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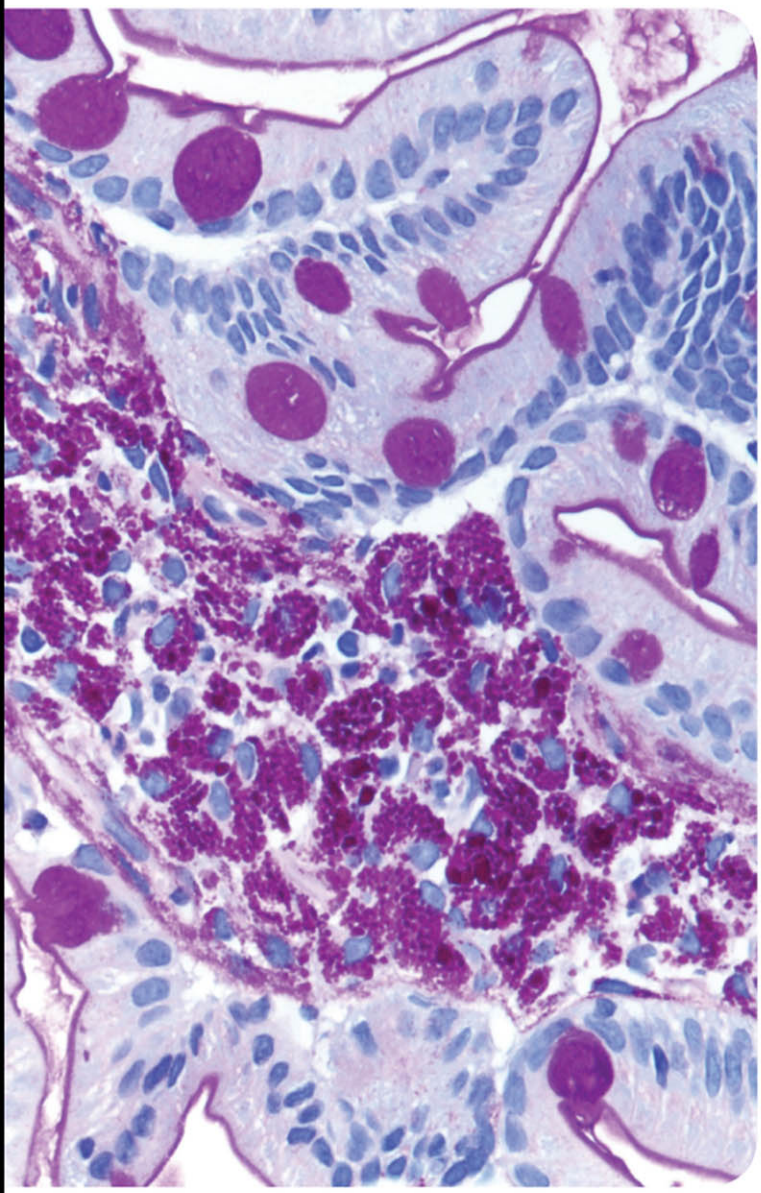
Anatomic Pathology



- Self-assessment guide for Anatomic Pathology and Maintenance of Certification (Part III) Examination
- 1700+ board-style questions, including 400+ high-resolution images
- Case-based scenarios for real-world application of knowledge
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Anatomic Pathology

Primary Certification and Maintenance of Certification

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Anatomic Pathology

Primary Certification and Maintenance of Certification

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PREFACE

This book has been designed as a self-assessment guide for pathology residents and fellows preparing for the Anatomic Pathology Board Examination and for practicing pathologists who are preparing for the Anatomic Pathology Maintenance of Certification (MOC) examination to fulfill the cognitive expertise component (Part III) of MOC. The subject matter covered in this book includes a spectrum of topics that incorporate fundamental knowledge necessary for daily practice as well as information on the latest molecular and genetic techniques, which are an essential element of understanding the pathophysiology and therapeutics of disease processes. This book will improve content knowledge of the readers and allow them to test this knowledge with case-based scenarios.

The chapters have been categorized into topics that are similar to the modules outlined for the MOC examination. In addition, this book also includes some clinical pathology topics, such as lymph node and spleen, and laboratory management as applicable to the practice of anatomic pathology as well. This book has board-style multiple-choice questions in a one-best-answer format. The answers have been sequenced alphabetically and include a brief discussion about the salient features of the entity, diagnostic pitfalls, differential diagnosis, and provide an explanation for the incorrect choices. For additional reading, the most useful review articles and references have been provided at the end of each chapter. High-resolution gross and microscopic images have also been included to supplement the review process.

This book is certainly not meant to replace the regular reading and the invaluable practical knowledge gained from daily previewing and didactic sessions from experienced pathologists. The authors have been extremely fortunate to be taught by extraordinary and patient teachers. We share a common passion for teaching and are thankful to our residents and fellows who not only continue to enrich this interactive experience but also make learning fun. We hope that this volume will serve as a valuable supplementary resource for a succinct and organized approach toward successful board preparations.

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ACKNOWLEDGMENT

We would like to express our gratitude to Ms. Shon Bryson for her contribution in organizing this book in a timely manner.

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CHAPTER 1

CELL INJURY, INFLAMMATION, REPAIR, AND HEMODYNAMIC DISORDERS

1. A patient presents with liver failure and congestive heart failure, and a liver biopsy shows the following changes (see Figure 1-1—Prussian blue stain). What material's abnormal accumulation results in cellular injury and death in this disease?

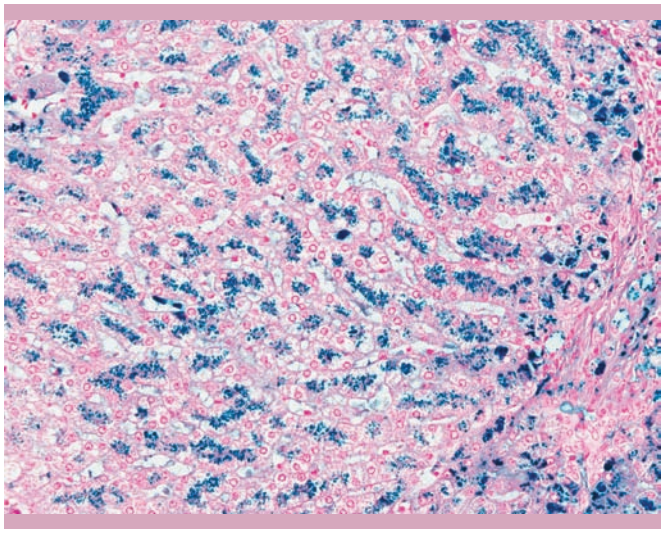

FIGURE 1-1

(A) Bilirubin
(B) Calcium
(C) Iron
(D) Lipofuscin
(E) Melanin

2. Cells with irreversible injury undergoing cell death can show nuclear shrinkage, basophilia, and nuclear fragmentation (see Figure 1-2 cell at arrow). This process is called

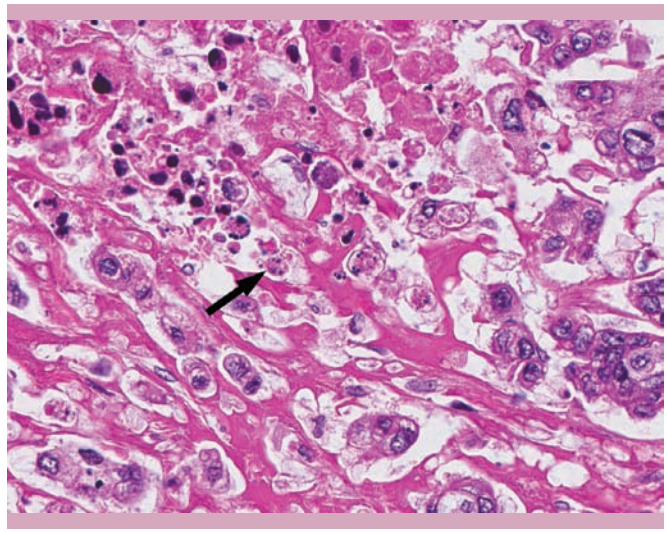

FIGURE 1-2

(A) Balloon degeneration
(B) Fatty change
(C) Karyolysis
(D) Karyorrhexis
(E) Pyknosis

3. An atherosclerotic plaque ruptures and obstructs blood flow to a segment of kidney (see Figure 1-3). At 6 hours after the event, the involved kidney would show what pattern of necrosis on microscopic examination?

