Comprehensive Pharmacy Review for NAPLEX

Eighth Edition

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Wolters Kluwer Health | Lippincott Williams & Wilkins

Study Questions

Directions for questions 1–30: Each question, statement, or incomplete statement in this section can be correctly answered or completed by **one** of the suggested answers or phrases. Choose the **best** answer.

1. If a vitamin solution contains 0.5 mg of fluoride ion in each milliliter, then how many milligrams of fluoride ion would be provided by a dropper that delivers 0.6 mL?

(A) 0.30 mg
(B) 0.10 mg
(C) 1.00 mg
(D) 0.83 mg

2. How many chloramphenicol capsules, each containing 250 mg, are needed to provide 25 mg/kg/d for 7 days for a person weighing 200 lb?

(A) 90 capsules
(B) 64 capsules
(C) 13 capsules
(D) 25 capsules

3. If 3.17 kg of a drug is used to make 50000 tablets, how many milligrams will 30 tablets contain?

(A) 1.9 mg
(B) 1900 mg
(C) 0.0019 mg
(D) 3.2 mg

4. A capsule contains ⅛ gr of ephedrine sulfate, ¼ gr of theophylline, and 1/16 gr of phenobarbital. What is the total mass of the active ingredients in milligrams?

(A) 20 mg
(B) 8 mg
(C) 28 mg
(D) 4 mg

5. If 1 fluid ounce of a cough syrup contains 10 gr of sodium citrate, how many milligrams are contained in 10 mL?

(A) 650 mg
(B) 65 mg
(C) 217 mg
(D) 20 mg

6. How many capsules, each containing ¼ gr of phenobarbital, can be manufactured if a bottle containing 2 avoirdupois ounces of phenobarbital is available?

(A) 771 capsules
(B) 350 capsules
(C) 3500 capsules
(D) 1250 capsules

7. Using the formula for calamine lotion, determine the amount of calamine (in grams) necessary to prepare 240 mL of lotion.

calamine	80 g
zinc oxide	80 g
glycerin	20 mL
bentonite magma	250 mL
calcium hydroxide topical solution	sufficient quantity to make 1000 mL

(A) 19.2 g
(B) 140.0 g
(C) 100.0 g
(D) 24.0 g

8. From the following formula, calculate the amount of white wax required to make 1 lb of cold cream. Determine the mass in grams.

cetyl esters wax	12.5 parts
white wax	12.0 parts
mineral oil	56.0 parts
sodium borate	0.5 parts
purified water	19.0 parts

(A) 56.75 g
(B) 254.24 g
(C) 54.48 g
(D) 86.26 g

9. How many grams of aspirin should be used to prepare 1.255 kg of the powder?

Aspirin	6 parts
phenacetin	3 parts
caffeine	1 part

(A) 125 g
(B) 750 g
(C) 175 g
(D) 360 g

10. A solution contains 1.25 mg of a drug per milliliter. At what rate should the solution be infused (drops per minute) if the drug is to be administered at a rate of 80 mg/hr? (1 mL = 30 drops)

(A) 64.00 drops/min
(B) 1.06 drops/min
(C) 32.00 drops/min
(D) 20.00 drops/min

11. The recommended maintenance dose of aminophylline for children is 1.0 mg/kg/hr by injection. If 10 mL of a 25-mg/mL solution of aminophylline is added to a 100-mL bottle of 5% dextrose, what should be the rate of delivery in mL/hr for a 40-lb child?

(A) 2.30 mL/hr
(B) 8.00 mL/hr
(C) 18.90 mL/hr
(D) 18.20 mL/hr

12. For children, streptomycin is to be administered at a dose of 30 mg/kg of body weight daily in divided doses every 6 to 12 hrs. The dry powder is dissolved by adding water for injection, in an amount to yield the desired concentration as indicated in the following table (for a 1-g vial).

Approximate Concentration (mg/mL)	Volume (mL)
200	4.2
250	3.2
400	1.8

Reconstituting at the lowest possible concentration, what volume (in mL) would be withdrawn to obtain a day's dose for a 50-lb child?

(A) 3.40 mL
(B) 22.73 mL
(C) 2.50 mL
(D) 2.27 mL

13. The atropine sulfate is available only in the form of 1/150 gr tablets. How many atropine sulfate tablets would you use to compound the following prescription?

atropine sulfate	1/200 gr
codeine phosphate	¼ gr
aspirin	5 gr
d.t.d.	#24 capsules
Sig:	1 capsule p.r.n.

