CHAPTER 2

Cellular Pathology

PBD9 Chapter 2: Cellular Responses to Stress and Toxic Insults: Adaptation, Injury, and Death

PBD8 Chapter 1: Cellular Responses to Stress and Toxic Insults

BP9 and BP8 Chapter 1: Cell Injury, Cell Death, and Adaptations

1 A 77-year-old woman has chronic renal failure. Her serum urea nitrogen is 40 mg/dL. She is given a diuretic medication and loses 2 kg (4.4 lb). She reduces the protein in her diet and her serum urea nitrogen decreases to 30 mg/dL. Which of the following terms best describes cellular responses to disease and treatment in this woman?

A Adaptation
B Apoptosis
C Necroptosis
D Irreversible injury
E Metabolic derangement

2 A 53-year-old woman with no prior illnesses has a routine checkup by her physician. On examination she has a blood pressure of 150/95 mm Hg. If her hypertension remains untreated for years, which of the following cellular alterations would most likely be seen in her myocardium?

A Apoptosis
B Dysplasia
C Fatty change
D Hemosiderosis
E Hyperplasia
F Hypertrophy
G Metaplasia

3 A 22-year-old woman becomes pregnant. A fetal ultrasound examination at 13 weeks' gestation shows her uterus measures 7 × 4 × 3 cm. At delivery of a term infant, her uterus measures 34 × 18 × 12 cm. Which of the following cellular processes has contributed most to the increase in her uterine size?

A Endometrial glandular hyperplasia
B Myometrial fibroblast proliferation
C Endometrial stromal hypertrophy
D Myometrial smooth muscle hypertrophy
E Vascular endothelial hyperplasia

4 A 20-year-old woman breastfeeds her infant. On examination, her breasts are slightly increased in size. Milk can be expressed from both nipples. Which of the following processes that occurred in her breasts during pregnancy enables her to breastfeed the infant?

A Ductal metaplasia
B Epithelial dysplasia
C Intracellular lipid deposition
D Lobular hyperplasia
E Stromal hypertrophy

5 A 16-year-old boy sustained blunt trauma to his abdomen when he struck a bridge abutment at high speed while driving a motor vehicle. Peritoneal lavage shows a hemoperitoneum, and at laparotomy, a small portion of the left lobe of the injured liver is removed. Two months later, a CT scan of the abdomen shows that the liver has nearly regained its size before the injury. Which of the following processes best explains this CT scan finding?

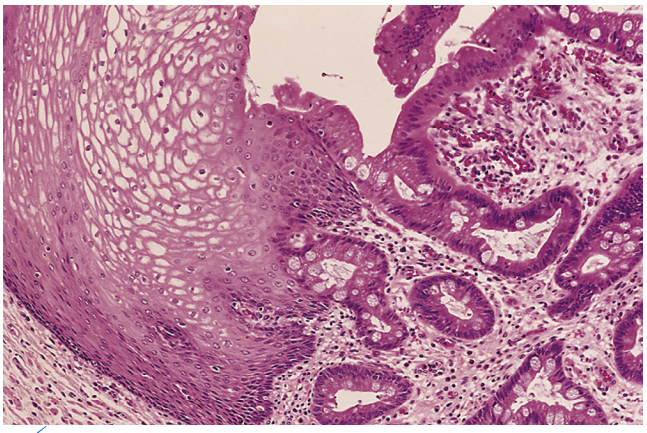
A Apoptosis
B Dysplasia
C Hyperplasia
D Hydropic change
E Steatosis

6 A 71-year-old man has had difficulty with urination, including hesitancy and increased frequency, for the past 5 years. A digital rectal examination reveals that his prostate gland is palpably enlarged to twice normal size. A transurethral resection of the prostate is performed, and the microscopic appearance of the prostate "chips" obtained is that of nodules of glands with intervening stroma. Which of the following pathologic processes has most likely occurred in his prostate?

A Apoptosis
B Dysplasia
C Fatty change
D Hyperplasia
E Hypertrophy
F Metaplasia

7 A 29-year-old man sustains a left femoral fracture in a motorcycle accident. His leg is placed in a plaster cast. After his left leg has been immobilized for 6 weeks, the diameter of the left calf has decreased in size. This change in size is most likely to result from which of the following alterations in his calf muscles?

A Aplasia
B Atrophy
C Dystrophy
D Hyalinosis
E Hypoplasia



8 A 34-year-old obese woman has experienced heartburn from gastric reflux for the past 5 years after eating large meals. She undergoes upper gastrointestinal endoscopy, and a biopsy specimen of the distal esophagus is obtained. Which of the following microscopic changes, seen in the figure, has most likely occurred?

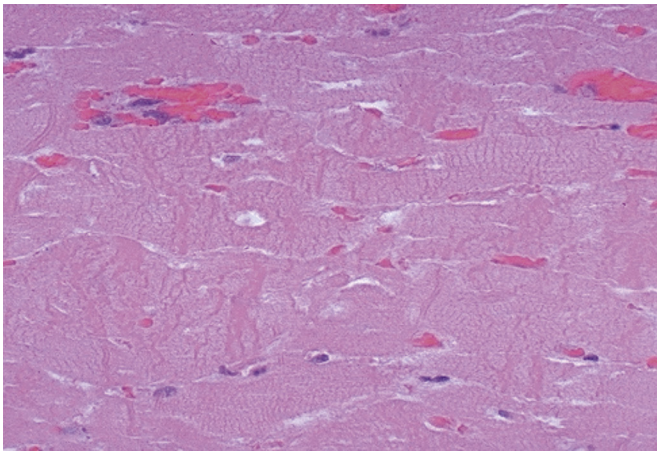
A Columnar metaplasia
B Goblet cell hyperplasia
C Lamina propria atrophy
D Squamous dysplasia
E Mucosal hypertrophy

9 An 11-year-old girl becomes infected with hepatitis A and experiences mild nausea for 1 week. On physical examination, she has minimal right upper quadrant tenderness and scleral icterus. Laboratory findings include a serum AST of 68 U/L, ALT of 75 U/L, and total bilirubin of 5.1 mg/dL. Her laboratory findings most likely result from which of the following changes in her hepatocytes?