FIGURE 1-3

(A) Caseous necrosis
(B) Coagulative necrosis
(C) Fibrinoid necrosis
(D) Gangrenous necrosis
(E) Liquefactive necrosis

4. A patient with renal failure on long-term dialysis and taking aluminum-based antacids presents with multiple lesions in the kidneys, lungs, and skin. A biopsy was performed (see Figure 1-4). This is an example of

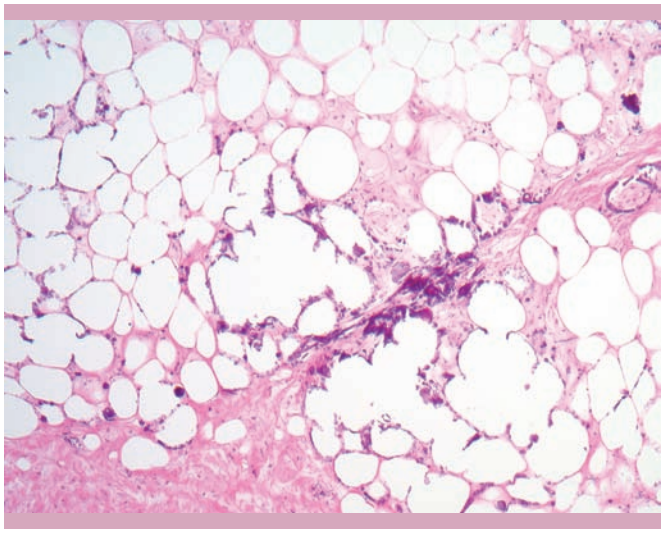

FIGURE 1-4

(A) Dystrophic calcification
(B) Fat necrosis
(C) Heterotopic bone formation
(D) Metastatic calcification
(E) Metastatic carcinoma

5. The changes present in this skin biopsy (see Figure 1-5) are an example of which morphologic pattern of acute inflammation?

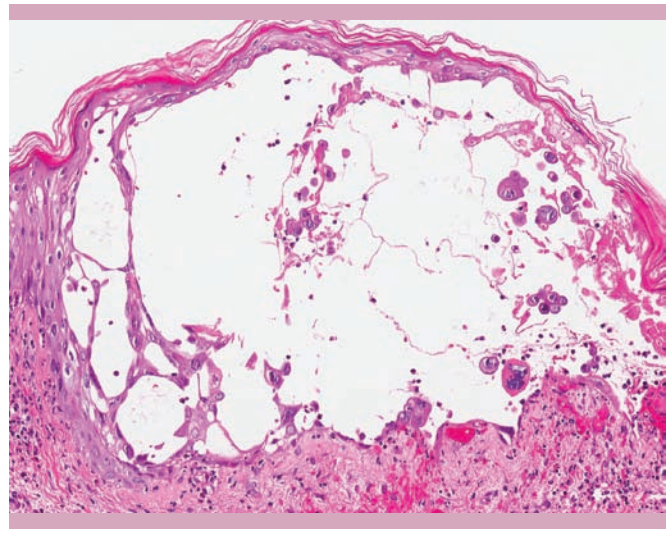

FIGURE 1-5

(A) Abscess formation
(B) Fibrinous inflammation
(C) Serous inflammation
(D) Suppurative inflammation
(E) Ulcer formation

6. This pattern of inflammation (see Figure 1-6) is associated with which of the following diseases?

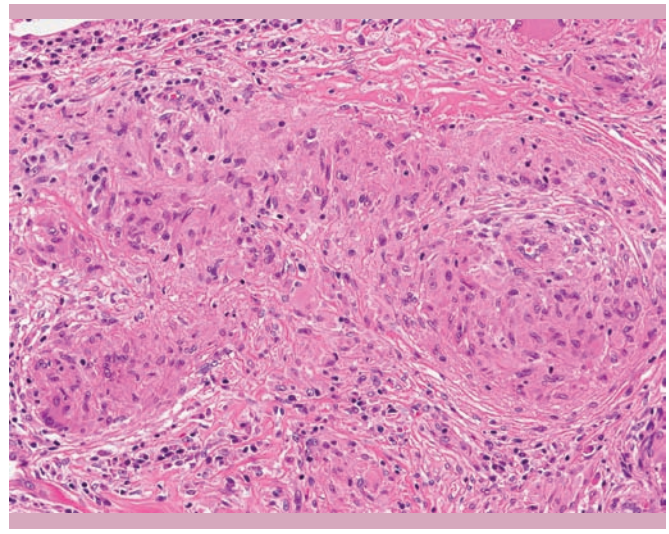

FIGURE 1-6

(A) Acute lung injury
(B) Nonspecific interstitial pneumonia
(C) Sarcoidosis
(D) *Staphylococcus aureus*
(E) Varicella virus

7. The thick pink material at the arrows in this photomicrograph (see Figure 1-7) is predominantly composed of what extracellular matrix protein?

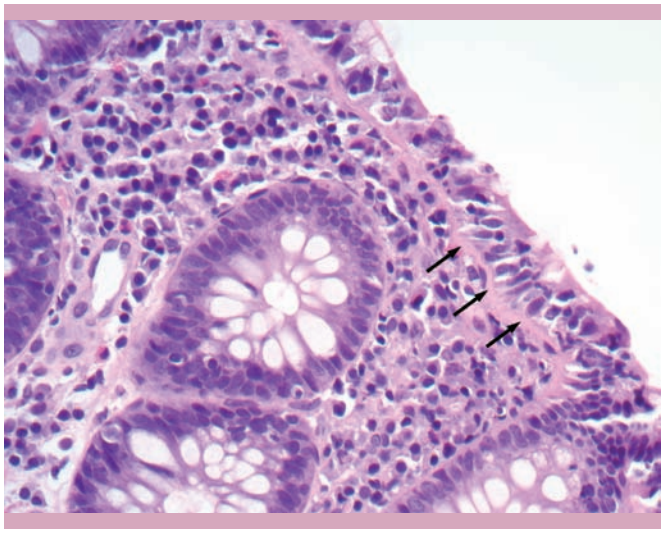

FIGURE 1-7

(A) Collagen type II
(B) Collagen type IV
(C) Elastin
(D) Fibrillin
(E) Hyaluronan

8. After a woman has her ear pierced, a keloid developed at the site of the piercing, which was subsequently excised (see Figure 1-8). Which of the following is incorrect about this abnormal repair response?

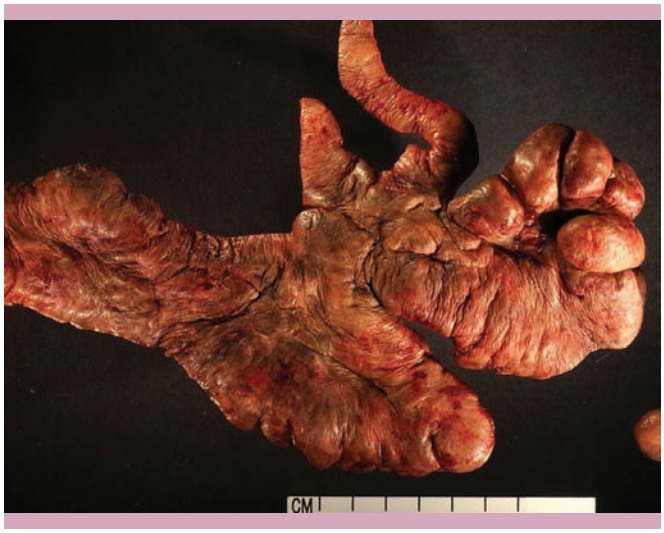

FIGURE 1-8

(A) Due to exuberant granulation tissue growth
(B) Fails to regress with normal remodeling
(C) May grow beyond the boundaries of the original wound
(D) Most common in African Americans
(E) Traumatic injury to the deep dermis is a typical inciting event

9. A patient with kidney disease (see Figure 1-9 electron micrograph of a typical glomerulus from this patient, CL = capillary lumen) and nephrotic syndrome has severe pitting edema in his lower legs. This edema is primarily caused by which of the following processes?

