bond is formed between the carboxyl group of the methionine and the amino group of the incoming amino acid to make a dipeptide that is attached to the new tRNA. Peptide bond formation requires GTP hydrolysis, which furnishes energy for the reaction. Thus, each elongation step requires two GTPs. Elongation is continued with each new charged tRNA binding to the A site, peptide bond formation, and translocation of the peptidyl-tRNA to the P site (with displacement of the now uncharged tRNA from the P site). In each translocation, the ribosome moves three nucleotides downstream of the mRNA; therefore, more than one polypeptide chain can be produced from one mRNA simultaneously (Fig. 1-5). FIGURE 1-5. Synthesis of secretory proteins on the endoplasmic reticulum (ER). An elongated signal recognition particle (SRP) binds to the signal sequence, and then the SRP, nascent

polypeptide, and ribosome bind to the ER membrane through the SRP receptor. The signal sequence inserts into the ER membrane and is elongated. The signal sequence is cleaved in the ER lumen by signal peptidase. Carbohydrates are added to asparagine residues by enzymes on the luminal surface. After synthesis is complete, the ribosomes are released and the remaining C-terminus is transferred to the ER lumen. mRNA, messenger RNA. Termination occurs when the ribosome reaches the termination codon of the mRNA. A termination factor supports the recognition of the nonsense codon, the release of the last tRNA, and the dissociation of the subunits. This final step also requires GTP hydrolysis. Once mRNA is transcribed and translated, several factors affect its stability. Degradation of mRNA is a regulated process. Several sequence elements have been detected on mRNAs that regulate decay. An example is the ARE (AU-rich elements) that contain the consensus sequence AUUUA repeated once or several times within the 3' untranslated region.

Congenital Heart Disease Incidence Estimates of the incidence of congenital heart disease (CHD) range from 0.3% to 1.2% in live neonates.1 Th is represents the most common form of congenital pathology and a major cause of mortality during the neonatal period.2 As medical, interventional, and surgical therapies continue to improve, survival into adulthood has become the expectation for most congenital cardiovascular malformations.3 At present it is estimated that there are more than a million adults with CHD in the United States, surpassing the number of children similarly aff ected for the fi rst time in history. A similar trend of an increasing number of adults with CHD, also known as “grown-up congenital heart disease” (or GUCH) patients, has also been reported in Canada and several European countries.4-8 SECTION IV CHAPTER 14 A Practice of Anesthesia for Infants and Children 294 Overall, a bicuspid aortic valve (Video Clip 14-1) is the most common cardiac defect, occurring in up to 1% of the population.9,10 Ventricular septal defects (Video Clip 14-2) represent the next most common congenital lesion,9,11-15 followed by secundum atrial septal defects (Video Clip 14-3).9,16 Among the cyanotic conditions, tetralogy of Fallot is the most common, aff ecting nearly 6% of children with CHD.17 In the fi rst week of life, however, d-transposition of the great arteries is the most common cause of cardiac cyanosis, because a subset of infants with tetralogy of Fallot will either be acyanotic or mildly desaturated at birth so that their cardiac disease will go undetected until later in life. Segmental Approach to Diagnosis A number of classifi cation schemes have been proposed to characterize and categorize the various congenital cardiac malformations.18-24 Th e one known as “the segmental approach to the diagnosis of CHD” assumes a sequential, systematic analysis of the three major cardiac segments (atria, ventricles, and great arteries) to characterize the abnormalities in a given patient. Th e guiding principle of this approach is that specifi c cardiac chambers and vascular structures have characteristic morphologic properties that determine their identities, rather than their positions within the body.25 An organized, systematic identifi cation of all cardiac structures or segments and their relationships to each other (connections or alignments between the segments) is carried out to defi ne a given patient’s anatomy.26 Th e initial steps to characterize the anomalies and classify a child’s cardiovascular disease are to determine the cardiac position within the

thorax and the situs of the thoracic and abdominal organs. Th e position of the heart can be described in terms of its location within the thoracic cavity and the direction of the cardiac apex. For simplicity, the following approach is frequently used. Th e term levocardia indicates that the heart is in the left hemithorax, as is normally the case. Dextrocardia specifi es that the heart is located in the right hemithorax and mesocardia that the heart is displaced rightward but not completely in the right thoracic cavity. It is important to consider that an abnormal location of the heart within the thorax (cardiac malposition) may result from displacement of the heart by adjacent structures or underlying noncardiac malformations (e.g., diaphragmatic hernia, lung hypoplasia, scoliosis). Th e visceral situs or sidedness of the abdominal organs (liver and