A Cell membrane defects
B Lysosomal autophagy
C Mitochondrial swelling
D Nuclear chromatin clumping
E Ribosomal dispersion

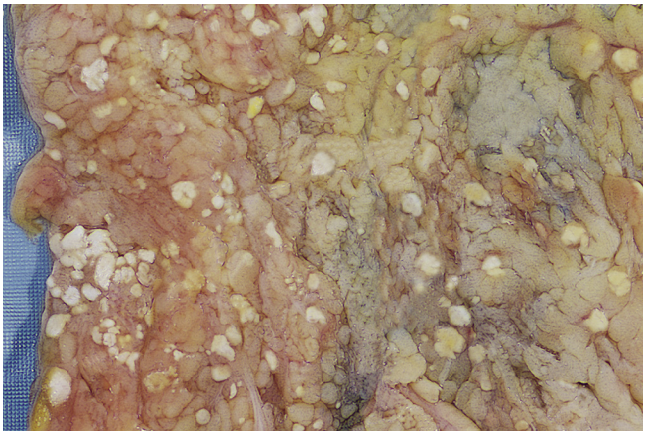
10 A 33-year-old woman has had increasing lethargy and decreased urine output for the past week. Laboratory studies show her serum creatinine is 4.3 mg/dL and urea nitrogen 40 mg/dL. A renal biopsy is performed, and the specimen is examined using electron microscopy. Which of the following morphologic cellular changes most likely suggests a diagnosis of acute tubular necrosis?

A Chromatin clumping
B Mitochondrial swelling
C Nuclear fragmentation
D Plasma membrane blebs
E Ribosomal disaggregation



11 A 50-year-old man has experienced an episode of chest pain for 6 hours. A representative histologic section of his left ventricular myocardium is shown in the figure. There is no hemorrhage or inflammation. Which of the following conditions most likely produced these myocardial changes?

A Arterial thrombosis
B Autoimmunity
C Blunt chest trauma
D Protein-deficient diet
E Viral infection

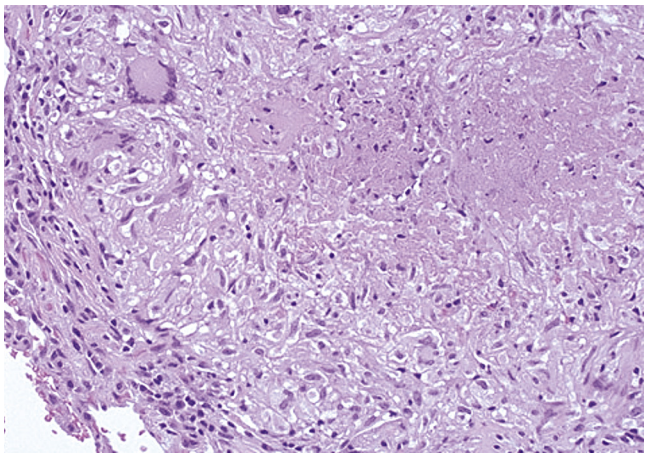


12 A 38-year-old woman has experienced severe abdominal pain over the past day. On examination she is hypotensive and in shock. Laboratory studies show elevated serum lipase. From the representative gross appearance of the mesentery shown in the figure, which of the following events has most likely occurred?

A Acute pancreatitis
B Gangrenous cholecystitis
C Hepatitis B virus infection
D Small intestinal infarction
E Tuberculous lymphadenitis

13 A 68-year-old woman suddenly lost consciousness and on awakening 1 hour later, she could not speak or move her right arm. Two months later, a head CT scan showed a large cystic area in the left parietal lobe. Which of the following pathologic processes has most likely occurred in her brain?

A Apoptosis
B Coagulative necrosis
C Fat necrosis
D Karyolysis
E Liquefactive necrosis



14 A screening chest radiograph of an asymptomatic 37-year-old man shows a 3-cm nodule in the middle lobe of his right lung. The nodule is excised with a pulmonary wedge resection, and sectioning shows a sharply circumscribed mass with a soft, white center. The microscopic appearance is shown in the figure. The serum interferon gamma release assay is positive. Which of the following pathologic processes has most likely occurred in this nodule?

A Apoptosis
B Caseous necrosis
C Coagulative necrosis
D Fat necrosis
E Fatty change
F Gangrenous necrosis
G Liquefactive necrosis

15 An experimental drug administered to a tissue preparation is found to inhibit cellular oxidative phosphorylation when given in high doses, and ATP production drops to 5% of normal. Cell membrane function is diminished. Which of the following substances is most likely to be present at increased concentration in culture fluid bathing the tissue?

A Calcium
B Glucose
C Ketones
D Potassium
E Sodium

16 A 47-year-old woman has poorly controlled diabetes mellitus and develops coronary artery disease. She now has decreasing cardiac output with blood pressure of 80/40 mm Hg and ejection fraction of 18%. An increase in which of the following substances in her blood is most indicative of reversible cell injury from decreased systemic arterial perfusion of multiple organs and tissues?

A Carbon dioxide
B Creatinine
C Glucose
D Lactic acid
E Troponin I

17 A tissue preparation is experimentally subjected to a hypoxic environment. The cells in this tissue begin to swell, and chromatin begins to clump in cell nuclei. ATPases are activated, and ATP production decreases. Which of the following ions accumulating in mitochondria and the cytosol contributes most to these findings and to eventual cell death?

A Ca^{2+}
B Cl^{-}
C HCO_3^{-}
D K^{+}
E Na^{+}
F PO_4^{3-}

18 In an experiment, a large amount of a drug is administered to experimental organisms and is converted by cytochrome P-450 to a toxic metabolite. Accumulation of this metabolite leads to increased intracellular lipid peroxidation. Depletion of which of the following intracellular substances within the cytosol exacerbates this form of cellular injury by this mechanism?

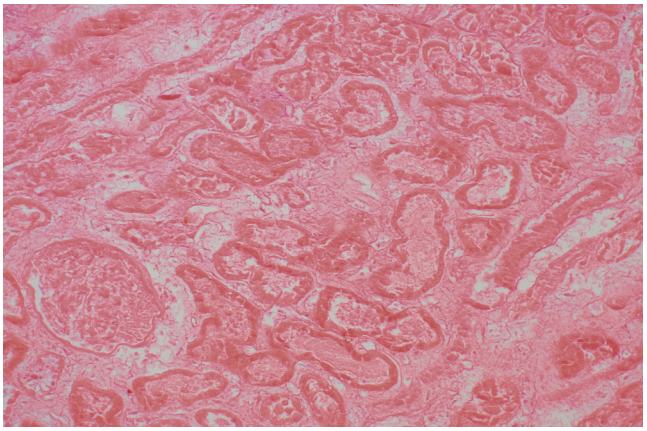
A ADP
B Glutathione
C NADPH oxidase
D Nitric oxide synthase
E mRNA
F Sodium

19 In an experiment, metabolically active cells are subjected to radiant energy in the form of x-rays. This results in cell injury caused by hydrolysis of water. Which of the following intracellular enzymes helps to protect the cells from this type of injury?