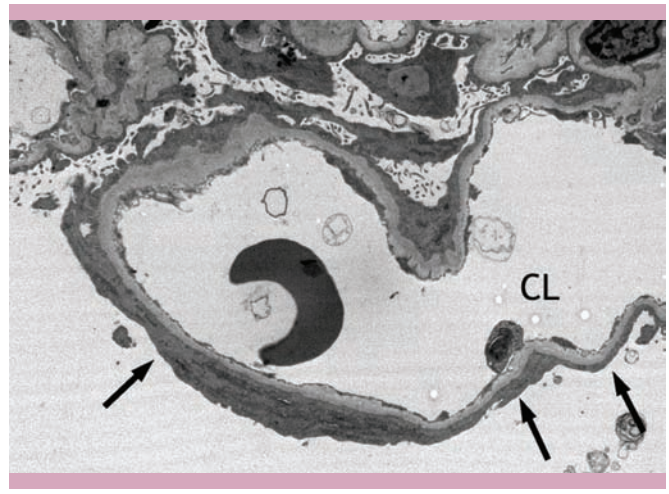

FIGURE 1-9

(A) Increased hydrostatic pressure due to arteriolar dilatation
(B) Increased hydrostatic pressure due to impaired venous return
(C) Increased vascular permeability
(D) Reduced plasma osmotic pressure
(E) Sodium retention

10. All of the following are examples of tissue hypertrophy except
(A) Biceps enlargement due to exercise
(B) Endometrial thickening due to excess estrogen
(C) Left ventricle enlargement due to high blood pressure
(D) Right ventricle enlargement due to pulmonary fibrosis
(E) Uterine enlargement during pregnancy

11. All of the following are examples of metaplasia except
(A) Apocrine change in the breast
(B) Barrett's esophagus
(C) Bronchial squamous mucosa in a smoker
(D) Myositis ossificans
(E) Notochord loss with development of the spinal cord

12. All of the following are true regarding ischemia except
    (A) Accumulation of toxic metabolites contributes to cell injury
    (B) Anaerobic glycolysis continues after the insult
    (C) Can be caused by reduced venous drainage
    (D) More rapid and severe than hypoxia alone
    (E) Most commonly due to blockage of arterial blood supply

13. Reversible cell injury is characterized by which of the following changes?
    (A) Apoptosis
    (B) Cell membrane disruption
    (C) Cellular swelling
    (D) Loss of mitochondrial function
    (E) Karyorrhexis

14. Which of the following situations would most likely result in liquefactive necrosis?
    (A) Acute pancreatitis
    (B) Pulmonary embolism
    (C) Pulmonary tuberculosis
    (D) Myocardial infarction
    (E) Stroke

15. A severely burned patient requires very high fluid replacement due to insensible losses from increased vascular permeability. All of the following are causes of increased vascular permeability and exudates in an inflammatory reaction except
    (A) Endothelial cell detachment
    (B) Endothelial cell necrosis
    (C) Leukocyte migration through vessel walls
    (D) Retraction of endothelial cells with gap formation
    (E) Transcytosis

16. During leukocyte recruitment to sites of cell injury, which of the following is not a phase of leukocyte recruitment?
    (A) Activation
    (B) Adhesion
    (C) Margination
    (D) Migration
    (E) Rolling

17. Which of the following is an example of chemotaxis?
    (A) Deposition of opsonins on target particles
    (B) Engulfment of microbes or dead cells by phagocytes
    (C) Expression of selectins on endothelial cell membranes
    (D) Increased vascular permeability due to cytokines
    (E) Movement of neutrophils along a gradient of bacterial products

18. Patients with chronic granulomatous disease suffer from recurrent bacterial infections that cannot be easily cleared despite normal numbers of leukocytes. This disease is an example of the importance of which function of leukocytes?
    (A) Engulfment of foreign particles
    (B) Oxidative burst
    (C) Production of cytokines
    (D) Recruitment to site of injury
    (E) Recognition of complement proteins

19. Nonsteroidal anti-inflammatory agents, such as aspirin, inhibit acute inflammatory reactions by what mechanism?
    (A) Down-regulating transcription of genes encoding cyclooxygenase 2 (COX)
    (B) Increasing vasoconstriction preventing leukocyte recruitment
    (C) Inhibiting conversion of cell membrane proteins to arachidonic acid
    (D) Preventing production of prostacyclin by COX1 and COX2
    (E) Reducing cell membrane expression of tumor necrosis factor (TNF) receptors

20. All of the following are true about chemokines except
    (A) Can be attached to cells or present in extracellular matrix
    (B) Different chemokines attract different leukocyte types
    (C) Function primarily as chemoattractants for leukocytes
    (D) Mediate the acute-phase systemic response
    (E) Some chemokine receptors mediate binding and entry of HIV into host cells

21. All of the following are true regarding the complement system except
    (A) Cleavage products of complement proteins are potent stimulators of other inflammatory responses
    (B) Does not interact with the coagulation cascade
    (C) Form the membrane attack complex (MAC)
    (D) Highly regulated system with many inhibitors
    (E) Present in the plasma in an inactive state

22. Acute-phase proteins, such as C-reactive protein (CRP), fibrinogen, and serum amyloid A (SAA), are up-regulated in acute inflammatory reactions. Which of the following is true regarding these proteins?

(A) Can bind to bacterial cells walls and act as opsonins
(B) CRP elevation is unreliable in predicting risk of myocardial infarction
(C) Not detectable in plasma in normal state
(D) Only certain acute inflammatory causes will result in up-regulation of these proteins
(E) Synthesized primarily by endothelial cells

23. All of the following tissues continuously proliferate throughout life, replacing destroyed cells except
(A) Bone marrow
(B) Duodenal mucosa
(C) Skeletal muscle
(D) Skin epithelium
(E) Uterine endometrium

24. A cell that retains the ability to continuously divide, but can only differentiate into one cell type (e.g., squamous epithelium) is called a(n)
(A) Embryonic stem cell
(B) Induced pluripotent stem cell
(C) Lineage-restricted stem cell
(D) Multipotent stem cell
(E) Pluripotent stem cell

25. Tyrosine kinase inhibitors, such as imatinib, most commonly act upon cell membrane receptors of growth factors, and prevent transduction of the signal across the cell membrane. Which of the following is true regarding cell membrane receptors with tyrosine kinase activity?
(A) Cyclic AMP pathway is the most common downstream effector molecule
(B) Ligand binding causes dimerization of the receptors, leading to tyrosine kinase activation
(C) Seven transmembrane alpha-helixes are almost always present
(D) Steroid hormones are ligands for receptors with tyrosine kinase activity
(E) The extracellular domain of the receptor has tyrosine kinase activity

26. The extracellular matrix of a tissue plays many important roles in tissue function and structure. Which of the following is not a function of the extracellular matrix?
(A) Creating a tissue microenvironment (e.g., barriers to solute diffusion in the kidney)
(B) Mechanical support of cells
(C) Production of signaling molecules
(D) Regulation of cell growth and proliferation
(E) Scaffolding for tissue renewal