stomach) and atrial situs are considered independently. Th e visceral situs is classifi ed as solitus (normal arrangement of viscera; liver on the right, stomach on the left and single spleen on the left), inversus (inversion of viscera; liver on the left, stomach on the right), or ambiguous (indeterminate visceral position). Abnormal arrangements or sidedness of the abdominal viscera, heart, and lungs suggests a high likelihood of complex cardiovascular pathology. Th e atrial situs, atrioventricular connections, ventricular looping (referring to the position of the ventricles as a result of the direction of bending of the straight heart tube in early development), ventriculoarterial connections, and relationship between the great vessels are then delineated. Finally, any associated malformations are described, including number and size of septal defects if present, valvar and/or great vessel abnormalities, and so on. Whereas many types of congenital defects fall neatly into this classifi cation scheme, others, such as heterotaxy syndromes (a condition associated with malposition of the heart and abdominal organs) are often more diffi cult to precisely defi ne. Physiologic Classifi cation of Defects Th e wide spectrum of cardiovascular pathology in the pediatric age group presents a unique challenge to the clinician who does not specialize in the care of these children. Even for those with a focus or interest in cardiovascular disease, the range of structural defects and the varied associated hemodynamic perturbations can be overwhelming. Although the segmental approach is extremely helpful in characterizing CHD, there are many instances when a physiologic classifi cation system can facilitate understanding of the basic hemodynamic abnormalities common to a group of lesions, congenital or acquired, and assist in patient management.27,28 Several pathophysiologic classifi cation schemes have been proposed, including some that categorize structural defects into simple versus complex lesions, consider the presence or absence of cyanosis or whether pulmonary blood fl ow is increased or decreased, and so on.29-31 Th e following classifi cation approach groups pediatric heart disease into six broad categories according to the underlying physiology or common features of the pathologies. Volume Overload Lesions Volume overload lesions are typically due to left-to-right shunting at the atrial, ventricular, or great artery levels. In general, if the location of the left-to-right shunt is proximal to the mitral valve (e.g., as is the case in atrial septal defects, partial anomalous pulmonary venous return, or unobstructed total anomalous pulmonary venous return), right heart dilation will occur. Lesions distal to the mitral valve (e.g., ventricular septal defect, patent ductus arteriosus, truncus arteriosus) lead to left-sided heart dilation. Children with atrioventricular septal defects (also known as atrioventricular canal defects) also fi t into this category. Th e magnitude of the shunt and resultant pulmonary to systemic blood fl ow ratio (Q. p : Q. s) dictates the presence and severity of the symptoms and similarly guides medical and surgical therapies. Diuretic therapy and afterload reduction are benefi cial in controlling pulmonary overcirculation and ensuring adequate systemic cardiac output. Transcatheter approaches or surgical interventions may be required to address the primary pathology associated with ventricular volume overload

(see Chapter 20). Obstruction to Systemic Blood Flow Lesions characterized by systemic outfl ow tract obstruction include those with ductal-dependent systemic blood fl ow. Th ese range from critical aortic stenosis, severe coarctation of the aorta, interruption of the aortic arch, and hypoplastic left heart syndrome. Prostaglandin E1 infusion maintains ductal patency and ensures adequate systemic blood fl ow until either surgical or transcatheter intervention is performed in the fi rst few days of life to relieve the systemic outfl ow tract obstruction. Often, inotropic and/or mechanical ventilatory support is necessary. Many of these infants also have signifi cantly increased pulmonary blood fl ow with a high Q. p : Q. s ratio, requiring diuretic therapy and manipulation of the systemic and pulmonary vascular resistances to control blood fl ow. Obstruction to Pulmonary Blood Flow Lesions with pulmonary outfl ow tract obstruction include those with ductal-dependent pulmonary blood fl ow. Pulmonary Essentials of Cardiology 295 14 atresia with intact ventricular septum and critical pulmonary valve stenosis are defects that rely on patency of the ductus arteriosus for pulmonary blood fl ow. Th ese infants may also require prostaglandin E1 infusions to manage their cyanosis until the pulmonary outfl ow tract obstruction is relieved or bypassed. Parallel Circulation In the neonate with d-transposition of the great arteries the pulmonary and systemic circulations operate in parallel rather than the normal confi guration in series. In this condition, deoxygenated blood from the right ventricle is ejected into the aorta and the left ventricle is in subpulmonary position ejecting oxygenated blood into the lungs. Neonates with this lesion depend on mixing of blood at the atrial, ventricular, or ductal levels. Although an infusion of prostaglandin E1 can maintain ductal