(A) 3 tablets
(B) 6 tablets
(C) 12 tablets
(D) 18 tablets

14. In 25.0 mL of a solution for injection, there are 4.00 mg of the drug. If the dose to be administered to a patient is 200 μg, what quantity (in mL) of this solution should be used?

(A) 1.25 mL
(B) 125.00 mL
(C) 12.00 mL
(D) None of the above

15. How many milligrams of papaverine will the patient receive each day?

R_x	papaverine hcl	1.0 g
	aqua	30.0 mL
	syrup tolu, q.s. a.d.	90.0 mL
	Sig:	1 teaspoon t.i.d.

(A) 56.0 mg
(B) 5.6 mg
(C) 166.0 mg
(D) 2.5 mg

16. Considering the following formula, how many grams of sodium bromide should be used in filling this prescription?

R_x	sodium bromide	1.2 g
	syrup tolu	2.0 mL
	syrup wild cherry, q.s. a.d.	5.0 mL
	d.t.d.	#24

(A) 1.2 g
(B) 1200.0 g
(C) 28.8 g
(D) 220.0 g

17. How many milliliters of a 7.5% stock solution of $KMnO_4$ should be used to obtain the KMnO needed?

$KMnO_4$, q.s.
Distilled water, a.d. 1000 mL
Sig: 2 teaspoons diluted to 500 mL yield a 1:5000 solution

(A) 267.0 mL
(B) 133.0 mL
(C) 26.7 mL
(D) 13.3 mL

18. The formula for Ringer's solution follows. How much sodium chloride is needed to make 120 mL?

R_x	sodium chloride	8.60 g
	potassium chloride	0.30 g
	calcium chloride	0.33 g
	water for injection, q.s. a.d.	1000 mL

(A) 120.00 g
(B) 1.03 g
(C) 0.12 g
(D) 103.00 g

19. How many grams of talc should be added to 1 lb of a powder containing 20 g of zinc undecylenate per 100 g to reduce the concentration of zinc undecylenate to 3%?

(A) 3026.7 g
(B) 2572.7 g
(C) 17.0 g
(D) 257.0 g

20. How many milliliters of a 0.9% aqueous solution can be made from 20.0 g of sodium chloride?

(A) 2222 mL
(B) 100 mL
(C) 222 mL
(D) 122 mL

21. The blood of a reckless driver contains 0.1% alcohol. Express the concentration of alcohol in parts per million.

(A) 100 ppm
(B) 1000 ppm
(C) 1 ppm
(D) 250 ppm

22. Syrup is an 85% w/v solution of sucrose in water. It has a density of 1.313 g/mL. How many milliliters of water should be used to make 125 mL of syrup?

(A) 106.25 mL
(B) 164.10 mL
(C) 57.90 mL
(D) 25.00 mL

23. How many grams of benzethonium chloride should be used in preparing 5 gal of a 0.025% w/v solution?

(A) 189.25 g
(B) 18.90 g
(C) 4.73 g
(D) 35.00 g

24. How many grams of menthol should be used to prepare this prescription?

R_x	menthol	0.8%
	alcohol, q.s. a.d.	60.0 mL

(A) 0.48 g
(B) 0.80 g
(C) 4.80 g
(D) 1.48 g

25. How many milliliters of a 1:1500 solution can be made by dissolving 4.8 g of cetylpyridinium chloride in water?

(A) 7200.0 mL
(B) 7.2 mL
(C) 48.0 mL
(D) 4.8 mL

26. The manufacturer specifies that one Domeboro tablet dissolved in 1 pint of water makes a modified Burow's solution approximately equivalent to a 1:40 dilution. How many tablets should be used in preparing ½ gal of a 1:10 dilution?

(A) 16 tablets
(B) 189 tablets
(C) 12 tablets
(D) 45 tablets

27. How many milliosmoles of calcium chloride ($CaCl_2 \cdot 2H_2O$ − mol wt = 147) are represented in 147 mL of a 10% w/v calcium chloride solution?

(A) 100 mOsmol
(B) 200 mOsmol
(C) 300 mOsmol
(D) 3 mOsmol

28. How many grams of boric acid should be used in compounding the following prescription?

Phenacaine HCl 1.0% (NaCl eq = 0.17)
Chlorobutanol 0.5% (NaCl eq = 0.18)
Boric acid, q.s. (NaCl eq = 0.52)
Purified H_2O, a.d. 30 mL
Make isotonic solution
Sig: 1 drop in each eye

(A) 0.37 g
(B) 0.74 g
(C) 0.27 g
(D) 0.47 g

29. A pharmacist prepares 1 gal of KCl solution by mixing 565 g of KCl (valence = 1) in an appropriate vehicle. How many milliequivalents of K^+ are in 15 mL of this solution? (atomic weights: K = 39; Cl = 35.5)

(A) 7.5 mEq
(B) 10.0 mEq
(C) 20.0 mEq
(D) 30.0 mEq
(E) 40.0 mEq

30. A vancomycin solution containing 1000 mg of vancomycin hydrochloride diluted to 250 mL with D_5W is to be infused at a constant rate with an infusion pump in 2 hrs. What is the rate of drug administration?