27. All of the following are true about desmosomes except
(A) Are important in resisting shear forces
(B) Connect skeletal muscle cells to skeletal muscle cells
(C) Connect squamous cells to basement membrane
(D) Connect squamous cells to squamous cells
(E) Target of autoimmune antibodies in pemphigus vulgaris

28. Scar formation occurs when sufficient stromal framework damage prevents healing by cell regeneration alone. Which of the following is an example of scar formation?
(A) Abscess cavity filling and healing
(B) Bone marrow reconstitution after chemotherapy
(C) Epidermal repair after minor abrasions
(D) Liver hypertrophy after partial liver transplant
(E) Replacement of gut epithelium after an ischemic event

29. A surgeon performing a kidney transplant closes the skin incision with sutures, and the skin incision heals within a few weeks. This type of cutaneous wound healing is characterized by all of the following except
(A) Called healing by primary union
(B) Creation of a thin scar
(C) Limited cell death and connective tissue disruption
(D) Rapid re-epithelialization over the wound
(E) Significant wound contraction

30. A patient presents with unilateral pitting edema of the lower leg. An ultrasound shows a deep venous thrombosis. This edema is primarily caused by which of the following processes?
(A) Increased hydrostatic pressure due to arteriolar dilatation
(B) Increased hydrostatic pressure due to impaired venous return
(C) Increased vascular permeability
(D) Reduced plasma osmotic pressure
(E) Sodium retention

31. Primary hemostasis after trauma is achieved by which of the following processes?
(A) Arteriolar vasoconstriction
(B) Fibrin meshwork formation
(C) Increased vascular permeability
(D) Platelet plug formation
(E) Tissue plasminogen activity (t-PA)

32. Endothelial cells play an important role in the maintenance of normal hemostasis and clot formation after injury. Which of the following is not a function of endothelial cells in hemostasis?
(A) Contain membrane-bound heparin-like molecules to inhibit thrombosis
(B) Prevent platelet exposure to extracellular matrix proteins
(C) Prostacyclin production to inhibit platelets
(D) Secrete adenosine diphosphate (ADP), which promotes platelet inactivation
(E) Synthesize tissue-type plasminogen activator (t-PA), which degrades clots

33. Platelets are critical in initially stopping tissue hemorrhage after injury. Which of the following is true regarding platelet function in hemostasis?
(A) Alpha-granules contain ADP, calcium, and serotonin
(B) Dense granules contain P-selectin, fibrinogen, and platelet factor 4
(C) Platelet contraction is reversible
(D) Platelets degrade thromboxane A2 to promote platelet aggregation
(E) von Willebrand factor binding to glycoprotein Ib is primarily used for platelet adhesion

34. Excessive clot formation is prevented by activation of the fibrinolytic cascade. Which of the following is not true regarding fibrinolysis?
(A) Fibrin degradation results in fibrin split products (FSP)
(B) Plasmin is generated from plasminogen by tissue factor
(C) Plasmin is the primary enzyme that breaks down fibrin
(D) Streptokinase, produced by some bacteria, can also convert plasminogen to plasmin
(E) Tissue plasminogen activator (t-PA) is most active when bound to fibrin

35. Abnormal blood flow (stasis and turbulence) promotes clot formation by which mechanism?
(A) Exposure of extracellular matrix proteins to platelets
(B) Increased activation of coagulation factors by shear forces
(C) Increased production of t-PA by injured endothelial cells
(D) Irregular flow presses platelets against endothelial cells
(E) Laminar flow presses platelets against endothelial cells

36. Factor V Leiden is an inherited hypercoagulable state. Thrombosis in patients with Factor V Leiden is caused by what mechanism?
(A) Absence of protein C, which cleaves factor V
(B) Constitutive activation of factor V
(C) Factor V resistance to cleavage by protein C
(D) Factor V resistance to cleavage by protein S
(E) Increased levels of factor V

37. A woman who was in a major motor vehicle accident has a femoral fracture. She develops shortness of breath, confusion, and thrombocytopenia shortly after arriving at the emergency room. What is the most likely cause of her symptoms?
(A) Air embolism
(B) Amniotic fluid embolism
(C) Fat embolism syndrome
(D) Pulmonary embolism
(E) Sepsis

38. Shock is the final common, often fatal, pathway for many different disorders. All of the following are true about shock except
(A) Compensatory mechanisms can initially maintain organ perfusion in shock
(B) Peripheral vasoconstriction (cool, blue skin) is seen in all types of shock
(C) Septic shock can occur even when the infection is localized
(D) Shock results in impaired tissue perfusion and cellular hypoxia
(E) Tissue hypoxia leads to cell death and release of toxins that accelerates shock

39. On routine serum chemistry testing, a patient is found to have elevated liver enzymes. A liver biopsy was performed and show chronic passive congestion (see Figure 1-10). What other pathologic process is this patient likely to have?

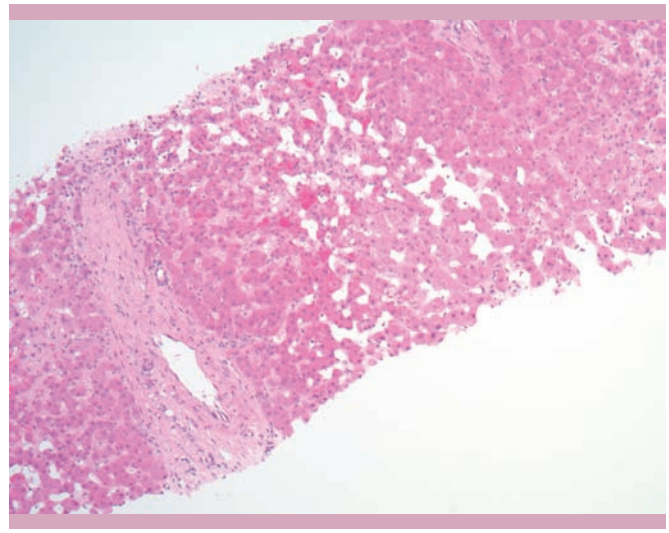

FIGURE 1-10

(A) Cirrhosis
(B) Congestive heart failure
(C) Hepatitis C
(D) Sepsis
(E) Thromboembolic disease

40. A patient with severe atherosclerosis presents with nausea, vomiting, and an elevated serum creatinine. A photomicrograph of what his kidney might look like is provided (see Figure 1-11). This macroscopic appearance is most consistent with which of the following processes?

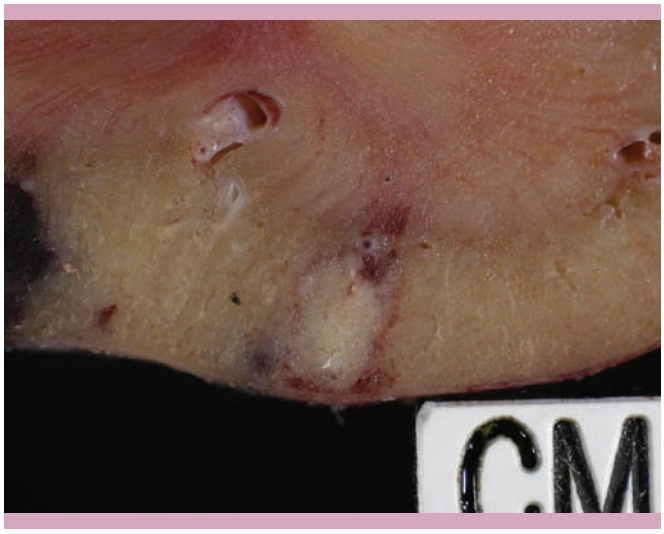

FIGURE 1-11

(A) Congestion
(B) Edema
(C) Hypertrophy
(D) Infarction
(E) Neoplasm

41. An important mechanism of cell injury is oxidative stress (often in the form of free radicals). An increase in free radicals would be seen in all of the following except
(A) Decreased glutathione peroxidase levels
(B) Elevated levels of vitamin E
(C) Ionizing radiation damage
(D) Leukocytes activated during inflammatory reactions
(E) Nitric oxide release