A Endonuclease
B Glutathione peroxidase
C Lactate dehydrogenase
D Phospholipase
E Protease

20 A 5-year-old child ingests 50 iron tablets, each with 27 mg of iron. Within 6 hours the child develops abdominal pain and lethargy. On physical examination he is hypotensive. Laboratory studies show metabolic acidosis. Through formation of which of the following compounds is the cell injury in this child most likely mediated?

A Ascorbic acid
B Hemosiderin
C Hydroxyl radical
D Nitric oxide
E Superoxide dismutase



21 A 63-year-old man has a 2-year history of worsening congestive heart failure. An echocardiogram shows mitral valve stenosis with left atrial dilation. A mural thrombus is present in the left atrium. One month later, he experiences left flank pain and notes hematuria. Laboratory testing shows an elevated serum AST. The representative microscopic appearance of the lesion is shown in the figure. Which of the following patterns of tissue necrosis is most likely to be present in this man?

A Caseous
B Coagulative
C Fat
D Gangrenous
E Liquefactive

22 A 54-year-old man experienced severe substernal chest pain for 3 hours. An ECG showed changes consistent with an acute myocardial infarction. After thrombolytic therapy with tissue plasminogen activator (t-PA), his serum creatine kinase (CK) level increased. Which of the following tissue events most likely occurred in the myocardium after t-PA therapy?

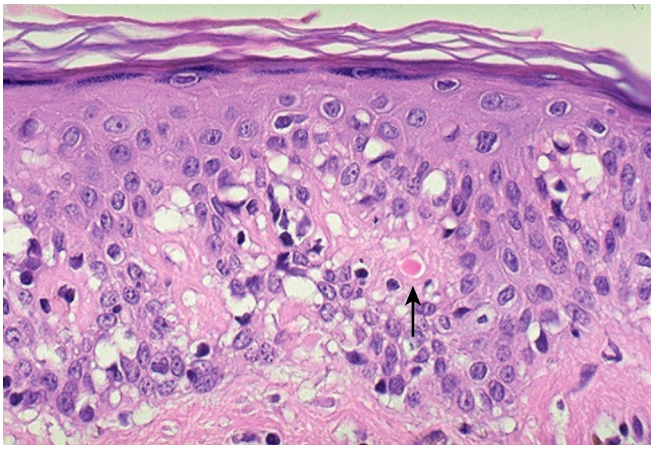
A Cellular regeneration
B Drug toxicity
C Increased synthesis of CK
D Myofiber atrophy
E Reperfusion injury

23 On day 28 of her menstrual cycle, a 23-year-old woman experiences onset of menstrual bleeding that lasts for 6 days. She has had regular cycles since menarche. Which of the following processes most likely occurs in her endometrial cells to initiate the onset of menstrual bleeding?

A Apoptosis
B Atrophy
C Caseous necrosis
D Heterophagocytosis
E Liquefactive necrosis

24 An experiment introduces a knockout gene mutation into a cell line. The frequency of shrunken cells with chromatin clumping, karyorrhexis, and cytoplasmic blebbing is increased compared with a cell line without the mutation. Overall survival of the mutant cell line is reduced. Which of the following genes is most likely to be affected by this mutation?

A *BAX*
B *BCL2*
C *C-MYC*
D *FAS*
E *p53*



25 A 22-year-old woman with leukemia undergoes bone marrow transplantation and receives a partially mismatched donor marrow. One month later, she has a scaling skin rash. A skin biopsy is obtained, and on microscopic examination, it has the cellular change shown in the figure. This change most likely results from which of the following biochemical reactions?

A Activation of caspases
B Elaboration of lipases
C Increase in glycolysis
D Peroxidation of lipids
E Reduction of ATP synthesis

26 A 47-year-old man has a lung carcinoma with metastases. He receives chemotherapy. A month later, histologic examination of a metastatic lesion shows many foci in which individual tumor cells appear shrunken and deeply eosinophilic. Their nuclei exhibit condensed aggregates of chromatin under the nuclear membrane. The pathologic process affecting these shrunken tumor cells is most likely triggered by release of which of the following substances into the cytosol?

A BCL2
B Catalase
C Cytochrome *c*
D Lipofuscin
E Phospholipase

27 In a study of viral hepatitis infection, it is observed that cytotoxic T lymphocytes (CTLs) induce death in virally infected hepatocytes. The CTLs release perforin to allow entry of their granules. Which of the following substances is found in those granules that directly activates programmed cell death?

A BCL2
B Endonuclease
C Granzyme B
D Nitric oxide
E p53

28 An experimental study of steatohepatitis in metabolic syndrome reveals that hepatocyte cell membrane injury with necrosis occurs in response to increased amounts of tumor necrosis factor (TNF). When a pharmacologic agent inhibiting caspases is administered, cell necrosis still occurs. Which of the following substances forms a supramolecular complex that increases the generation of reactive oxygen species?

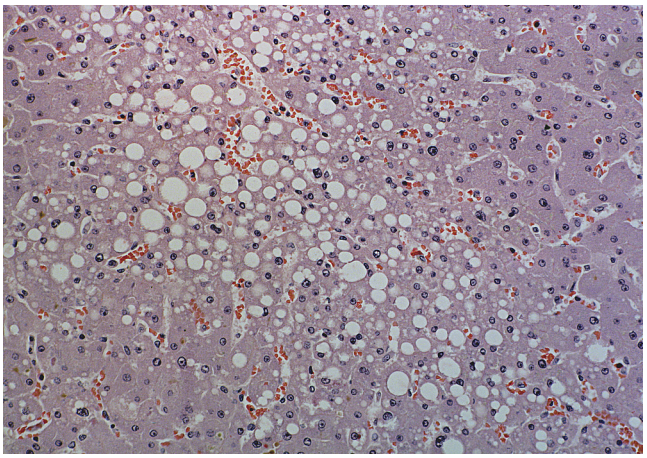
A Catalase
B Cytochrome *c*
C Interleukin 1-beta converting enzyme
D Receptor-interacting protein
E Ubiquitin ligase

29 A 71-year-old man diagnosed with pancreatic cancer is noted to have decreasing body mass index. His normal connective tissues undergo atrophy by sequestering organelles and cytosol in a vacuole, which then fuses with a lysosome. However, the cancer continues to increase in size. Which of the following processes is most likely occurring in the normal cells but is inhibited in the cancer cells of this man?

A Aging
B Apoptosis
C Autophagy
D Hyaline change
E Karyorrhexis

30 A new drug is developed that binds to cellular microtubules. The function of the microtubules is diminished, so that mitotic spindle formation is inhibited. Which of the following is the most likely use for this drug?

