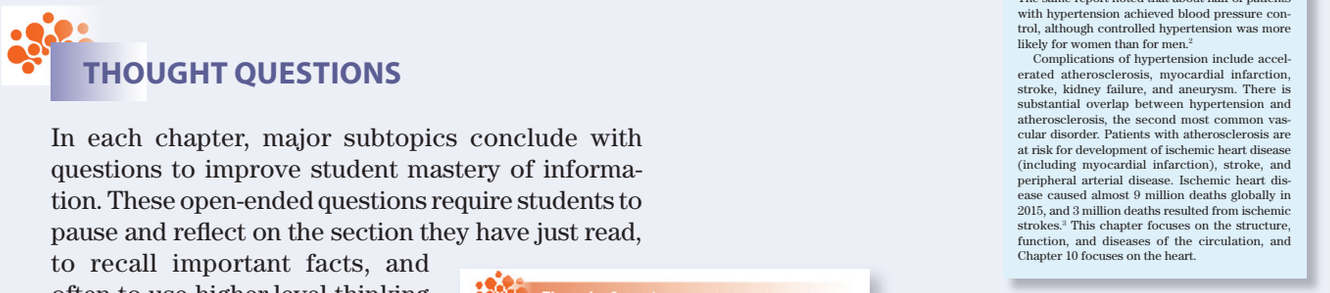
HOW TO USE THIS BOOK

Physiology and pathophysiology are subjects that are loved by some students even as they scare others! These disciplines cover challenging topics that, while necessary for success in future clinical courses, can be seen as a painful rite of passage or as an enlightening journey to clinical competence. The features of the book were developed by master pathophysiology teachers and clinician faculty members with the goal of helping students to synthesize complex content and extend that synthesis to clinical application. The following features, recognizable by their easy-to-find design elements, appear consistently in the chapters to help reinforce the physiologic and pathophysiologic concepts discussed in this book.

THE CLINICAL CONTEXT

Each chapter begins with a short introduction that sets the stage for the content's relevance to clinical practice. This section introduces the common disease states of that organ system, briefly highlighting their incidence and prevalence.



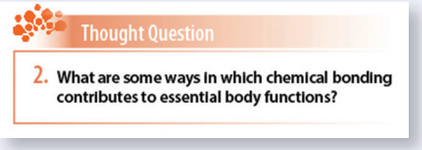
THE CLINICAL CONTEXT

Cardiovascular disease is the most common cause of adult morbidity and mortality, accounting for 31% of deaths worldwide.1 The most common disorder of the vascular system is hypertension, defined by the American College of Cardiology and the American Heart Association as blood pressure greater than 130/80 mm Hg. In the United States from 2015 to 2016, hypertension prevalence was 29% overall. Hypertension increases with age, and prevalence was 63.1% in people aged 60 years and older during this period. The same report noted that about half of patients with hypertension achieved blood pressure control, although controlled hypertension was more likely for women than for men.[2]

Complications of hypertension include accelerated atherosclerosis, myocardial infarction, stroke, kidney failure, and aneurysm. There is substantial overlap between hypertension and atherosclerosis, the second most common vascular disorder. Patients with atherosclerosis are at risk for development of ischemic heart disease (including myocardial infarction), stroke, and peripheral arterial disease. Ischemic heart disease caused almost 9 million deaths globally in 2015, and 3 million deaths resulted from ischemic strokes.[3] This chapter focuses on the structure, function, and diseases of the circulation, and Chapter 10 focuses on the heart.

THOUGHT QUESTIONS

In each chapter, major subtopics conclude with questions to improve student mastery of information. These open-ended questions require students to pause and reflect on the section they have just read, to recall important facts, and often to use higher-level thinking to synthesize and apply what they have learned. Answers are provided in the online student supplement on Springer Publishing Company Connect™ to encourage self-instruction, immediate feedback, and remediation.