patency, many neonates benefi t from a balloon atrial septostomy shortly after birth to create or enlarge an existing restrictive interatrial communication and optimize mixing. Th is is because mixing at the atrial level is much more eff ective than either the ventricular or ductal levels. Single-Ventricle Lesions Th is category is the most heterogeneous group, consisting of defects associated with atrioventricular valve atresia (i.e., tricuspid atresia), heterotaxy syndromes, and many others.32 In some cases, both atria empty into a dominant ventricular chamber (i.e., double-inlet left ventricle); and although a second rudimentary ventricle is typically present, the physiology is that of a single ventricle or univentricular heart. Other cardiac malformations with two distinct ventricles (i.e., unbalanced atrioventricular septal defect) may also be considered in the functional single-ventricle category because of associated defects that may preclude a biventricular repair. A common feature among these lesions is complete mixing of the systemic and pulmonary venous blood at the atrial or ventricular level. Another frequent fi nding is aortic or pulmonary outfl ow tract obstruction. Th ese children require careful delineation of their anatomy because each child represents a unique challenge to the practitioner. An important goal in single-ventricle management involves optimization of the balance between the pulmonary and systemic circulations early in life. Th is relates to the fact that a low pulmonary vascular resistance is an essential prerequisite for later palliative strategies and favorable outcomes. Th ese considerations are also relevant in the anesthetic management of these children during noncardiac surgery.30,33,34 Intrinsic Myocardial Disorders Children with primary cardiomyopathies or other forms of acquired heart disease such as myocarditis are characterized as having heart muscle disease (see later). Th ey frequently have impaired ventricular function, either systolic or diastolic, and benefi t from therapies tailored to their particular disease process. Acquired Heart Disease Cardiomyopathies Th e term cardiomyopathy usually refers to diseases of the myocardium associated with cardiac dysfunction.35,36 Th ese have been classifi ed into primary and secondary forms. Th e most common types in children are hypertrophic, dilated or congestive, and restrictive cardiomyopathies. Other forms include left ventricular

noncompaction37-39 and arrhythmogenic right ventricular dysplasia.40 Secondary forms of cardiomyopathies are those associated with neuromuscular disorders such as Duchenne muscular dystrophy, glycogen storage diseases (i.e., Pompe disease), hemochromatosis or iron overload, and mitochondrial disorders. In addition, chemotherapeutic agents such as anthracyclines may result in dilated cardiomyopathies.41 It is important to understand the basic hemodynamic processes behind the myocardial disease and implications for acute and chronic management. Hypertrophic cardiomyopathy (HCM) is characterized by ventricular hypertrophy without identifi able hemodynamic etiology resulting in increased myocardial thickness. Th is is one of the most common forms, accounting for nearly 40% of cardiomyopathies in children.42-45 Th e condition represents a heterogenous group of disorders, with the majority of the identifi ed genetic defects exhibiting autosomal dominant inheritance patterns.46,47 Th e mutations typically involve genes that encode sarcomeric proteins. Th is type of cardiac muscle disease is the most common cause of sudden cardiac death (SCD) in athletes, with an overall incidence estimated to be approximately 1% per year, with children and young adults aff ected most frequently.48,49 Most children aff ected by HCM do not have left ventricular outfl ow tract obstruction (nonobstructive cardiomyopathy). It is unclear if the remaining minority with hypertrophic obstructive cardiomyopathy (HOCM), previously known as idiopathic hypertrophic subaortic stenosis (IHSS), are at an increased risk of SCD as compared with children without obstruction.44 Hypertrophic cardiomyopathy may also involve the right ventricle. Th e diagnosis of HCM begins with a history and physical examination. Most children are identifi ed upon evaluation of a heart murmur, syncope, palpitations, or chest pain. Occasionally, an abnormal electrocardiogram (ECG) leads to referral. An accurate family history is essential. A prominent apical impulse is often present. Auscultation may reveal a systolic ejection outfl ow murmur that becomes louder with maneuvers that decrease preload or afterload (standing, Valsalva maneuver) or increase contractility. Th e murmur decreases in intensity with squatting and isometric handgrip. A mitral regurgitant murmur may also be present. An ECG will meet criteria for left ventricular hypertrophy in most children (Fig. 14-1). In some, the ECG fi ndings may be striking (Fig. 14-2). Echocardiography demonstrating a hypertrophied nondilated left ventricle is diagnostic (Video Clip 14-4).49 In many children, the hypertrophy may be asymmetrical (Video Clip 14-5). Echocardiography is the primary imaging modality for long-term assessment of wall thickness, ventricular dimensions, presence and severity of obstruction, systolic and diastolic function, valve competence, and response to therapy. Other