A Antimicrobial therapy
B Chemotherapy
C Pain management
D Prevention of atherosclerosis
E Weight reduction



31 A 46-year-old man has noted increasing abdominal size for the past 6 years. On physical examination his liver span is increased to 18 cm. An abdominal CT scan shows an enlarged liver with diffusely decreased attenuation. Laboratory findings include increased total serum cholesterol and triglyceride levels, increased prothrombin time, and a decreased serum albumin concentration. The representative microscopic appearance of his liver is shown in the figure. Which of the following activities most likely led to these findings?

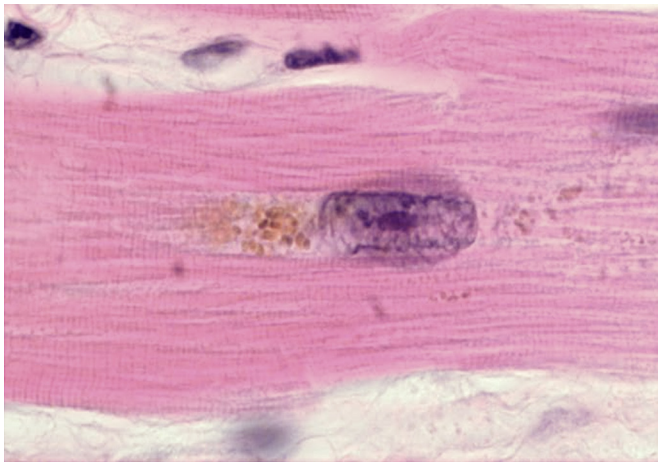
A Drinking beer
B Ingesting aspirin
C Injecting heroin
D Playing basketball
E Smoking cigarettes

32 A 69-year-old woman has had transient ischemic attacks for the past 3 months. On physical examination, she has an audible bruit on auscultation of the neck. A right carotid endarterectomy is performed. The curetted atheromatous plaque has a grossly yellow-tan, firm appearance. Microscopically, which of the following materials can be found in abundance in the form of crystals within cleftlike spaces?

A Cholesterol
B Glycogen
C Hemosiderin
D Immunoglobulin
E Lipofuscin

33 A 45-year-old woman has had worsening dyspnea for the past 5 years. A chest CT scan shows panlobular emphysema. Laboratory studies show a deficiency of α_1-antitrypsin (AAT). Her AAT genotype is PiZZ. A liver biopsy specimen examined microscopically shows abundant PAS-positive globules within periportal hepatocytes. Which of the following molecular mechanisms is most likely responsible for this finding in her hepatocytes?

A Decreased catabolism of AAT in lysosomes
B Excessive hepatic synthesis of AAT
C Impaired dissociation of AAT from chaperones
D Inability to metabolize AAT in Kupffer cells
E Retained misfolded AAT in endoplasmic reticulum



34 At autopsy, the heart of a 63-year-old man weighs only 250 g (normal 330 g) and has small right and left ventricles. The myocardium is firm, with a dark chocolate-brown color throughout. The coronary arteries show minimal atherosclerotic changes. An excessive amount of which of the following substances, shown in the figure, would most likely be found in the myocardial fibers of this heart?

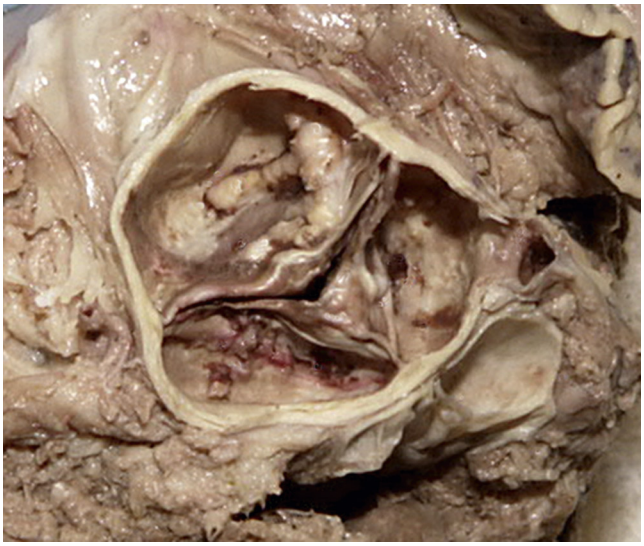
- **A** Bilirubin
- **B** Glycogen
- **C** Hemosiderin
- **D** Lipofuscin
- **E** Melanin

35 A 69-year-old woman has had a chronic cough for the past year. A chest radiograph shows a 6-cm mass in the left lung. A needle biopsy specimen of the mass shows carcinoma. A pneumonectomy is performed, and examination of the hilar lymph nodes reveals a uniform, dark black cut surface. Which of the following factors most likely accounts for the appearance of these lymph nodes?

- **A** Aging effects
- **B** Bleeding disorder
- **C** Cigarette smoking
- **D** Liver failure
- **E** Multiple metastases

36 A 22-year-old woman from Albania has a congenital anemia requiring multiple transfusions of RBCs for many years. On physical examination, her skin has a bronze color. Liver function tests show reduced serum albumin. Which of the following findings would most likely appear in a liver biopsy specimen?

- **A** Amyloid in portal triads
- **B** Bilirubin in canaliculi
- **C** Glycogen in hepatocytes
- **D** Hemosiderin in hepatocytes
- **E** Steatosis in hepatocytes



37 A 72-year-old man died suddenly from congestive heart failure. At autopsy, his heart weighed 580 g (normal 330 g) and showed marked left ventricular hypertrophy and minimal coronary arterial atherosclerosis. A serum chemistry panel ordered before death showed no abnormalities. Which of the following pathologic processes best accounts for the appearance of the aortic valve seen in the figure?

- **A** Amyloidosis
- **B** Dystrophic calcification
- **C** Hemosiderosis
- **D** Hyaline change
- **E** Lipofuscin deposition

38 A 70-year-old man with hypercalcemia died suddenly. At autopsy, microscopic examination showed noncrystalline amorphous deposits of calcium salts in gastric mucosa, renal interstitium, and alveolar walls of lungs. Which of the following underlying conditions would most likely explain these findings?

- **A** Chronic active hepatitis
- **B** Diffuse parathyroid hyperplasia
- **C** Disseminated tuberculosis
- **D** Generalized atherosclerosis
- **E** Normal aging process
- **F** Pulmonary emphysema

39 An experiment analyzes cells for enzyme activity associated with sustained cellular proliferation. Which of the following cells is most likely to have the highest telomerase activity?

- **A** Endothelial cells
- **B** Erythrocytes
- **C** Germ cells
- **D** Neurons
- **E** Neutrophils

40 A study of aging shows that senescent cells have accumulated damage from toxic byproducts of metabolism. There is increased intracellular lipofuscin deposition. Prolonged ingestion of which of the following substances is most likely to counteract this aging mechanism?