Thought Question

2. What are some ways in which chemical bonding contributes to essential body functions?

PEDIATRIC CONSIDERATIONS

These sections briefly review prenatal and postnatal development as it relates to physiology and pathophysiology. Congenital malformations and genetic conditions generally present at birth or in the pediatric population. Additionally, children metabolize therapeutic agents differently than adults—critical information to understand when treating children. All the system chapters as well

PEDIATRIC CONSIDERATIONS

Randall L. Johnson

EMBRYOLOGICAL DEVELOPMENT OF THE CIRCULATORY SYSTEM

All structures of the cardiovascular system—heart and blood vessels—are lined with a single layer of endothelial cells. In fact, endothelial cells make up the first tube-like structures that will develop into heart and vessels. Cardiac development is described in Chapter 10, Heart; vessels must develop simultaneously, to deliver oxygen and nutrients to support embryonic and fetal growth. By the fifth week of development, vessels destined to become arteries develop distinctive characteristics first, followed by the vessels destined to become veins. The properties of pulmonary vessels and the embryonic circulation that brings oxygenated blood from the placenta prenatally are determined by the unique requirements of fetal circulation. After birth, pulmonary vascular resistance decreases and connecting vessels normally close. The postnatal pattern of blood flow is then established—from the right side of the heart to the lungs, and back to the left side of the heart for pumping to the systemic circulation—as the fetal circulation adjusts to extrauterine existence. There is a brief, though slightly variable, time period as the neonate transitions during which circulation may be reduced or impaired until structures have modified to their final pattern.

BLOOD PRESSURE AND PEDIATRIC HYPERTENSION

Hypertension is the most common disorder of the circulatory system in children, and prevalence is increasing, partly because of sedentary lifestyle, obesity, and type 2 diabetes mellitus. The child's blood pressure should be measured annually during well-child visits in an ambulatory setting. Appropriately sized equipment must be used for accuracy. Bladder cuff length should be 80% to 100% of the circumference of the arm, and the width should be around 40% of the arm length.[a] Although screening with an oscillometric device validated for pediatric use is acceptable, confirmation of elevated blood pressure should be performed with auscultatory measurement.[b] Recommendations for frequency of obtaining blood pressure in children are changed for other conditions, such as obesity, diabetes, or kidney disease.

The determination of elevated blood pressure is based on normative tables that were revised in 2017. The tables are different for boys and girls and are adjusted for age and height. Up to the age of 13 years, the identification of elevated blood pressure, stage 1 or stage 2 hypertension, is based on measurements falling between the 90th and 95th percentiles for age, sex, and height; greater than the 95th percentile and less than the 95th percentile plus 12 mm Hg; or greater than the 95th percentile plus 12 mm Hg.[c] After the age of 13, the current ranges for adults apply. Elevated blood pressure should be confirmed with three separate measurements and should be measured by auscultation, as the tables were generated from auscultated measurements. It is estimated that 1.5% of children without diabetes, obesity, or kidney disease have primary hypertension, whereas the rate of hypertension in children with type 2 diabetes is about 9.5%.[d]

The clinical significance of early identification and treatment of pediatric hypertension is high: pediatric hypertension induces early vascular aging. Thus, the types of vascular changes associated with aging—including vascular wall stiffness, inflammation, endothelial damage, and increased left ventricular mass—are promoted in children with hypertension, accelerating their development of cardiovascular disease in later life.[e]

as Chapter 3, Molecular Biology, Genetics, and Genetic Diseases, provide an in-depth look at the most common conditions, genetic disorders, and important treatment considerations related to this patient population.

GERONTOLOGICAL CONSIDERATIONS

Understanding how aging affects organ systems is imperative in providing competent patient care. Healthy aging is inevitably associated with certain trends in organ function, for example, reduced liver biotransformation of drugs, decreased renal glomerular filtration, and other alterations that must be considered when assessing disease and planning management in older adults. Additionally, certain diseases are more prevalent in older adults, and phenomena such as frailty and complex comorbidities become more common with aging. All of these considerations factor into the special care that must be taken when providing clinical care to older adults. This section appears in all system chapters as well as in Chapter 4, Cell Physiology and Pathophysiology.


GERONTOLOGICAL CONSIDERATIONS

Ryan Prince

AGE-RELATED CHANGES IN THE KIDNEY

Age-related changes in the kidney include changes in organ size, number of nephrons, GFR, vasculature, and metabolism. Knowledge of age-associated changes in kidney function and histology has been greatly informed by studying tissue biopsies from healthy kidney donors of different ages (Box 12.2).[1]

CHANGES IN KIDNEY MASS AND VOLUME

The kidneys start to decrease in both weight and volume starting at about the fourth decade of life.[2,3] Loss of mass occurs mainly in cortical tissue owing to reduction in number and function of nephrons, while medullary mass is generally preserved.