diagnostic approaches such as cardiac catheterization and magnetic resonance imaging (MRI) may add helpful information in some cases. Th e care of children with HCM includes maintenance of adequate preload, particularly in those with dynamic obstruction. Diuretics are generally not indicated and will often worsen the hemodynamic state by reducing left ventricular volume and increasing the outfl ow obstruction. Drugs that augment myocardial contractility (inotropic agents, calcium infusions) are not well tolerated. Patients usually undergo continuous ECG monitoring (Holter recording) and exercise testing for risk stratifi cation.50 β blockers and calcium-channel blockers are the primary A Practice of Anesthesia for Infants and Children 296 I aVR V1 V4 V3R II II aVL V2 V5 V4R III aVF V3 V6 V7 Figure 14-1. ECG in adolescent female with hypertrophic cardiomyopathy demonstrating left ventricular hypertrophy (deep S wave in V1 and tall R waves over the left precordial leads). There is ST-segment depression and T-wave inversion over the left precordial leads related to repolarization changes associated with left ventricular hypertrophy, also known as a “strain” pattern. Reciprocal ST-segment elevation is noted over the right precordial leads. I aVR V1 V4 V3R II II aVL V2 V5 V4R III aVF V3 V6 V7

Figure 14-2. Tracing in a patient with Pompe disease, a severe form of hypertrophic cardiomyopathy displaying dramatic right and left ventricular voltages, as well as ST-segment and T-wave abnormalities. The recording is displayed at full standard (10 mm/mV, meaning that the ECG was not reduced in size to fi t on the paper) as are all other ECG tracings in this chapter for reference. Essentials of Cardiology 297 14 agents for outpatient drug therapy.51 Long-term treatment is individualized and based on the degree of hypertrophy, presence of ventricular ectopy, symptomatology (including syncope and congestive heart failure), family history, and genetic mutation analysis when available. Th erapies range widely and include longitudinal observation with medical management of heart failure and arrhythmias, implantation of cardioverter-defi brillators, surgical myotomy/myectomy, transcatheter alcohol septal ablation, and cardiac transplantation. Patients with HCM are usually restricted from participating in competitive sports activities.50 Dilated cardiomyopathy (DCM), also known as congestive cardiomyopathy, is characterized by thinning of the left ventricular myocardium, dilation of the ventricular cavity, and impaired systolic function.52-54 Th ere is a broader range of etiologies than with HCM, ranging from genetic/familial forms with multiple types of inheritance patterns to those caused by infections (adenovirus, coxsackievirus, human immunodefi - ciency virus55), metabolic derangements (thyroid disorders, mitochondrial disorders, carnitine defi ciency), toxic exposures (anthracyclines), and degenerative disorders (Becker and Duchenne muscular dystrophy).56,57 Chronic tachyarrhythmias can also lead to DCM that may or may not improve once the rhythm disturbance is controlled.58-60 Most children with DCM present with signs and symptoms of congestive heart failure (tachypnea, tachycardia, gallop rhythm, diminished pulses, hepatomegaly). Th e chest radiograph typically demonstrates cardiomegaly, pulmonary vascular congestion, and, in some cases, atelectasis (Fig. 14-3). An ECG may identify the likely cause of the cardiac dysfunction in those with cardiomyopathy secondary to rhythm disorders or anomalous origin of the left coronary artery from the pulmonary root. Th e echocardiogram is essential for diagnosis and characteristically demonstrates a dilated left ventricle and systolic functional impairment (reduced shortening fraction and ejection fraction) (Video Clip 14-6).61 Th erapy in the short term is supportive and aimed at stabilization by controlling congestive heart failure and ventricular dysfunction. Management may include inotropic support (including phosphodiesterase inhibition) and mechanical ventilation. Unlike children with HCM, those with DCM have a volume-loaded, poorly contractile ventricle(s); therefore, gentle diuresis is benefi cial. Th e infusion of large fl uid boluses might be poorly tolerated and result in hemodynamic decompensation and cardiovascular collapse. Th e outcome of children with dilated cardiomyopathy is variable. In most, recovery of left ventricular systolic function occurs; however, others eventually require cardiac transplantation.62 In a subset of children with severe disease, mechanical circulatory support may be necessary as a bridge to recovery or cardiac transplantation (Fig. 14-4, see Chapter 19).63-65 Once initial stabilization is achieved, the treatment strategy typically switches to β blockade and afterload reduction with angiotensin-converting enzyme inhibitors. Restrictive cardiomyopathy (RCM) is the least common of the major subsets of cardiomyopathies (5%) and portends a worse prognosis when it presents during childhood (survival <50% at 2 years from diagnosis).66-71 Th e disorder is characterized by diastolic dysfunction related to a marked increase in myocardial stiff ness resulting in impaired ventricular fi lling. Most cases are thought to be idiopathic. Th e presenting symptoms are generally nonspecifi c and primarily relate to the respiratory system.