- **A** Antioxidants
- **B** Analgesics
- **C** Antimicrobials
- **D** Antineoplastic agents
- **E** Glucocorticoids

ANSWERS

1 A Normal cells handle physiologic demands and maintain metabolic functions within narrow ranges, termed *homeostasis*. Under disease conditions with stress on cells, there is adaptation to a new steady state. In this case, the loss of renal function leads to a higher urea nitrogen level as well as retention of fluid. The diuretic induces loss of the excess fluid to yield a new steady state. The protein restriction reduces urea nitrogen excretion, which also leads to a new steady state. Both are adaptations. Apoptosis refers to single cell necrosis in response to injury. An irreversible injury leads to cell death, but the changes described here are not evidence for cellular necrosis. The metabolism of cells is maintained for adaptation, with response to the diuretic and to protein restriction.

PBD9 32–33 BP9 2 PBD8 4–5 BP8 2

2 F The pressure load on the left ventricle results in an increase in myofilaments in the existing myofibers, so they enlarge. The result of continued stress from hypertension is eventual heart failure with decreased contractility. Apoptosis would lead to loss of cells and diminished size. Dysplasia is not a diagnosis made for the heart. Hemosiderin deposition in the heart is a pathologic process resulting from increased iron stores in the body. Though hyperplasia from proliferation of myofibroblasts is possible, this does not contribute significantly to cardiac size. Metaplasia of muscle does not occur, although loss of muscle occurs with aging and ischemia as myofibers are replaced by fibrous tissue.

PBD9 34–35 BP9 3–4 PBD8 6–8 BP8 3–4

3 D The increase in uterine size is primarily the result of an increase in the size of myometrial smooth muscle cells. The endometrium also increases in size, mainly via hyperplasia, but it remains as a thin lining to the muscular wall and does not contribute as much to the change in size. There is little stroma in myometrium and a greater proportion in endometrium, so stroma contributes a smaller percentage to the gain in size than muscle. The vessels are a minor but essential component in this increase in size, but not the largest component.

PBD9 34–35 BP9 3–4 PBD8 6–8 BP8 2–3

4 D Breast lobules have an increased number of cells under hormonal influence (mainly progesterone) to provide for normal lactation. Ductal metaplasia in the breast is a pathologic process. Epithelial dysplasia denotes disordered growth and maturation of epithelial cells that may progress to cancer. Accumulation of fat within cells is a common manifestation of sublethal cell injury or, uncommonly, of inborn errors in fat metabolism. The breast stroma plays no role in lactation and may increase with pathologic processes.

PBD9 35–36 BP9 3 PBD8 8–9 BP8 4

5 C The liver is one of the few organs in the human body that can partially regenerate. This is a form of compensatory hyperplasia. The stimuli to hepatocyte mitotic activity cease when the liver has attained its normal size. Hepatocytes can reenter the cell cycle and proliferate to regenerate the liver; they do not just hypertrophy (increase in size). Apoptosis is single cell death and frequently occurs with viral hepatitis. Dysplasia is disordered epithelial cell growth that can be premalignant. Hydropic change, or cell swelling, does not produce regeneration. Steatosis (fatty change) can lead to hepatomegaly, but not as a regenerative process. It is the result of toxic/metabolic hepatocyte injury.

PBD9 35–36 BP9 4 PBD8 8–9 BP8 4

6 D Nodular prostatic hyperplasia (also known as benign prostatic hyperplasia [BPH]) is a common condition in older men that results from proliferation of both prostatic glands and stroma. The prostate becomes more sensitive to androgenic stimulation with age. This is an example of pathologic hyperplasia. Apoptosis results in a loss of, not an increase in, cells. Dysplasia refers to disordered epithelial cell growth and maturation. Fatty change in hepatocytes may produce hepatomegaly. Although BPH is often called "benign prostatic hypertrophy," this term is technically incorrect; it is the number of glands and stromal cells that is increased, rather than the size of existing cells. A change in the glandular epithelium to squamous epithelium around a prostatic infarct would be an example of metaplasia.

PBD9 35–36 BP9 4 PBD8 8–9 BP8 4

7 B Reduced workload causes cell to shrink through loss of cell substance, a process called *atrophy*. The cells are still present, just smaller. Aplasia refers to lack of embryonic development; hypoplasia describes poor or subnormal development of tissues. Dystrophy of muscles refers to inherited disorders of skeletal muscles that lead to muscle fiber destruction, weakness, and wasting. Hyaline change (hyalinosis) refers to a nonspecific, pink, glassy eosinophilic appearance of cells.

PBD9 36–37 BP9 4–5 PBD8 9–10 BP8 4–5

8 A Inflammation from reflux of gastric acid has resulted in replacement of normal esophageal squamous epithelium by intestinal-type columnar epithelium with goblet cells. Such conversion of one adult cell type to another cell type is called *metaplasia*, and it occurs when stimuli reprogram stem cells. Goblet cells are not normal constituents of the esophageal mucosa, and they are a minor part of this metaplastic process. The lamina propria has some inflammatory cells, but it does not atrophy. The squamous epithelium does not become dysplastic from acid reflux, but the columnar metaplasia may progress to dysplasia, not seen here, if the abnormal stimuli continue. These cells are not significantly increased in size (hypertrophic).

PBD9 37–38 BP9 5 PBD8 10–11 BP8 5

9 A Irreversible cell injury is associated with loss of membrane integrity. This allows intracellular enzymes such as AST and ALT to leak into the serum. All other morphologic

changes listed are associated with reversible cell injury, in which the cell membrane remains intact and the cells do not die.

PBD9 38–39 BP9 7–8 PBD8 11–12 BP8 8–12

10 C Cell death occurs with loss of the cell nucleus, and tubular cells become necrotic. All other cellular morphologic changes listed represent forms of reversible cellular injury. The plasma membrane and intracellular organelles retain some function unless severe damage causes loss of membrane integrity.

PBD9 39, 42 BP9 8–9 PBD8 12 BP8 6, 9

11 A The figure shows deep eosinophilic staining, loss of myocardial fiber nuclei, and loss of cell structure consistent with an early ischemic injury, resulting in coagulative necrosis. Myocardial ischemia and infarction are typically caused by loss of coronary arterial blood flow. An immunological process may produce focal myocardial injury. Blunt trauma produces hemorrhage. Lack of protein leads to a catabolic state with gradual decrease in cell size, but it does not cause ischemic changes. Viral infection could cause focal necrosis of the myocardium, but this is usually accompanied by an inflammatory infiltrate consisting of lymphocytes and macrophages.