CHANGES IN RENAL BLOOD FLOW AND GLOMERULAR FILTRATION RATE

In the adult, RBF is about 1,000 to 1,200 mL/min in the absence of kidney disease, and GFR is about 10% of that. Each decade after age 40, RBF is reduced by about 10% and average GFR decreases by about 8 mL/min/1.73 m^{2}.[4] The reduction in GFR and RBF are interconnected and primarily involve structural changes within the kidney and its vasculature. As noted earlier, studies such as the one described in Box 12.2 have shown that many of these processes will occur independently of comorbid pathological processes. However, metabolic syndromes such as diabetes and hypertension, as well as pathological processes such as atherosclerosis and vasculitis, correlate with more pronounced structural changes and decreases in kidney function. Finally, muscle mass and creatinine production can decline with aging, so serum creatinine may remain normal despite reduced GFR.[5]

CHANGES IN NEPHRON NUMBERS AND FUNCTION

At approximately age 40, the number of nephrons begins to decrease by more than 6,000 per kidney per year, partially explaining the decreased RBF and GFR described earlier.[6] Because nephron number at birth

BOX 12.2
Relationship Between Age and Nephrosclerosis in Older Adults

A cross-sectional study of more than 1,200 living kidney donors examined directly mGFR as well as eGFR estimates (using the MDRD equation), urine 24-hour albumin and protein measurements, blood pressure monitoring, and blood glucose measurements to learn whether abnormalities in the kidney are more prevalent with age, and whether those findings are explained by age-related differences in kidney function or by CKD risk factors.[6]

Among these healthy donors, mGFR had a significant relationship with age, showing a decrease with aging. These biopsies were analyzed for nephrosclerosis, which was defined as having signs of two or more of the following histological changes: glomerulosclerosis, tubular atrophy, arteriolar narrowing, and interstitial fibrosis. Although nephrosclerosis increased with age, the relationship between mGFR and age was not influenced by degree of nephrosclerosis. Thus, the relationship between histological findings and their functional implications remains unclear. Key findings were as follows:

- Nephrosclerosis was significantly associated with 24-hour urine albumin, nocturnal systolic and diastolic blood pressure, and hypertension (defined as use of antihypertensive medications).
- Kidney donors aged 18 to 29 years had mGFR of 114 ± 10 mL/min/1.73 m^{2}, whereas donors aged 60 to 69 years old had mGFR of 90 ± 12 mL/min/1.73 m^{2}.
- Prevalence of nephrosclerosis was 2.7% in the younger age group and 58% in the older age group.

This suggests that, although GFR declines with normal healthy aging, histological changes may occur to a greater extent and may not produce a direct impact on GFR. It is important to note, however, that prospective kidney donors were selected for healthy kidney function and absence of diabetes. Across the entire population of older adults, it is very likely that average GFR is lower than that observed in this study.[6]

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; mGFR, measured glomerular filtration rate.

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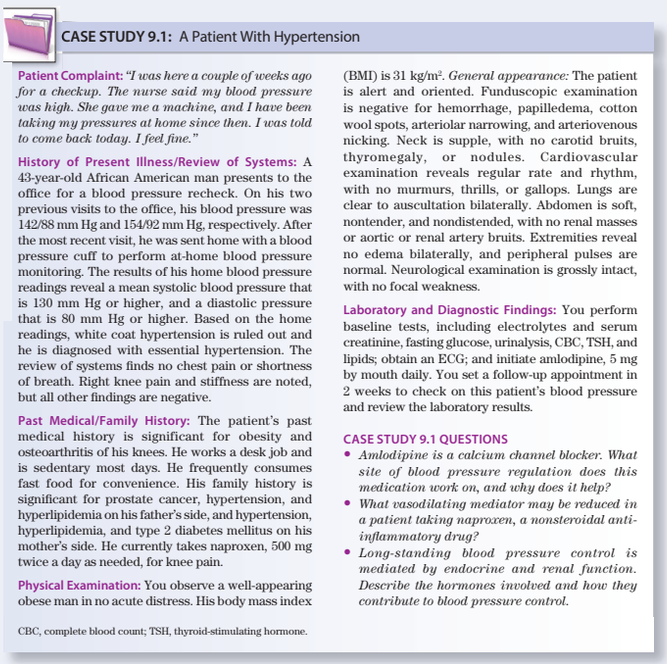