42. Most cells have a fixed number of divisions before becoming senescent. All of the following are causes of cellular aging except
(A) Calorie restriction
(B) Defective DNA replication
(C) Free radical generation
(D) Increasing cellular damage
(E) Telomere shortening

43. All of the following statements about apoptosis are true except
(A) Apoptosis is an integral part of embryogenesis
(B) Appears as cell fragments with intact cytoplasmic membranes
(C) Can be activated by FAS-FAS ligand binding
(D) Incites a brisk inflammatory response
(E) Occurs in normal germinal centers

44. All of the following are true about histamine except
(A) Histamine causes increased permeability of vessels
(B) Histamine is a plasma-derived protein
(C) Histamine release can be activated by C3a
(D) Histamine results in dilation of arterioles
(E) Histamine is stored in mast cell granules

45. A patient with a chronic autoimmune disease suffers from severe weight loss and anorexia, or cachexia. Which of the following inflammatory mediators is primarily responsible for this pathologic state?
(A) Complement proteins
(B) Histamine
(C) Nitric oxide
(D) Prostaglandin
(E) Tumor necrosis factor (TNF)

46. Macrophages are the main cellular component of chronic inflammatory processes. All of the following are true about macrophages except
(A) Able to ingest foreign particles
(B) Activated by interferon-gamma
(C) Derived from bone marrow stem cells
(D) Produce reactive oxygen species
(E) Short lived (6 hours or less)

47. Angiogenesis is a critically important part of all wound healing. All of the following are steps in angiogenesis except
(A) Basement membrane degradation
(B) Migration of endothelial cells
(C) Recruitment of peri-endothelial cells
(D) Vasodilation
(E) Wound contraction

48. Which is of the following is an example of autocrine signaling in cell growth?
    (A) Antigen presenting lymphocyte secretes cytokines that causes itself to proliferate
    (B) Injured hepatocyte releases cytokines, causing a nearby stem cell to proliferate
    (C) Macrophage secretes cytokines, causing a nearby fibroblast to proliferate
    (D) Pituitary cell secretes growth hormone, causing osteoblasts to proliferate
    (E) T-cell recognizing foreign viral particles induces a tissue cell to undergo apoptosis

49. At the end of 1 week, a healing skin wound has approximately 10% of the tensile strength of unwounded skin. At 3 months, what is the tensile strength of a healing skin wound (compared with unwounded skin)?
    (A) 20%
    (B) 40%
    (C) 50%
    (D) 80%
    (E) 100%

50. A patient with severe chronic renal failure goes out for dinner to a restaurant and eats a large amount of salted fish. The next day, he finds his legs are both swollen with edema. This edema is primarily caused by which of the following processes?
    (A) Increased hydrostatic pressure due to arteriolar dilatation
    (B) Increased hydrostatic pressure due to impaired venous return
    (C) Increased vascular permeability
    (D) Reduced plasma osmotic pressure
    (E) Sodium retention

51. Which of the following statements is incorrect regarding water as a component of the body?
    (A) Around 60% of lean body weight is water
    (B) Close to 25% of the body's water is in blood plasma
    (C) More than 50% of the body's water is within cells
    (D) Nearly 33% of the body's water is in extracellular spaces
    (E) The balance of intracellular and extracellular water is partially controlled by solutes

52. The coagulation cascade's primary purpose is to promote clot formation through thrombin generation. All of the following are true regarding the extrinsic pathway of the coagulation cascade except
    (A) Includes factor XII (Hageman factor)
    (B) Is identical to the intrinsic pathway from factor X onward
    (C) Is the primary pathway for clotting in vivo after injury
    (D) Prothrombin time (PT) primarily tests the extrinsic pathway
    (E) Requires the addition of tissue lysates to promote clotting in vitro

53. Virchow's triad predicts that three abnormalities can result in abnormal thrombus formation. Virchow's triad includes
    (A) Endothelial injury, abnormal blood flow, and hypercoagulability
    (B) Endothelial injury, abnormal blood flow, and hypocoagulability
    (C) Endothelial injury, increased blood flow, and hypercoagulability
    (D) Endothelial secretion of prothrombotic products, abnormal blood flow, and hypercoagulability
    (E) Endothelial secretion of prothrombotic products, increased blood flow, and hypercoagulability

ANSWERS

1. **(C) Iron.**
Accumulation of normal and abnormal intracellular proteins and materials can result in cell injury and death. The photomicrograph demonstrates abnormal accumulation of iron in the hepatocytes, which stains blue on Prussian blue stain. Patients with hemochromatosis have abnormal iron absorption regulation; systemic increased deposition of iron in otherwise normal tissues results in damage, and cell loss results in liver and heart failure. Abnormal calcium deposition can result in dystrophic and metastatic calcifications. Lipofuscin is composed of lipids and phospholipids, and is not injurious to cells, but is a common sign of other cellular injuries. Melanin deposition can rarely be abnormally deposited in the disorder ochronosis. Bilirubin is the main pigment of bile, and excess accumulation results in jaundice.
2. **(D) Karyorrhexis.**
Karyorrhexis is a pattern of nuclear breakdown that shows pyknosis with subsequent nuclear fragmentation. Karyolysis occurs when nuclear DNA and chromatin are enzymatically degraded, resulting in faded nuclear staining. Pyknosis is characterized by nuclear shrinkage and increased basophilia without nuclear fragmentation. Balloon degeneration is a cytoplasmic change in hepatocytes characterized by cell swelling and vacuolation. Fatty change is

a cytoplasmic alteration seen in reversible cellular injury.

3. **(B) Coagulative necrosis.**
Coagulative necrosis most often occurs when an interruption in blood supply results in tissue ischemia and death. This pattern of necrosis preserves the tissue architecture for several days, but the cells are eosinophilic and lack nuclei. Liquefactive necrosis is characterized by digestion of the dead cells, resulting in a liquid, viscous mass; this pattern is frequently seen in bacterial infections and CNS infarction. Gangrenous necrosis refers to cell death, typically in a limb, which has superimposed infection. Caseous necrosis is most common in tuberculous infection, resulting in cheese-like white friable material. Fibrinoid necrosis is a special form of necrosis around vessels where immune complexes are deposited, resulting in a "bright pink" amorphous appearance.
4. **(D) Metastatic calcification.**
The photomicrograph demonstrates dark purple deposits of calcium within fibroadipose tissue, consistent with metastatic calcification. Metastatic calcification occurs in patients with severe hypercalcemia, and most commonly occurs in skin, mucosal sites, kidneys, lungs, systemic arteries, and pulmonary veins. Morphologically, the deposits resemble dystrophic calcification. However, dystrophic calcifications occur in the absence of hypercalcemia, and occur in sites of prior tissue injury, such as areas of necrosis or atherosclerotic plaques. Fat necrosis occurs in areas of fat destruction with saponification, most commonly in pancreatitis. Heterotopic bone formation can occur in areas of previous injury, and shows variably organized bone formation. Metastatic carcinoma would demonstrate neoplastic epithelial cells on biopsy.
5. **(C) Serous inflammation.**
The photomicrograph shows a skin blister caused by varicella virus (chicken pox) that resulted in an outpouring of thin fluid (serous fluid) due to vasodilation and increased vascular permeability. This is an example of serous inflammation, and is frequently seen in effusions from peritoneal, pleural, and pericardial cavities. Fibrinous inflammation occurs when even greater vascular permeability permits outpouring of both fluid and larger molecules, such as fibrin, which organize into a meshwork of eosinophilic threads (fibrinous material). Suppurative inflammation occurs when large numbers of neutrophils involve an area that often has undergone liquefactive necrosis; an abscess forms when this area forms a cavity trapped in a confined space or organ. Ulcer formation occurs when necrotic tissue close to a surface (skin, mucosal, etc.) is sloughed, leaving a marked inflammatory response at the base of the defect.
6. **(C) Sarcoidosis.**
The photomicrograph depicts granulomatous inflammation, which is a distinctive pattern of chronic inflammation. Granulomatous inflammation is associated with *Mycobacterium tuberculosis* infection, sarcoidosis, syphilis, and many other processes. Acute lung injury is characterized by a serous or fibrinous inflammation, due to trauma of the lung microvasculature. Nonspecific interstitial pneumonia is characterized by a chronic inflammatory response composed predominantly of lymphocytes. *Staphylococcus aureus* usually incites a suppurative inflammatory response, and varicella infection leads to blisters, which are formed by a serous inflammatory response.
7. **(B) Collagen type IV.**
The structure at the arrows in the photomicrograph is basement membrane underlying epithelium. Basement membranes are predominantly composed of collagen type IV, along with laminin. Collagen type II is the predominant component of cartilage. Elastin fibers are an important component of large blood vessels, uterus, skin, and ligaments. Fibrillin is a glycoprotein that surrounds and supports elastin fibers, and alterations in this protein are the cause of Marfan syndrome. Hyaluronan is a glycosaminoglycan, which is abundant in many tissue types and provides lubrication for joints.
8. **(A) Due to exuberant granulation tissue growth.**
Keloid formation (hypertrophic scar formation) is caused by excessive collagen deposition, which persists and/or resists remodeling. This wound healing response can extend beyond the boundaries of the original wound, and is most commonly caused by a traumatic injury, which penetrates to the deep dermis. This aberration is more common in African Americans, for unknown reasons. Granulation tissue does not play a part in this abnormal wound healing response.
9. **(D) Reduced plasma osmotic pressure.**
Edema can be caused by an imbalance in solutes, plasma osmotic pressure, or hydrostatic pressure. Nephrotic syndrome can be caused by a variety of diseases; the photomicrograph in this example is suggestive of minimal change disease, with effacement of the normal podocyte foot structure (arrows) around capillary lumens (CL). In nephrotic syndrome, excessive albumin and protein are lost from the kidneys into the urine. This results in reduced plasma osmotic pressure, which results in movement of water from the plasma