PBD9 42–43 BP9 9–10 PBD8 15–16 BP8 2, 7, 10

12 A The many focal, chalky white deposits in the mesentery, composed mainly of adipocytes, are areas of fat necrosis. The deposits result from the release of pancreatic enzymes such as lipases in a patient with acute pancreatitis. Gangrenous necrosis is mainly coagulative necrosis, but occurs over an extensive area of tissues. Viral hepatitis does not cause cell necrosis in organs other than liver, and hepatocyte necrosis from viral infections occurs mainly by means of apoptosis. Intestinal infarction is a form of coagulative necrosis. Infection with tuberculosis leads to caseous necrosis.

PBD9 43–44 BP9 10–11 PBD8 16–17 BP8 11

13 E The high lipid content of central nervous system tissues results in liquefactive necrosis as a consequence of ischemic injury, as in this case of stroke. Apoptosis affects single cells and typically is not grossly visible. Coagulative necrosis is the typical result of ischemia in most solid organs. Fat necrosis is seen in breast and pancreatic tissues. Karyolysis refers to fading away of cell nuclei in dead cells.

PBD9 43 BP9 10–11 PBD8 16–17 BP8 10–11

14 B The grossly cheeselike appearance gives this form of necrosis its name—caseous necrosis. The figure shows amorphous pink acellular material at the upper right surrounded by epithelioid macrophages, and a Langhans giant cell is visible at the upper left. In the lung, tuberculosis and fungal infections are most likely to produce this pattern of tissue injury. Apoptosis involves individual cells, without grossly apparent extensive or localized areas of tissue necrosis. Coagulative necrosis is more typical of ischemic tissue injury. Fat necrosis most often occurs in the breast and pancreas. Fatty change is most often a feature of hepatocyte injury, and the cell integrity is maintained. Gangrene characterizes extensive necrosis of multiple cell types in a body region or organ. Liquefactive necrosis is seen in neutrophilic abscesses or ischemic cerebral injury.

PBD9 43–44 BP9 10–11 PBD8 16 BP8 10

15 D Reduction in oxidative phosphorylation leads to reduction in synthesis of ATP and diminished activity of the plasma membrane sodium pump, which maintains high intracellular potassium concentration. Loss of ATP leads to efflux of intracellular potassium, while net influx of sodium and water promote cell swelling. A marked rise in plasma potassium can indicate significant cell damage or death (such as skeletal muscle crush injury or hemolysis). When cells are not consuming glucose via oxidative metabolism, the glucose is metabolized via other pathways, and glucose is maintained within normal ranges. Though cell membranes are composed of lipid, dysfunction or disruption of those membranes does not significantly alter plasma lipid concentrations.

PBD9 45–46 BP9 12–13 PBD8 14–15 BP8 14–15

16 D Decreased tissue perfusion from hypotensive shock leads to hypoxemia and depletion of ATP when cell metabolism shifts from aerobic to anaerobic glycolysis. This shift causes depletion of glycogen stores and increased production and accumulation of lactic acid, reducing intracellular pH. Creatinine would increase with reduced renal function from decreased renal perfusion, but this would not explain the changes in other tissues. An increased glucose level would be indicative of poorly controlled diabetes mellitus, not decreased perfusion. Carbon dioxide is likely to be cleared via normal lungs, which are still sufficiently perfused by a failing heart. An increase in troponin I suggests irreversible myocardial injury.

PBD9 45–46 BP9 12–13 PBD8 14–15 BP8 14, 18

17 A Irreversible cellular injury is likely to occur when cytoplasmic calcium increases. Calcium can enter cells and also accumulate in mitochondria and endoplasmic reticulum. The excess calcium activates ATPases, phospholipases, proteases, and endonucleases, which injure cell components. Mitochondrial permeability is increased to release cytochrome *c,* which activates caspases leading to apoptosis. Of the other ions listed, sodium enters the cell, while potassium diffuses out when the sodium pump fails as ATP levels fall; but this is potentially reversible.

PBD9 46–47 BP9 13–14 PBD8 18–20 BP8 15

18 B The drug acetaminophen can be converted to toxic metabolites in this manner. Glutathione in the cytosol helps to reduce cellular injury from many toxic metabolites and free radicals. ADP is converted to ATP by oxidative and glycolytic cellular pathways to provide energy that drives

cellular functions, and a reduction in ATP leaves the cell vulnerable to injury. NADPH oxidase generates superoxide, which is used by neutrophils in killing bacteria. Nitric oxide synthase in macrophages produces nitric oxide, which aids in destroying organisms undergoing phagocytosis. Protein synthesis in cells depends on mRNA for longer survival and recovery from damage caused by free radicals. Failure of the sodium pump leads to increased cytosolic sodium and cell swelling with injury.

PBD9 48, 52 BP9 14–15 PBD8 20–21 BP8 15–17

19 B The body has intracellular mechanisms that prevent damage from free radicals generated by exposure to x-rays. Glutathione peroxidase reduces such injury by catalyzing the breakdown of hydrogen peroxide. Endonucleases damage DNA in nuclear chromatin. Lactate dehydrogenase is present in a variety of cells, and its elevation in the serum is an indicator of cell injury and death. Phospholipases decrease cellular phospholipids and promote cell membrane injury. Proteases can damage cell membranes and cytoskeletal proteins.

PBD9 47–48 BP9 14–15 PBD8 20–21 BP8 15–17

20 C Excessive iron ingestion, particularly by a child, can overwhelm the body's ability to bind the absorbed free iron with the transport protein transferrin. The free iron contributes to generation of cellular free radicals via the Fenton reaction. Ascorbic acid (vitamin C) and vitamin E both act as antioxidants to protect against free radical injury, albeit over a long time frame. Hemosiderin is a storage form of iron from excess local or systemic accumulation of ferritin, and by itself does not cause cell injury until large amounts are present, as with hemochromatosis. Nitric oxide generated within macrophages can be to kill microbes. It can be converted to a highly reactive peroxynitrite anion. Superoxide dismutase helps break down superoxide anion to hydrogen peroxide, thus scavenging free radicals.

PBD9 47–48 BP9 14–15 PBD8 20–22 BP8 16

21 B Embolization of the thrombus led to blockage of a renal arterial branch, causing an acute renal infarction in this patient. An ischemic injury to most internal organs produces a pattern of cell death called *coagulative necrosis*. Note the faint outlines of renal tubules and glomerulus in the figure, but no cellular nuclei. Caseous necrosis can be seen in various forms of granulomatous inflammation, typified by tuberculosis. Fat necrosis is usually seen in pancreatic and breast tissue. Gangrenous necrosis is a form of coagulative necrosis that usually results from ischemia and affects limbs. Liquefactive necrosis occurs after ischemic injury to the brain and is the pattern seen with abscess formation.