CASE STUDY 9.1: A Patient With Hypertension

Patient Complaint: *"I was here a couple of weeks ago for a checkup. The nurse said my blood pressure was high. She gave me a machine, and I have been taking my pressures at home since then. I was told to come back today. I feel fine."*

History of Present Illness/Review of Systems: A 43-year-old African American man presents to the office for a blood pressure recheck. On his two previous visits to the office, his blood pressure was 142/88 mm Hg and 154/92 mm Hg, respectively. After the most recent visit, he was sent home with a blood pressure cuff to perform at-home blood pressure monitoring. The results of his home blood pressure readings reveal a mean systolic blood pressure that is 130 mm Hg or higher, and a diastolic pressure that is 80 mm Hg or higher. Based on the home readings, white coat hypertension is ruled out and he is diagnosed with essential hypertension. The review of systems finds no chest pain or shortness of breath. Right knee pain and stiffness are noted, but all other findings are negative.

Past Medical/Family History: The patient's past medical history is significant for obesity and osteoarthritis of his knees. He works a desk job and is sedentary most days. He frequently consumes fast food for convenience. His family history is significant for prostate cancer, hypertension, and hyperlipidemia on his father's side, and hypertension, hyperlipidemia, and type 2 diabetes mellitus on his mother's side. He currently takes naproxen, 500 mg twice a day as needed, for knee pain.

Physical Examination: You observe a well-appearing obese man in no acute distress. His body mass index (BMI) is 31 kg/m^{2}. *General appearance:* The patient is alert and oriented. Funduscopic examination is negative for hemorrhage, papilledema, cotton wool spots, arteriolar narrowing, and arteriovenous nicking. Neck is supple, with no carotid bruits, thyromegaly, or nodules. Cardiovascular examination reveals regular rate and rhythm, with no murmurs, thrills, or gallops. Lungs are clear to auscultation bilaterally. Abdomen is soft, nontender, and nondistended, with no renal masses or aortic or renal artery bruits. Extremities reveal no edema bilaterally, and peripheral pulses are normal. Neurological examination is grossly intact, with no focal weakness.

Laboratory and Diagnostic Findings: You perform baseline tests, including electrolytes and serum creatinine, fasting glucose, urinalysis, CBC, TSH, and lipids; obtain an ECG; and initiate amlodipine, 5 mg by mouth daily. You set a follow-up appointment in 2 weeks to check on this patient's blood pressure and review the laboratory results.

CASE STUDY 9.1 QUESTIONS

- *Amlodipine is a calcium channel blocker. What site of blood pressure regulation does this medication work on, and why does it help?*
- *What vasodilating mediator may be reduced in a patient taking naproxen, a nonsteroidal anti-inflammatory drug?*
- *Long-standing blood pressure control is mediated by endocrine and renal function. Describe the hormones involved and how they contribute to blood pressure control.*

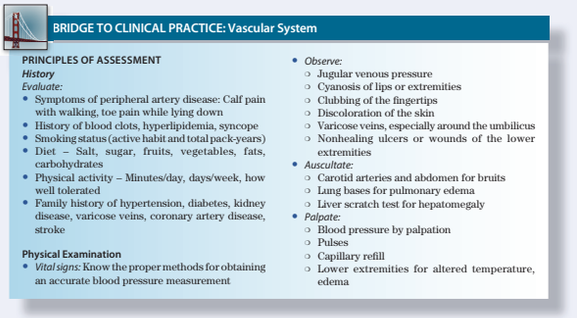
CBC, complete blood count; TSH, thyroid-stimulating hormone.

CASE STUDIES

In each system chapter, one to three case studies help students apply concepts learned from the chapter to a patient scenario, setting the stage for the Bridge to Clinical Practice. Focusing primarily on common disorders managed in a primary care setting, the case studies detail a patient complaint, history and system review, physical examination, and laboratory/diagnostic findings. Application-based open-ended questions guide students through the underlying pathophysiology of the patient's condition. Answers to the case study questions are found in the online student supplement on Springer Publishing Company Connect™.