Cptr 1 Structure and function of the skin Introduction he skin is the largest organ in the body and the heaviest—an adult's skin weighs 4–5kg. Skin is not an inert barrier but plays an active part in defending against insults (microbial, physical, and chemical) from the external environment. In this chapter, we aim to give you an insight into what your skin is doing for you, in the hope that this will encourage you to care for the skin of your patients (and your own skin) with the respect it deserves. An understanding of cutaneous physiology will also help you to analyse what has gone wrong or what might happen in patients with skin problems, including skin failure. We discuss the structure of the skin and consider how this finely tuned organ functions as a barrier ('keeping the inside in and the outside out') and reduces water loss, is part of the immune system, is a metabolic organ synthesizing vitamin D and cytokines, regulates body temperature, and senses noxious stimuli (skin on the tips of your fingers is particularly sensitive; see Box 1.1). Most of us will, at some stage, worry about the appearance of our skin, hair, and/or nails. 'Looking good' gives us confidence, and we may try to enhance the appearance (or smell) of our skin if we want to display ourselves to make a positive impression or attract a sexual partner. It is no surprise that fortunes are spent on lotions, potions, and procedures designed to conceal blemishes (actual or imagined) and to restore the appearance of youth. he psychological aspects of skin problems are discussed in more detail in E Chapter 28, pp. 570–1. Box 1.1 Dermatoglyphics (fingerprints) • Fingertips, palms, soles, and toes are covered with a pattern of epidermal ridges called dermatoglyphics. •he three basic patterns (loops, arches, and whorls) are unique to each individual. • Characteristic dermatoglyphic patterns accompany many chromosomal abnormalities. •he ridges amplify vibrations when your finger brushes across a rough surface. •he ridges enhance grip. • Autosomal dominant adermatoglyphia (SMARCAD1 mutation)— absence of epidermal ridges, also known as 'immigration delay disease'. Also absent in some rare genodermatoses and in cases of palmoplantar dysaesthesias secondary to chemotherapy drugs. Introuton 3 Summary of functions of the skin Prevention of water loss • Stratum corneum—overlapping cells and intercellular lipid. Immune defence • Structural integrity of stratum corneum. • Keratinocytes produce antimicrobial peptides (AMs) including defensins, cathelicidins, and members of the granin family, e.g. catestatin. • Langerhans cells trap antigens and migrate to lymph nodes where antigens are presented to -cells (see E p. 14). • Cytokines secreted by lymphocytes, macrophages, and keratinocytes regulate inflammatory and immune responses. • Acid pH of sweat and stratum corneum. • Fungistatic activity of sebaceous secretions. • Dermcidin (AM) produced by eccrine sweat glands activates keratinocytes to produce cytokines/chemokines important in skin immunity. Protection against ultraviolet damage • Melanin synthesized by melanocytes protects keratinocyte nuclei from harmful effects of ultraviolet (V) radiation by absorbing and scattering rays and by scavenging free radicals (see E Chapter 16, pp. 320–1). • Enzymes repair V-damaged deoxyribonucleic acid (DA) (see E Chapter 16, pp. 320–1). Temperature regulation • Vasoconstriction and vasodilation control blood flow and transfer of heat to the body surface. • Evaporation of sweat cools the body. Synthesis of vitamin D • Skin is the 1° source of vitamin D. 7-dehydrocholesterol is photoactivated to cholecalciferol (vitamin D3), which is metabolized in the liver to 25-(H)D3 and in the kidney to the active form of vitamin D calcitriol (1,25-(H)2 D3). nly small amounts of vitamin D are

obtained from the diet. Vitamin D is required for calcium absorption and has essential roles in bone metabolism, neuromuscular function, and immune function. Deficiency can lead to rickets (in children), osteomalacia, and osteoporosis (see E Chapter 16, pp. 319–39). Sensation • Free nerve endings detect potentially harmful stimuli (heat, pain). • Specialized end-organs detect pressure, vibration, and touch (see Box 1.1). • Autonomic nerves supply blood vessels, sweat glands, and arrector pili muscles. Aesthetic •he skin has an important role in social interaction. 4 Cptr 1 Structure and function of the skin Epidermis he epidermis originates from embryonic neuroectodermal cells. he epidermis is a stratified squamous epithelium composed of layers of keratinocytes that differentiate as they move towards the skin surface (see Box 1.2). he epidermis is attached to an underlying collagenous dermis, which contains the blood vessels that nourish the epidermis. Downward projections of epidermal rete pegs interlock with upward projecting dermal papillae, stabilizing the structure and making it difficult to shear the epidermis from the dermis (see Fig. 1.1). Structure of the epidermis (See Fig. 1.2.) • A single layer of columnar keratinocytes in the deepest layer of the epidermis (basal layer) is attached to a basement membrane that is an interface between the epidermis and the underlying dermis. he basal cells are anchored to the basement membrane by adhesion junctions called hemidesmosomes (see E p. 262). •egeneration of the epidermis (and hair follicles; see E p. 10) depends on populations of epidermal stem cells. •he middle layers of the epidermis (spinous or prickle cell layers) have a spiky appearance under a light microscope, because of the intercellular junctions (desmosomes) that are the main adhesive force between adjacent keratinocytes (see E p. 262). •he outermost horny layer or stratum corneum is composed of layers of flattened keratinocytes (corneocytes) locked