PBD9 50–51 BP9 17 PBD8 23–24 BP8 2, 3, 10

22 E If existing cell damage is not great after myocardial infarction, the restoration of blood flow can help prevent further cellular damage. However, the reperfusion of damaged cells results in generation of oxygen-derived free radicals, causing a reperfusion injury. The elevation in the CK level is indicative of myocardial cell necrosis, because this intracellular enzyme does not leak in large quantities from intact myocardial cells. Myocardial fibers do not regenerate to a significant degree, and atrophic fibers would have less CK to release. t-PA does not produce a toxic chemical injury; it induces thrombolysis to restore blood flow in occluded coronary arteries.

PBD9 51 BP9 17 PBD8 24 BP8 18

23 A The onset of menstruation is orderly, programmed cell death (apoptosis) through hormonal stimuli, an example of the intrinsic (mitochondrial) apoptotic pathway. As hormone levels drop, the endometrium breaks down, sloughs off, and then regenerates. With cellular atrophy, there is often no visible necrosis, but the tissues shrink, something that occurs in the endometrium after menopause. Caseous necrosis is typical of granulomatous inflammation, resulting most commonly from mycobacterial infection. Heterophagocytosis is typified by the clearing of an area of necrosis through macrophage ingestion of the necrotic cells. Liquefactive necrosis can occur in any tissue after acute bacterial infection or in the brain after ischemia.

PBD9 52–56 BP9 18 PBD8 25–29 BP8 19–22

24 B These histologic findings are typical of apoptosis. The *BCL2* gene product inhibits cellular apoptosis by binding to Apaf-1. Hence, the knockout removes this inhibition The *BAX* gene product promotes apoptosis, and a knockout would protect against apoptosis. The *C-MYC* gene is involved with oncogenesis. The *FAS* gene encodes for a cellular receptor for Fas ligand that signals apoptosis. Activity of the *p53 (TP53)* gene normally stimulates apoptosis, but mutation favors cell survival.

PBD9 54–55 BP9 18, 20–28 PBD8 28–30 BP8 19–22

25 A There is an apoptotic cell (*arrow*) that is shrunken and has been converted into a dense eosinophilic mass. There is a surrounding inflammatory reaction with cytotoxic lymphocytes. This pattern is typical of apoptosis. Caspase activation is a universal feature of apoptosis, regardless of the initiating cause. Apoptosis induced in recipient cells from donor lymphocytes occurs with graft-versus-host disease. Lipases are activated in enzymatic fat necrosis. Reduced ATP synthesis and increased glycolysis occur when a cell is subjected to anoxia, but these changes are reversible. Lipid peroxidation occurs when the cell is injured by free radicals.

PBD9 53–54 BP9 18–19 PBD8 26–27 BP8 13–14

26 C This histologic picture is typical of apoptosis produced by chemotherapeutic agents. The release of cytochrome *c* from the mitochondria is a key step in many forms of apoptosis, and it leads to the activation of caspases. BCL2 is an antiapoptotic protein that prevents cytochrome *c* release and prevents caspase activation. Catalase is a scavenger of hydrogen peroxide. Lipofuscin is a pigmented residue representing

undigested cellular organelles in autophagic vacuoles, much like old clothes in a closet. Phospholipases are activated during necrosis and cause cell membrane damage.

PBD9 57 BP9 19–21 PBD8 30 BP8 19–22

27 C Granzyme B is a serine protease found in CTLs that can directly trigger apoptosis. CTLs express Fas ligand on their surfaces, and when contacting Fas receptors on the target cell, the ligand can induce apoptosis by the extrinsic (death receptor–initiated) pathway. BCL2 favors cell survival. Nitric oxide helps destroy phagocytized microbes. Endonucleases are generated following caspase activation and lead to nuclear fragmentation. When p53 is activated by intrinsic DNA damage during cell proliferation, apoptosis is triggered. Mutations in *p53* may allow accumulation of genetic damage, a process that promotes unregulated cell growth (neoplasia).

PBD9 58 BP9 19–20 PBD8 31 BP8 21–22

28 D Necroptosis occurs when the mechanism of apoptosis yields morphologic necrosis following cell membrane rupture, independent of caspase release. The RIP1-RIP3 complex is called a *necrosome*. Catalases help destroy hydrogen peroxide to prevent free radical damage. Cytochrome *c* participates in apoptosis and an inflammasome in necroptosis. Ubiquitin ligase is part of misfolded protein processing in proteasomes.

PBD9 58–59

29 C Autophagy is a form of cellular downsizing in response to stress, as the cell consumes itself, by upregulating *Atgs* genes. Lipofuscin granules are residual bodies left over from this process. Cell death may eventually be triggered by autophagy, but by a different mechanism than apoptosis, a form of single cell necrosis in which cell fragmentation occurs. Cancer cells acquire the ability to prevent autophagy, perhaps by downregulating *PTEN* gene expression, and maintain a survival advantage even as the patient is dying. There is slow autophagy with aging, but autophagy is accelerated with stressors such as malnutrition and chronic disease. Hyaline is a generic term for intracellular or extracellular protein accumulations appearing pink and homogeneous with H&E staining. Karyorrhexis is nuclear fragmentation in a necrotic cell.

PBD9 59–60 BP9 22–23 PBD8 32, 304 BP8 12

30 B Microtubules are cytoskeletal components required for cell movement. Mitotic spindles are required for cell division, and if cancer cells cannot divide, then the neoplasm cannot grow. Antibiotics are directed at microorganisms that do not have microtubules. Pain is produced largely through release of mediators of inflammation. Atheroma formation is affected by endothelial damage and lipid accumulation, and though there is cellular proliferation, it occurs over many years. Weight reduction is accomplished primarily via atrophy of adipocytes, not inhibition of cell proliferation.

PBD9 60 PBD8 34

31 A The appearance of lipid vacuoles in many of the hepatocytes is characteristic of fatty change (steatosis) of the liver. Abnormalities in lipoprotein metabolism can lead to steatosis. Alcohol is a hepatotoxin acting via increased acetaldehyde accumulation that promotes hepatic steatosis. Decreased serum albumin levels and increased prothrombin time suggest alcohol-induced hepatocyte damage. Aspirin has a significant effect on platelet function, but not on hepatocytes. Substance abuse with heroin produces few organ-specific pathologic findings. Exercise has little direct effect on hepatic function. Smoking directly damages lung tissue, but has no direct effect on the liver.