BRIDGE TO CLINICAL PRACTICE

This unique feature is designed to help students transition from the basic pathophysiology covered in the chapter to the implications for the clinical role. For each system this section provides a succinct summary of system-specific aspects of the history and physical examination, the most common laboratory tests and diagnostic tools, major drug classes used for disorders of that system, and other commonly used non-pharmacologic modalities that students will encounter as they transition into clinical settings.


BRIDGE TO CLINICAL PRACTICE: Vascular System

PRINCIPLES OF ASSESSMENT

History

Evaluate:

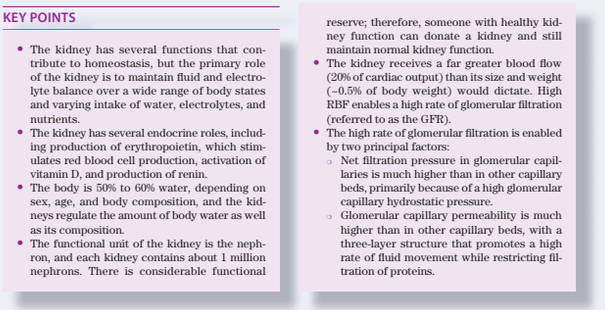
- Symptoms of peripheral artery disease: Calf pain with walking, toe pain while lying down
- History of blood clots, hyperlipidemia, syncope
- Smoking status (active habit and total pack-years)
- Diet – Salt, sugar, fruits, vegetables, fats, carbohydrates
- Physical activity – Minutes/day, days/week, how well tolerated
- Family history of hypertension, diabetes, kidney disease, varicose veins, coronary artery disease, stroke

Physical Examination

- *Vital signs:* Know the proper methods for obtaining an accurate blood pressure measurement
- *Observe:*
  - Jugular venous pressure
  - Cyanosis of lips or extremities
  - Clubbing of the fingertips
  - Discoloration of the skin
  - Varicose veins, especially around the umbilicus
  - Nonhealing ulcers or wounds of the lower extremities
- *Auscultate:*
  - Carotid arteries and abdomen for bruits
  - Lung bases for pulmonary edema
  - Liver scratch test for hepatomegaly
- *Palpate:*
  - Blood pressure by palpation
  - Pulses
  - Capillary refill
  - Lower extremities for altered temperature, edema

KEY POINTS

This feature highlights the important takeaways for which students should be able to demonstrate an understanding at the conclusion of each chapter. These points are not intended as a comprehensive summary of the chapter; instead, they capture the main ideas conveyed throughout the chapter in short bullet points that students can reflect upon as they assess their mastery of the content.

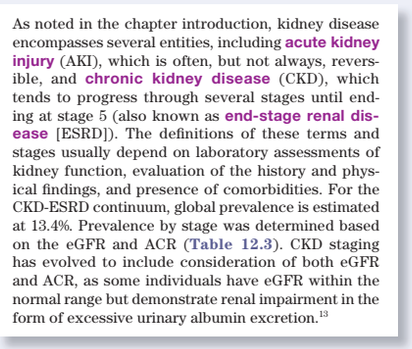


KEY POINTS

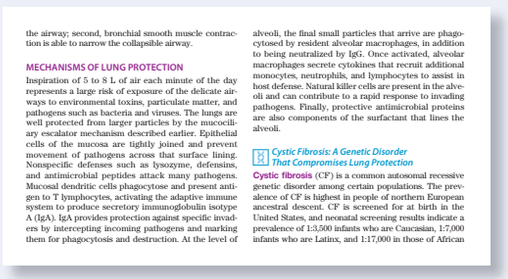
- The kidney has several functions that contribute to homeostasis, but the primary role of the kidney is to maintain fluid and electrolyte balance over a wide range of body states and varying intake of water, electrolytes, and nutrients.
- The kidney has several endocrine roles, including production of erythropoietin, which stimulates red blood cell production, activation of vitamin D, and production of renin.
- The body is 50% to 60% water, depending on sex, age, and body composition, and the kidneys regulate the amount of body water as well as its composition.
- The functional unit of the kidney is the nephron, and each kidney contains about 1 million nephrons. There is considerable functional reserve; therefore, someone with healthy kidney function can donate a kidney and still maintain normal kidney function.
- The kidney receives a far greater blood flow (20% of cardiac output) than its size and weight (~0.5% of body weight) would dictate. High RBF enables a high rate of glomerular filtration (referred to as the GFR).
- The high rate of glomerular filtration is enabled by two principal factors:
  - Net filtration pressure in glomerular capillaries is much higher than in other capillary beds, primarily because of a high glomerular capillary hydrostatic pressure.
  - Glomerular capillary permeability is much higher than in other capillary beds, with a three-layer structure that promotes a high rate of fluid movement while restricting filtration of proteins.