into extracellular tissues. Reduced plasma osmotic pressure can also be caused by reduced synthesis of plasma proteins, which occurs in liver failure (cirrhosis) or starvation.

10. **(B) Endometrial thickening due to excess estrogen.**
Hypertrophy is a process of cellular adaptation to stress or injury, which results in enlargement of cells, without an increase in the number of cells. This adaptation most commonly occurs in tissues that cannot undergo cellular division, such as cardiac (answers C and D) and skeletal muscle (answer A). An increase in protein and myofilaments allows each muscle fiber to generate increased force. In pregnancy, the myometrial smooth muscle cells undergo significant hypertrophy in response to hormonal alterations (e.g., physiologic hypertrophy). In contrast, endometrium stimulated with estrogen demonstrates a marked increase in epithelial and stromal cells, which remain normal in size (hyperplasia).

11. **(E) Notochord loss with development of the spinal cord.**
Metaplasia is a reversible adaptive cellular response to injury where one cell type is replaced by another cell type without an overall change in tissue architecture. The most common metaplasia is conversion from columnar or respiratory epithelium to squamous epithelium, often in the trachea and bronchi in smokers. Other examples include Barrett's esophagus (squamous to glandular metaplasia), myositis ossificans (muscle to bone), and apocrine metaplasia of the breast (normal ductal epithelium to apocrine epithelium). In contrast, the notochord undergoes atrophy during fetal development to make room for later development of the spinal cord with a completely different architecture.

12. **(B) Anaerobic glycolysis continues after the insult.**
Ischemia is the most common type of cell injury and results in both hypoxia (reduction in oxygen supply to tissues), loss of nutrients, and loss of removal of toxic metabolites. Therefore, it results in more rapid and severe injury than hypoxia alone. It is most commonly caused by a blockage in arterial blood supply, but can be caused by reduced venous drainage that prevents adequate arterial perfusion. When hypoxia occurs in isolation, cells usually remain supplied with sufficient nutrients to continue anaerobic glycolysis for a period of time after the initial insult, but in ischemia, the nutrient supply is restricted, and cells rapidly exhaust glycolytic substrates.

13. **(C) Cellular swelling.**
Reversible injury to cells is characterized by a reduction in energy stores (ATP) and changes in ion concentrations, resulting in water influx. Morphologically, this is demonstrated by cellular swelling, microscopic vacuoles, and lipid vacuoles. Eventually, sufficient cellular injury occurs such that the damage becomes irreversible, resulting in cell death by either necrosis or apoptosis. Irreversible changes of injury resulting in necrosis are characterized by cell membrane disruption, lysosomal rupture, and severe mitochondrial damage. Apoptosis is a form of cell death that is more controlled and results in nuclear dissolution (karyorrhexis) and cell fragmentation without loss of membrane integrity.

14. **(E) Stroke.**
Liquefactive necrosis occurs when necrotic cells are digested, resulting in transformation of the dead cells into a liquid, viscous mass. This is most commonly seen in bacterial infections (abscess), but is also the pattern of CNS necrosis from ischemic events (e.g., stroke). Acute pancreatitis is an example of fat necrosis. Pulmonary tuberculosis is an example of caseous necrosis. Myocardial infarction is an example of coagulative necrosis. Pulmonary embolism does not typically result in necrosis due to the dual blood supply to the lungs.

15. **(C) Leukocyte migration through vessel walls.**
During acute inflammatory reactions, substantial fluid exudation occurs due to increased vascular permeability. This is accentuated in burned patients, who lose a substantial volume of exudate into the environment. The most common mechanisms of increased vascular permeability are formation of interendothelial spaces (through contraction and retraction of endothelial cells), endothelial injury (leading to necrosis or detachment), and transcytosis (transport of fluids and proteins across intact endothelial cells). While leukocyte migration is an important part of acute inflammatory responses, it does not contribute to fluid shifts.

16. **(A) Activation.**
The process of leukocyte recruitment to sites of cell injury is critically important in the inflammatory response. Leukocytes start this process by margination (moving to a peripheral location in the bloodstream along the vessel wall), and slow by rolling that is mediated by the selectin family of proteins. Once leukocytes come to rest, they adhere to the endothelium by integrin proteins, and then migrate through the endothelial wall. Activation does not occur until leukocytes have arrived at the site of cell injury and infection.