PBD9 61–62 BP9 23 PBD8 33–34 BP8 23–24

32 A Cholesterol is a form of lipid commonly deposited within atheromas in arterial walls, imparting a yellow color to these plaques and a glistening appearance if abundant. Direct damage to the atheroma can yield cholesterol emboli. Glycogen is a storage form of carbohydrate seen mainly in liver and muscle. Hemosiderin is a storage form of iron that appears in tissues of the mononuclear phagocyte system (e.g., marrow, liver, spleen), but can be widely deposited with hereditary hemochromatosis. Immunoglobulin occasionally may be seen as rounded globules in plasma cells (i.e., Russell bodies). Lipofuscin is a golden brown pigment that increases with aging in cell cytoplasm, mainly in cardiac myocytes and in hepatocytes.

PBD9 62 BP9 23 PBD8 34–35 BP8 24

33 E Mutations in the *AAT* gene give rise to AAT molecules that cannot fold properly. In the PiZZ genotype, both alleles have the mutation. The partially folded molecules accumulate in hepatocyte endoplasmic reticulum and cannot be secreted. Impaired dissociation of the CFTR protein from chaperones causes many cases of cystic fibrosis. There is no abnormality in the synthesis, catabolism, or metabolism of AAT in patients with AAT deficiency. AAT is the major circulating alpha globulin that protects tissues such as lung from damaging proteases.

PBD9 63 PBD8 35

34 D Lipofuscin is a "wear-and-tear" pigment that increases with aging, particularly in liver and myocardium. This granular golden brown pigment seen adjacent to the myocyte nucleus in the figure has minimal effect on cellular function in most cases. Rarely, there is marked lipofuscin deposition in a small heart, a so-called brown atrophy. Bilirubin, another breakdown product of hemoglobin, imparts a yellow appearance (icterus) to tissues. Hemosiderin is the breakdown product of hemoglobin that contains the iron. Hearts with excessive iron deposition tend to be large. Glycogen is increased in some inherited enzyme disorders, and when the heart is involved, heart size increases. Melanin pigment is responsible for skin tone: the more melanin, the darker the skin.

PBD9 64 BP9 24 PBD8 39–40 BP8 25

35 C Lung and hilar lymph nodes accumulate anthracotic pigmentation when carbon pigment is inhaled from polluted air. The tar in cigarette smoke is a major source of such carbonaceous pigment. Older individuals generally have more anthracotic pigment, but this is not inevitable with aging—individuals living in rural areas with good environmental air quality have less pigment. Resolution of hemorrhage can produce hemosiderin pigmentation, which imparts a brown color to tissues. Hepatic failure may result in jaundice, characterized by a yellow color in tissues. Metastases are mass lesions that impart a tan-to-white appearance to tissues.

PBD9 64 BP9 24 PBD8 36 BP8 25

36 D Each unit of blood contains about 250 mg of iron. The body has no mechanism for getting rid of excess iron. About 10 to 20 mg of iron per day is lost with normal desquamation of epithelia; menstruating women lose slightly more. Any excess iron becomes storage iron, or hemosiderin. Over time, hemosiderosis involves more and more tissues of the body, particularly the liver, but also skin. Initially, hemosiderin deposits are found in Kupffer cells and other mononuclear phagocytes in the bone marrow, spleen, and lymph nodes. With great excess of iron, liver cells also accumulate iron. Amyloid is an abnormal protein derived from a variety of precursors, such as immunoglobulin light chains. Bilirubin, a breakdown product of blood, can be excreted in the bile so that a person does not become jaundiced. Glycogen storage diseases are inherited and present in childhood. Steatosis usually occurs with ingestion of hepatotoxins, such as alcohol.

PBD9 64–65 BP9 24 PBD8 36 BP8 26

37 B The valve is stenotic because of nodular deposits of calcium. The process is "dystrophic" because calcium deposition occurs in damaged tissues. The damage in this patient is a result of excessive wear and tear with aging. Amyloid deposition in the heart typically occurs within the myocardium and the vessels. Hereditary hemochromatosis is a genetic defect in iron absorption that results in extensive myocardial iron deposition (hemosiderosis). *Hyaline change* is a descriptive term used by histologists to describe protein deposits that are glassy and pale pink. The amount of lipofuscin increases within myocardial fibers (not valves) with aging.

PBD9 65 BP9 25–26 PBD8 38 BP8 26–27

38 B The microscopic findings suggest metastatic calcification, with deposition of calcium salts in tissues that have physiologic mechanisms for losing acid, creating an internal alkaline environment that favors calcium precipitation. Hypercalcemia can have a variety of causes, including primary and secondary hyperparathyroidism, bone destruction secondary to metastases, paraneoplastic syndromes, and, less commonly, vitamin D toxicity or sarcoidosis. Chronic renal disease reduces phosphate excretion by the kidney, resulting in an increase in serum phosphate. Because the solubility product of calcium and phosphorus must be maintained, the serum calcium is depressed, triggering increased parathyroid hormone output to increase the calcium level, which promotes calcium deposition. Chronic hepatitis leads to hyperbilirubinemia and jaundice. The granulomas of tuberculosis have caseous necrosis with dystrophic calcification. Another form of dystrophic calcification occurs when atherosclerotic lesions calcify. Dystrophic calcification is seen more often in the elderly, but it is the result of a lifetime of pathologic changes, not aging itself. Pulmonary emphysema can lead to respiratory acidosis that is compensated by metabolic alkalosis, with the result that the serum calcium level remains relatively unchanged.

PBD9 65 BP9 25–26 PBD8 38–39 BP8 26–27

39 C Germ cells have the highest telomerase activity, and the telomere length can be stabilized in these cells. This allows testicular germ cells to retain the ability to divide throughout life. Normal somatic cells have no telomerase activity, and telomeres progressively shorten with each cell division until growth arrest occurs. Erythrocytes do not even have a nucleus.

PBD9 67 BP9 26–27 PBD8 39–40 BP8 28–29

40 A Antioxidants may counteract the effects of reactive oxygen species (ROS) that may accumulate acutely and chronically within cells as a consequence of environmental insults and pathologic processes. Certainly, health food stores promote this concept with sales of products such as vitamin E. However, cellular damage is multifactorial, and proving that one compound has a significant effect is difficult. Analgesics ameliorate the perception of pain from cellular damage, but they do not prevent or diminish cell damage; they only mask it. Antimicrobials may help the body's own immune defenses against infectious agents and shorten and/or diminish tissue damage. However, long-term use of antimicrobials is discouraged because it may alter the body's own useful microbial flora, and it can promote development of drug-resistant strains that pose a serious health risk for the general population. (As Mr. Spock noted, "The needs of the many outweigh the needs of the few.") Antineoplastic agents are given for malignancies and rarely have benefit for cancer prevention. Glucocorticoids provide short-term improvement in well-being, but when used for longer periods, they have deleterious effects.

PBD9 66–67 BP9 26–27 PBD8 40–41 BP8 28–29