together by modified desmosomes (corneodesmosomes) in a lipid matrix. • All keratinocytes contain keratin intermediate filaments, but the structure of the keratins changes as the cells differentiate (see Box 1.2). • Melanocytes are dendritic cells that are interspersed amongst the basal keratinocytes (approximate ratio 1:6) (see E pp. 12–3). • Epidermal Langerhans cells (dendritic antigen-presenting cells) are found throughout the epidermis (see E p. 14). • Migratory leucocytes are present in small numbers in the epidermis. Proliferation and shedding •he thickness of normal epidermis (0.05–0.1mm) is regulated by the balance between proliferation of basal keratinocytes and shedding of cells at the surface (desquamation). • It takes 740 days for a keratinocyte to move upwards from the basal layer to the horny layer where, after proteolytic breakdown of adhesion junctions, cells flake off (desquamate) (see Box 1.2). •he activity of epidermal proteases and their inhibitors regulate cornification and desquamation. Epr 5 Fat Dermis Epidermis Basement membrane zone Hair follicle Rete peg Basal cells Dermal papilla Blood vessels Sebaceous gland Fig. 1.1 Diagram of skin: epidermis, dermis, and fat. Tough outermost horny layer Strong cell envelope Melanocyte Basement membrane Desmosomes hold keratinocytes together Hemidesmosomes attach keratinocytes to basement membrane Keratin laments Dierentiation as cells move up through epidermis Fig. 1.2 Structure of epidermis. 6 Cptr 1 Structure and function of the skin Differentiation and the skin barrier Further reading Cork MJ et al. J Invest Dermatol 2009;129:1892–908. Box 1.2 Keeping the outside out • Each keratinocyte has a cytoskeleton of microfilaments containing actin, microtubules containing tubulin, and intermediate keratin filaments composed of type I and type II keratins (from the Greek ‘keras’ meaning horn). • Keratinocytes are held together by desmosomes (see Fig. 1.2). A glycoprotein intercellular substance aids cell cohesion. In acute eczema, hyaluronan secreted by keratinocytes into the intercellular space takes up water and may dilute noxious chemicals (see E pp. 214–16). • Keratinocytes change (differentiate), as they move from the basal layer towards the skin surface: •he types of

keratins in the cells and the composition of the desmosomes change. • A protein called filaggrin aggregates and cross-links the keratin filaments, giving the keratinocytes internal strength. Loss-offunction mutations in filaggrin are associated with ichthyosis vulgaris, atopic eczema, and food allergies in older children. •he cell envelope is strengthened by Ca2+-dependent crosslinking of proteins, such as involucrin and loricrin, and is catalysed by transglutaminase-1 (GM1). Mutations in TGM1 cause ichthyosis (abnormalities in the cell envelope and desquamation). • Lipid is synthesized by keratinocytes and accumulates in the intercellular space. • By the time the keratinocytes reach the outermost horny layer, they have lost their nuclei and subcellular organelles and are densely packed with keratin filaments. •he outermost horny layer is composed of 720 layers of flattened horny cells (corneocytes) with tough insoluble cell membranes (cornified envelopes) locked together by corneodesmosomes and a thick intercellular layer of lipids (like mortar). his impermeable layer enables the skin to withstand chemical and mechanical injury and restricts loss of water and electrolytes. Darkly pigmented skin seems to provide a better epidermal barrier than lightly pigmented skin—the stratum corneum is less permeable and more cohesive. •ermeability of the skin depends primarily on the balance between intercellular cohesion and desquamation in the stratum corneum. Serine proteases, such as kallikreins, degrade corneodesmosomes, so cells can desquamate. Inhibitors, such as lymphoepithelial Kazaltype 5 serine protease inhibitor (LEKI), control protease activity. In etherton syndrome, mutations in the SPINK5 gene encoding LEKI lead to defective LEKI expression, unregulated proteolytic activity, increased desquamation, and highly permeable skin (see E Box 31.11, p. 603). DIFFE 7 EIAI & HE SKI BAIE 8 Cptr 1 Structure and function of the skin Dermis and glands he dermis is a layer of connective tissue beneath the epidermis. A layer of subcutaneous fat separates the dermis from the underlying fascia and muscle. he dermis has a rich supply of blood vessels, lymphatics, nerves, and sensory receptors. he thickness of the dermis varies with body site and may measure as much as 5mm on the back. Structural components • Collagen, mainly type I but some type III, gives the dermis tensile strength. Ageing skin is characterized by reduced collagen synthesis and increased collagen breakdown by matrix metalloproteinases. • Elastic fibres, containing a core of elastin, supply elasticity and resilience, but elastin functions poorly in aged skin. • Ground substance of proteoglycans and glycoproteins that binds water and hydrates the dermis. • Skin appendages: hair follicles, sebaceous glands, eccrine sweat glands, and apocrine sweat glands (see E p. 9, and p. 10). • Blood vessels: superficial and deep vascular plexuses. Vasodilatation and vasoconstriction help to regulate heat loss. • Lymphatics: afferent capillaries in dermal papillae pass via a superficial plexus to deeper horizontal plexuses and collecting lymphatics (see E Skin immune system, p. 14). •erve fibres: most sensory nerves end in the dermis, but a few penetrate the epidermis. Free nerve endings detect heat and pain; acinian corpuscles detect pressure and vibration, and Meissner corpuscles detect pressure and touch. Autonomic innervation is cholinergic to the eccrine sweat glands, and adrenergic to eccrine and apocrine glands, arterioles, and arrector pili muscle.