17. **(E) Movement of neutrophils along a gradient of bacterial products.**
Chemotaxis is defined as cellular locomotion along a chemical gradient, which can be composed of bacterial products, cytokines, or complement proteins. While expression of selectins on endothelial cell membranes is important in the rolling phase of leukocyte recruitment, a gradient is not present. Opsonins are placed on target particles for engulfment, but this targeting for destruction does not necessarily result in cell locomotion. While cytokines can act as the chemical gradient for chemotaxis, their effect on vessel walls does not play a part in locomotion.
18. **(B) Oxidative burst.**
In chronic granulomatous disease (CGD), an inherited defect in phagocyte oxidase reduces the amount of oxygen-free radicals that can be produced inside the leukocyte lysosome, which then combines with engulfed foreign particles (specifically bacteria) and destroys the foreign material. Patients with CGD have normal or increased numbers of leukocytes, which are appropriately recruited to sites of injury and engulf bacterial organisms, but are unable to kill them. They eventually develop a brisk macrophage infiltrate, which forms granulomas in an attempt to control the infection. While recognition of complement proteins, particularly C5a, is important in recognizing foreign particles by leukocytes, free radicals are still required for destruction.
19. **(D) Preventing production of prostacyclin by COX1 and COX2.**
Nonsteroidal anti-inflammatory agents (NSAIDs), such as aspirin, block the activity of COX1 and COX2 enzymes, which convert arachidonic acid to prostaglandins, potent mediators of the inflammatory response. Steroids cause down-regulation in the transcription of COX genes, as well as many other inflammatory genes, and can also decrease the conversion of cell membrane lipids to arachidonic acid. Although reduction in TNF receptors would reduce the inflammatory response, this is not mediated by NSAIDS. NSAIDS do not play a direct role in vasoconstriction or vasodilation.
20. **(D) Mediate the acute-phase systemic response.**
Chemokines are small proteins that function primarily as chemoattractants for various leukocytes. The CXC group attracts neutrophils; the CC group attracts monocytes, eosinophils, basophils, and lymphocytes; the C group attracts lymphocytes; and the CX3C group attracts monocytes and T-cells. The chemokine receptors CXCR4 and CCR5 have been implicated in the binding HIV-1 viral particles, and mediate viral entry into host cells. Chemokines can be present on cell membranes or in the extracellular matrix. The acute-phase systemic response is primarily mediated by TNF and IL-1, which are not classified as chemokines.
21. **(B) Does not interact with the coagulation cascade.**
The complement system contains more than 20 proteins that function in a variety of ways: stimulate other inflammatory reactions (particularly C3a and C5a), act as opsonins to promote phagocytosis, and cause cell lysis when the MAC is formed. These proteins are synthesized by the liver, and are present ubiquitously in the plasma, in an inactivated state. Given the highly dangerous properties of an unchecked complement cascade, many potent inhibitors of this system exist in both the plasma and on the surface of healthy cells. This system is intimately connected with other plasma-derived systems; it can promote the coagulation cascade, and products of the coagulation cascade can initiate the complement cascade.
22. **(A) Can bind to bacterial cells walls and act as opsonins.**
Acute-phase reaction proteins, the best known of which are CRP, fibrinogen, and SAA, are normally detected in plasma, but increase to more than 100x their normal plasma concentrations in the setting of an acute inflammatory reaction. The increase is regulated by several cytokines, including IL-1, IL-6, and TNF, which are common to nearly all acute inflammatory responses. These proteins can then bind to foreign materials and act as opsonins, help to clear chromatin debris, and alter normal lipid metabolism to help sustain inflammatory cells. Nearly all acute-phase proteins are produced by hepatocytes, not endothelial cells. CRP elevation has recently been found to be a sensitive marker of increased risk of myocardial infarction in patients with coronary artery disease.
23. **(C) Skeletal muscle.**
The tissues of the body are generally classified into three groups: continually dividing, quiescent, and nondividing. Most mucosal sites of the body (gastrointestinal tract, oral cavity), skin, and bone marrow undergo continuous proliferation to replace cells that are lost on a daily basis. The endometrium of the uterus is another example of a continuously dividing tissue. In contrast, skeletal muscle, cardiac muscle, and nerves cannot undergo division to replace lost tissues except in limited circumstances. Quiescent tissues, such as liver, usually are not proliferating, but after injury can undergo significant proliferation to replace the lost tissue.

24. **(C) Lineage-restricted stem cell.**
Stem cells are cells capable of continuously dividing and self-renewing, and have the capacity to give rise to cells that are highly differentiated. Embryonic stem cells or pluripotent stem cells are present in the early stages of embryogenesis, and are capable of differentiating into nearly all tissue cell types in the body. Induced pluripotent stem cells are adult somatic cells from a differentiated tissue (e.g., liver), which, when the nucleus is implanted into an enucleated oocyte, are then able to differentiate into any tissue type in the body, similar to embryonic stem cells. Multipotent stem cells are able to differentiate along a restricted set of divergent tissue types (e.g., marrow stem cells can become chondrocytes, osteoblasts, adipocytes, and endothelial cells). Lineage-restricted stem cells are most commonly found as reserve cells within a specific tissue type, and are only able to produce differentiated cells of that type.

25. **(B) Ligand binding causes dimerization of the receptors, leading to tyrosine kinase activation.**
Many signaling molecules have receptors with tyrosine kinase activity, including epidermal growth factor, vascular endothelial growth factor, platelet-derived growth factor, c-KIT ligand, and insulin. These receptors are characterized by an intracytoplasmic domain that has tyrosine kinase activity. When ligand binds to the receptor it dimerizes, which activates the tyrosine kinase activity. Then, downstream effector molecules, such as MAP kinase, or phosphatidyl inositol-3 kinase (PI3), transmit the signal. G-protein-coupled receptors, which do not have tyrosine kinase activity, are characterized by seven transmembrane alpha-helixes coupled to the cyclic AMP pathway. Steroid hormones are unusual in that they diffuse through the cell membrane and bind to receptors in the nucleus that directly affect transcription.

26. **(C) Production of signaling molecules.**
The extracellular matrix is composed of several macromolecules, such as collagen, which form a scaffolding on which tissue cells reside. It provides both structural support and cell anchorage, as well as mediating interactions between cells. Varied construction of the extracellular matrix can also result in different tissue microenvironments within the same organ (e.g., kidney compartments which concentrate urine in the nephron). Through interactions of extracellular matrix components and cell receptors (integrins), cellular growth and proliferation can be stimulated or suppressed. While signaling molecules can be stored in the extracellular matrix, they must be initially produced by a cell.

27. **(C) Connect squamous cells to basement membrane.**
Desmosomes are part of the cadherin family of proteins that form junctions between cells of the same type. Desmosomes are important in connecting and holding together squamous cells and skeletal muscle cells and resisting shear forces. However, hemidesmosomes are responsible for binding squamous cells to the basement membrane underneath. In pemphigus vulgaris, autoantibodies against desmoglein 3, the major component of desmosomes, results in loss of keratinocyte to keratinocyte adhesion and blister formation.

28. **(A) Abscess cavity filling and healing.**
When an abscess forms, extensive tissue damage and destruction of the extracellular matrix result in cavitation. The loss of stromal framework results in wound healing through scar formation, which involves deposition of collagen and other extracellular matrix components to fill the defect. Choices B, C, and E all are examples of tissue injury that do not affect the stromal framework and result in complete tissue restoration upon cellular regeneration. Choice D, liver hypertrophy after liver transplant, involves an increase in the number of hepatocytes within a normal tissue framework.

29. **(E) Significant wound contraction.**
Cutaneous wound healing can occur by primary union or secondary union. Primary union occurs when sutures reapproximate thin wounds from clean surgical incisions. This type of healing involves very little cell death and tissue disruption, results in rapid re-epithelialization over the wound and ultimately a thin scar. In contrast, secondary union occurs when a large volume of tissue has been lost, resulting in significant cell death and connective tissue disruption. Secondary union is characterized by substantial collagen deposition that forms a large scar that over time will contract a substantial amount.

30. **(B) Increased hydrostatic pressure due to impaired venous return.**
Edema can be caused by an imbalance in solutes, plasma osmotic pressure, or hydrostatic pressure. Deep venous thrombosis results in regional impaired venous return of blood to the heart, and the resultant increased hydrostatic pressure causes excess water to move into the extracellular tissues. An example of generalized impaired venous return is congestive right heart failure: the weakened pumping ability of the heart to return blood to the arterial system causes a buildup of blood within the venous system. This increase in hydrostatic venous pressure results in edema throughout the body, which is called anasarca.

31. **(D) Platelet plug formation.**
Hemostasis after injury proceeds through several distinct phases: initial vasoconstriction, primary hemostasis (platelet plug formation), secondary hemostasis (fibrin meshwork formation), and permanent plug formation with clot organization. Primary hemostasis is primarily driven by exposure of extracellular matrix proteins to the blood plasma, which promotes platelet adhesion and activation, ultimately forming a platelet plug that stops the extravasation of blood.

32. **(D) Secrete adenosine diphosphate (ADP), which promotes platelet inactivation.**
Endothelial cells are key players in the maintenance of normal hemostasis. Normal endothelial cells generally promote antithrombotic pathways, while injured endothelial cells promote thrombosis. Normal endothelial cells secrete several products that decrease thrombosis, including prostacyclin (an inhibitor of platelet activation), tissue-type plasminogen activator (which starts a cascade to degrade fibrin clots), and thrombomodulin (which binds thrombin and inactivates it). In addition, endothelial cells contain membrane-bound heparin-like molecules that help to inhibit thrombosis in the local environment. Finally, endothelial cells cover extracellular matrix proteins, which are potent stimulators of thrombosis. Endothelial cells also secrete adenosine diphosphatase, which degrades ADP, an essential molecule in platelet activation.