KEY DISORDERS

All disorders reviewed in this book are highlighted within the text to facilitate quick identification and discovery. These disorders are also listed in the List of Disorders to help students locate content rapidly. Highlighted disorders appear throughout each chapter, in the main discussion as well as in the pediatric and geriatric consideration sections.



As noted in the chapter introduction, kidney disease encompasses several entities, including **acute kidney injury** (AKI), which is often, but not always, reversible, and **chronic kidney disease** (CKD), which tends to progress through several stages until ending at stage 5 (also known as **end-stage renal disease** [ESRD]). The definitions of these terms and stages usually depend on laboratory assessments of kidney function, evaluation of the history and physical findings, and presence of comorbidities. For the CKD-ESRD continuum, global prevalence is estimated at 13.4%. Prevalence by stage was determined based on the eGFR and ACR (**Table 12.3**). CKD staging has evolved to include consideration of both eGFR and ACR, as some individuals have eGFR within the normal range but demonstrate renal impairment in the form of excessive urinary albumin excretion.[13]



the airway; second, bronchial smooth muscle contraction is able to narrow the collapsible airway.

MECHANISMS OF LUNG PROTECTION

Inspiration of 5 to 8 L of air each minute of the day represents a large risk of exposure of the delicate airways to environmental toxins, particulate matter, and pathogens such as bacteria and viruses. The lungs are well protected from larger particles by the mucociliary escalator mechanism described earlier. Epithelial cells of the mucosa are tightly joined and prevent movement of pathogens across that surface lining. Nonspecific defenses such as lysozyme, defensins, and antimicrobial peptides attack many pathogens. Mucosal dendritic cells phagocytose and present antigen to T lymphocytes, activating the adaptive immune system to produce secretory immunoglobulin isotype A (IgA). IgA provides protection against specific invaders by intercepting incoming pathogens and marking them for phagocytosis and destruction. At the level of alveoli, the final small particles that arrive are phagocytosed by resident alveolar macrophages, in addition to being neutralized by IgG. Once activated, alveolar macrophages secrete cytokines that recruit additional monocytes, neutrophils, and lymphocytes to assist in host defense. Natural killer cells are present in the alveoli and can contribute to a rapid response to invading pathogens. Finally, protective antimicrobial proteins are also components of the surfactant that lines the alveoli.

Cystic Fibrosis: A Genetic Disorder That Compromises Lung Protection

Cystic fibrosis (CF) is a common autosomal recessive genetic disorder among certain populations. The prevalence of CF is highest in people of northern European ancestral descent. CF is screened for at birth in the United States, and neonatal screening results indicate a prevalence of 1:3,500 infants who are Caucasian, 1:7,000 infants who are Latinx, and 1:17,000 in those of African

GENETIC CONDITIONS

As the fields of molecular biology and genetics provide ever more understanding of the genetic basis of disease and disease risk factors, the book uses an easily identifiable icon next to all genetic conditions described throughout the text for quick reference and discovery. These disorders are also included among the key disorders found in the List of Disorders.

SHARE YOUR FEEDBACK AND FOLLOW DR. TKACS ON TWITTER

The editors would like to hear your feedback on this first edition. If you would like to share your thoughts on potential additions, corrections, or updates that you believe should be incorporated into this book, please contact Nancy Tkacs at tkacs@nursing.upenn.edu.

You can also follow Dr. Tkacs on Twitter: @DrTkacsPatho.