1 Basic Science of Bone and Cartilage Metabolism John N. Delahay Normal Bone Growth and Development Bone is a biphasic connective tissue consisting of an inorganic mineral phase and an organic matrix phase. The hardness of bone allows it to provide several specialized mechanical functions: the protection of internal organs, the scaffold that provides points of attachment for other structural elements, and the levers needed to improve the efficiency of muscle action. In addition, bone serves two biologic functions: a site for hematopoietic activity and a reservoir of minerals needed for metabolic interchange. Embryology The major components of the musculoskeletal system originate from the mesoderm layer of the trilaminar embryo. This “middle layer” is populated by mesenchymal cells that are totipotent and capable of differentiating into a number of tissues. The sequence of events important in bone growth and development begins with the appearance of the limb bud around the fifth week of life. It is at that time that a tubular condensation of mesenchyme develops centrally in the limb bud. Discrete areas, called interzones, are seen between these condensations (Fig. 1-1) and represent the primitive joints. During the sixth week, the mesenchyme differentiates into cartilage through the process of chondrification (Fig. 1-2). Interstitial and appositional growth occurs from within and from the surface, respectively. In the seventh week, the cartilage model is penetrated by a vascular spindle, which occurs coincidentally with the necrosis of the central cartilage cells. Once this vascular spindle is established, the central portion of the model is populated by osteoblasts. Matrix is secreted and this in turn is ossified, making immature (woven) bone. 1 2 J.N. Delahay Figure 1-1. Histologic study of fetus, approximately 6 weeks gestation, depicting early joint formation. Note the identifiable cartilage and the condensed mesenchymal tissue of the interzone destined to become the joint. (From Bogumill GP. Orthopaedic Pathology: A Synopsis with Clinical Radiographic Correlation. Philadelphia: Saunders, 1984. Reprinted by permission.) Figure 1-2. Histologic study of fetus, approximately 8 weeks gestation. Earliest ossification is depicted here. A sleeve, or collar, of bone is present on the outer surface of the cartilage model. (From Bogumill GP. Orthopaedic Pathology: A Synopsis with Clinical Radiographic Correlation. Philadelphia: Saunders, 1984. Reprinted by permission.) 1. Basic Science of Bone and Cartilage Metabolism 3 Once the central portion of the model is ossified, it is referred to as a primary ossification center (Fig. 1-3). Further ossification of the skeleton occurs via one of two mechanisms: (1) enchondral ossification within a cartilage model (i.e., long bones), and (2) intramembranous ossification within a mesenchymal model (i.e., most flat bones and the clavicle). From the second through the sixth embryonic months, progressive changes occur in the tubular bones. First, the central (medullary) canal cavitates, leaving a hollow tube of bone with a large mass of cartilage persisting at each end (Fig. 1-4). Within these masses of cartilage, the secondary ossification center, or epiphysis, will form (Fig. 1-5). A cartilage plate, the physis or growth plate (Fig. 1-6), persists between the developing epiphysis and metaphysis. This structure is responsible for growth in length, whereas the covering of the bone, the periosteum, is primarily responsible for growth in girth. Figure 1-3. Primary ossification center of fetus, approximately 14 weeks gestation. The cartilage cells have been removed almost entirely from the center, leaving remnants of acellular cartilage matrix. Bone deposits on the cartilage remnants will form primary trabeculae. Note that the primary sleeve, or collar, of bone has extended along both margins and is located adjacent to the hypertrophied cartilage at each epiphyseal end. (From Bogumill GP. Orthopaedic Pathology: A Synopsis with Clinical Radiographic Correlation. Philadelphia: Saunders, 1984. Reprinted by permission.) Figure 1-4. Primary ossification center, near term. There is complete replacement of cartilage in the diaphyseal portion of the cartilage model. The remaining cartilage is confined to both epiphyseal ends of the model.