33. **(E) von Willebrand factor binding to glycoprotein Ib is primarily used for platelet adhesion.**
Platelets go through three phases during hemostatic plug formation. Initially, platelets adhere to the site of injury through binding of glycoprotein Ib (on platelet membranes) to von Willebrand factor (in the extracellular matrix). Then platelets secrete material stored in granules: alpha-granules contain P-selectin, fibrinogen, and platelet factor 4, while dense granules contain ADP, calcium, and serotonin. These products promote fibrin clot formation over the still-reversible platelet aggregate. Once a clot has formed, the platelets contract to form an irreversible mass that cements the clot in place. Platelets also synthesize thromboxane A2, which is a potent vasoconstrictor as a well as a promoter of platelet aggregation.

34. **(B) Plasmin is generated from plasminogen by tissue factor.**
The fibrinolytic cascade is initiated by the formation of fibrin clots in order to limit the extent of clot formation. Plasmin is the primary enzyme that breaks down fibrin, and is formed by the breakdown of plasminogen by either plasminogen activators or the coagulation factor XII pathway. t-PA, which is used as a clinical clot-busting drug, is most active when bound to fibrin, which is helpful in confining the activity to recent sites of thrombosis. Other enzymes can also activate plasmin, including urokinase-like PA and streptokinase (which is produced by some bacteria). When fibrin is broken down by plasmin, FSPs are released, which are elevated in states of high clot turnover, such as disseminated intravascular coagulation.

35. **(D) Irregular flow presses platelets against endothelial cells.**
Normal blood flow is laminar, which causes cellular products, including platelets, to flow in the central portion of the vessel, away from the endothelium, and pushes cell-poor plasma to the periphery of the vessel. Stasis and turbulence both result in platelets coming into contact with endothelium more easily, as well as preventing washing away of clotting factors. While over time endothelial cells may be damaged by turbulent blood flow, endothelial cells generally continue to prevent exposure of extracellular matrix proteins to blood plasma. t-PA increases fibrinolysis and destroys clots. It is generally produced by intact endothelial cells.

36. **(C) Factor V resistance to cleavage by protein C.**
Factor V Leiden is an inherited hypercoagulable state, which is caused by a mutation in factor V rendering it immune to cleavage by protein C. It results in a modest increase in hypercoagulability, and most commonly manifests by deep venous thrombosis. Protein C deficiency is the cause of another rare hypercoagulable state. The level of factor V is normal or slightly decreased in patients with Factor V Leiden, rather than increased. An increase in prothrombin is the cause of a different hypercoagulable state. Factor V Leiden still needs to be modified by thrombin to be activated (V to Va). Protein S is a cofactor for protein C, but is not the primary mechanism of inactivation of factor V in this disease.

37. **(C) Fat embolism syndrome.**
Embolisms occur when blood clots or other materials (air, amniotic fluid, or fat and bone marrow) are carried by the blood to distant sites in the body. The most common is embolism of a deep venous thrombosis to the pulmonary artery, termed a pulmonary embolism. This patient has had a recent major bone fracture, which predisposes her to fat and bone marrow embolism throughout the body. Patients who become symptomatic have fat embolism syndrome, which typically results in pulmonary problems, neurologic symptoms, anemia, and thrombocytopenia. This

syndrome is partly caused by vasculature occlusion by the embolized fat and partly due to toxic injury of the vessels from fatty acid release, and can be fatal in up to 15% of patients.

38. **(B) Peripheral vasoconstriction (cool, blue skin) is seen in all types of shock.**
Shock is a final pathway that results in decreased tissue perfusion, tissue hypoxia, and cell death, and can be fatal in over 20% of patients. Multiple different types of shock occur: cardiogenic (inability of the heart to maintain perfusion), hypovolemic (low blood volume due to fluid losses), septic shock (in the setting of infection), and neurogenic (anesthesia or neural injury). In the beginning, compensatory mechanisms can maintain tissue perfusion, such as vasoconstriction or catecholamine release. However, eventually this compensation will be inadequate and tissue hypoxia will result in cell death, which often accelerates the development of shock by releasing toxins and lysosomal enzymes. Septic shock can occur even when the infection is localized due to the cytokine release that results in a systemic response. Most patients with shock will have peripheral vasoconstriction (cool, blue extremities) in an attempt to maintain tissue perfusion, but in septic shock, patients will have peripheral vasodilation (warm, red extremities) due to vasodilation mediated by bacterial product release.

39. **(B) Congestive heart failure.**
Chronic congestion can result in tissue injury if longstanding in duration. Congestion is caused by a buildup of blood within vessels, causing dilatation and increased hydrostatic pressure. Tissues with congestion often appear cyanotic in color due to buildup of unoxygenated blood. In this example, congestive right heart failure resulted in chronic congestion of the liver. The biopsy demonstrates dilated central veins with deposition of hemosiderin and atrophy of hepatocytes around the central vein. Eventually, this process can lead to fibrosis and cirrhosis of the liver, imparting a "nutmeg" appearance on cut section. None of the other choices would result in this pattern of liver injury.

40. **(D) Infarction.**
Infarcts are areas of necrosis most commonly caused by interrupted blood supply from arteries or veins. Arterial infarcts are most commonly caused by either embolic material (e.g., atherosclerotic plaque) or local clot formation (e.g., from endothelial injury) that occludes blood flow. These infarcts appear wedge shaped as in this photomicrograph. In contrast, venous occlusions typically result in excess pooled blood that is unable to drain. Edema and hypertrophy would both result in increased size of the organ, and edema would also cause the organ to look pale and wet. Congestion would result in a diffusely red organ. Neoplasms can have a variety of appearances, but most commonly would demonstrate expansile growth, irregular coloration, and an infiltrative border.

41. **(B) Elevated levels of vitamin E.**
Oxidative stress or generation of free radicals is an important mechanism of cell injury and death. Free radicals are chemical species that have a single unpaired electron in an outer orbit, and the unstable configuration can react with key components of the cell. The most common free radical is superoxide. Ionizing radiation, nitric oxide, and some chemicals can generate free radicals. Leukocytes produce free radicals in a carefully controlled reaction within lysosomes to destroy engulfed bacterial organisms. Glutathione peroxidase is an enzyme that breaks down free radicals. Vitamin E is a natural antioxidant that inactivates free radicals, and when increased, helps to reduce free radicals.

42. **(A) Calorie restriction.**
Cellular aging (senescence) is the result of progressive cellular functional decline and viability due to the accumulation of cellular damage. Multiple molecular mechanisms are responsible for this process, including free radical generation, which is a common cause of cellular injury. DNA repair mechanism failure also results in shortening of cellular longevity. Telomeres are short repeated DNA sequences (TTAGGG) at the end of chromosomes; during replication a short portion of the telomere is lost in most somatic tissues due to low-level expression of telomerase, with an eventual loss of cell replicative ability. In contrast, calorie restriction is one of the most effective ways of prolonging cell life span in vitro, and is mediated by proteins called sirtuins.

43. **(D) Incites a brisk inflammatory response.**
Apoptosis is a pathway of cell death caused by a tightly regulated cell suicide program, which can be mediated internally due to release of certain proteins, and externally through membrane receptors, most notably FAS and FAS-ligand. It is a normal component of many cellular processes, including germinal centers and embryogenesis. Morphologically, it is characterized by cell fragmentation but maintenance of cellular membranes prevents an inflammatory response.

44. **(B) Histamine is a plasma-derived protein.**
Histamine is a potent vasoactive amine, which is primarily stored in mast cells, basophils, and platelets. It is not a normal component of plasma due to its potent effects on blood vessels. Histamine