Note the increasing thickness of the cortical portion of bone, which is a result of conversion of periosteum to bone. A light-staining cambium layer is identifiable. The narrowest portion of the shaft is the site of initial vascular invasion and remains identifiable throughout life in many bones, especially in hands and feet. The eccentric position of this narrowed area indicates the disproportionate contribution to growth in length from each epiphysis. (From Bogumill GP. Orthopaedic Pathology: A Synopsis with Clinical Radiographic Correlation. Philadelphia: Saunders, 1984. Reprinted by permission.) 1. Basic Science of Bone and Cartilage Metabolism 5 Figure 1-5. Early secondary ossification center of mature fetus. The formation of the secondary ossification centers in the lower tibia and upper femur coincide with fetal maturity. The secondary center begins not in the center of the epiphysis but nearer the growth plate. Expansion, therefore, is eccentric. (From Bogumill GP. Orthopaedic Pathology: A Synopsis with Clinical Radiographic Correlation. Philadelphia: Saunders, 1984. Reprinted by permission.) Figure 1-6. Schematic diagram of growth plate, consisting of resting zone, proliferative zone, secretory zone, zone of hypertrophy, and zone of calcification. The cross-sectional view helps place events at the growth plate in three-dimensional perspective. (From Bogumill GP. Orthopaedic Pathology: A Synopsis with Clinical Radiographic Correlation. Philadelphia: Saunders, 1984. Reprinted by permission.) 6 J.N. Delahay Postnatal Development The physis and the periosteum continue to function postnatally in the growth and development of the infantile skeleton. Numerous local and systemic factors impact on their activity; vascular, hormonal, and genetic effects all play important roles. In essence, the reworking or remodeling of bone that is already present occurs so that the bone can meet the mechanical and biologic demands placed on it. Bone: The Tissue Bone, whether it is immature or mature, consists of cells and a biphasic blend of mineral and matrix that coexist in a very exact relationship. The matrix phase consists of collagen and glycosaminoglycans, which are dimeric disaccharides. Both are products of the osteoblast. Calcium hydroxyapatite is the basic mineral crystal in bone. Despite the presence of some less structured amorphous calcium phosphate, the bulk of calcium in the skeletal reservoir is bound in the crystals of hydroxyapatite. Osteoblasts are bone-forming cells that secrete the matrix components described. As ossification progresses, the osteoblasts become trapped in the matrix they produce and are then referred to as osteocytes. These cells are rather inert but are capable of a small degree of bone resorption. Osteoclasts are those cells whose primary function is the degradation and removal of mineralized bone. It is important to remember that the osteoclasts can remove only mineralized bone, and not unmineralized matrix. Bone Organization Microscopically, bone is generally described as mature or immature. Mature bone (Fig. 1-7) has an ordered lamellar arrangement of Haversian systems and canalicular communications that give it its classic histologic appearance. Immature bone (Fig. 1-8), in contrast, has a much more random appearance of collagen fibers dispersed in a matrix of irregularly spaced cells. It is produced rapidly by osteoblasts and “remodeled” by the local cell population, until the mature lamellar pattern is achieved. Immature bone is seen in the adult skeleton only under pathologic conditions (i.e., fracture callus, osteogenic sarcoma, myositis, etc.). Macroscopically (Fig. 1-9), the lamellar bone is configured either as dense cortical bone or as delicate spicules called trabeculae. In both areas, the cortex and the trabecular metaphysis, the bone is histologically the same (i.e., mature lamellar bone). Turnover and Remodeling Although the tendency is to think of adult bone as an inert tissue, nothing could be further from the truth. Throughout adult life there is a constant ebb and flow of bone formation and bone resorption. These two processes 1. Basic Science of Bone and Cartilage Metabolism 7 Figure 1-7. Mature bone: osteonal structure as seen in undecalcified material. Numerous interstitial

fragments (osteonal fragments without an associated Haversian canal) are readily observed. (From Bogumill GP. Orthopaedic Pathology: A Synopsis with Clinical Radiographic Correlation. Philadelphia: Saunders, 1984. Reprinted by permission.) Figure 1-8. Immature bone (early callus). Note the large number of osteoblasts and osteocytes. (From Bogumill GP. Orthopaedic Pathology: A Synopsis with Clinical Radiographic Correlation. Philadelphia: Saunders, 1984. Reprinted by permission.) 8 J.N. Delahay are delicately balanced and keep the skeletal mass in a state of equilibrium. A number of authors have popularized the concept of “coupling”; bone formation and bone resorption generally increase or decrease in the same direction. When one process increases, so does the other, and vice versa. It is important, however, to consider the net effect of the rate changes in these two processes. For example, in osteoporosis, both formation and bone resorption increase, but resorption increases at a much greater rate, so that despite a coupled increase in bone formation the net effect is an overall decrease in bone mass. A number of factors, systemic and local, affect these processes and hence impact bone turnover and remodeling. Perhaps the most well defined factor is mechanical stress, which forms the basis for the classic Wolff’s law. Simply stated, trabecular, and to a lesser degree cortical, bone remodels along lines of mechanical stress. Bone forms where it is needed to meet mechanical demands, and it is resorbed where the need is less. Current research suggests that bone functions as a transducer, converting mechanical energy from the applied load into electrical energy and a voltage gradient. In turn, this voltage gradient that is generated modulates cellular differentiation. Osteoblastic activity is thus seen in regions where the mechanical demands are the greatest. OsteoclasMETRIC 1 Figure 1-9. Cross section of the radius at the distal metaphysis. The majority of bone is cortical bone, in which the annual rate of turnover is only 2%. 1. Basic Science of Bone and Cartilage Metabolism 9 tic activity predominates the pattern when those mechanical demands decrease and less bone is required. This phenomenon has been called the “piezoelectric effect.” Specifically, the deformation of bone apatite crystals by superimposed load generates the voltage gradient, which in turn alters the cell population to respond to that load.