(A) 2.08 mg/min
(B) 8.33 mg/min
(C) 4.17 mg/min
(D) 16.70 mg/min
(E) 5.21 mg/min

Answers and Explanations

1. **The answer is A** *[see I.A.2]*.

2. **The answer is B** *[see II]*.

3. **The answer is B** *[see II]*.

4. **The answer is C** *[see II]*.

5. **The answer is C** *[see I.A.2]*.

6. **The answer is C** *[see II]*.

7. **The answer is A** *[see III]*.

8. **The answer is C** *[see II; III.A]*.
The formula tells the pharmacist that white wax (W.W.) represents 12 parts out of the total 100 parts in the prescription. What we wish to determine is the mass of white wax required to prepare 454 g (1 lb) of the recipe. This can be easily solved by proportion:

$$\frac{12 \text{ parts W.W.}}{100 \text{ parts total}} = \frac{x}{454 \text{ parts (grams)}}; x = 54.48 \text{ g}$$

9. **The answer is B** *[see III.A]*.

10. **The answer is C** *[see IV.E]*.

11. **The answer is B** *[see II; IV]*.

12. **The answer is A** *[see IV]*.

13. **The answer is D** *[see II; III.B]*.

14. **The answer is A** *[see I.A.2; II]*.
Dimensional analysis is often useful for calculating doses. Considering that 4 mg of the drug is present in each 25 mL of solution, we can easily calculate the number of milliliters to be used to give a dose of 0.200 mg (200 μg). Always include units in your calculations.

$$\frac{25 \text{ mL}}{4 \text{ mg}} \times 0.200 \text{ mg} = 1.25 \text{ mL}$$

15. **The answer is C** *[see III.B]*.

16. **The answer is C** *[see III.B]*.

17. **The answer is B** *[see V.A; VI]*.
First, determine the mass of drug in the final diluted solution.

$$\frac{1 \text{ part}}{5000 \text{ parts}} = \frac{x \text{ g}}{500 \text{ g}}; x = 0.1 \text{ g}$$

Now, if 0.1 g of drug is present in 500 mL of 1:5000 solution, 2 teaspoons (10 mL) of the prescription contains the same amount of drug (0.1 g) before dilution. From this, the amount of drug in 1000 mL (the total volume) of the prescription can be determined:

$$\frac{0.1 \text{ g}}{10 \text{ mL}} = \frac{x \text{ g}}{1000 \text{ mL}}; x = 10 \text{ g}$$

Finally, to obtain the correct amount of drug to formulate the prescription (10 g), we are to use a 7.5% stock solution. Recalling the definition of percentage strength w/v

$$\frac{100 \text{ mL}}{7.5 \text{ g}} \times 10 \text{ g} = 133.3 \text{ mL or } 133 \text{ mL}$$

18. **The answer is B** *[see III.B]*.

19. **The answer is B** *[see V.C; VI.C]*.

20. **The answer is A** *[see I.A.2; V.A]*.
Using dimensional analysis

$$\frac{20 \text{ g} \times 100 \text{ mL}}{0.9 \text{ g}} = 2222 \text{ mL}$$

21. **The answer is B** *[see V.D.1]*.

22. **The answer is C** *[see I.A; V.A.1]*.
Using the density, the weight of 125 mL of syrup can be calculated:

$$125 \text{ mL} \times 1.313 \text{ g/mL} = 164.125 \text{ g}$$

Using proportion and the sucrose concentration in w/v, the weight of sucrose in 125 mL of syrup can be calculated:

$$\frac{100 \text{ mL}}{125 \text{ mL}} = \frac{85 \text{ g}}{x \text{ g}}; x = 106.25 \text{ g}$$

Finally, the weight of water in 125 mL of syrup can be calculated:

$$164.125 \text{ g} - 106.25 \text{ g} = 57.875 \text{ g}$$

which has a volume of 57.90 mL.

23. **The answer is C** *[see I; II; V]*.

24. **The answer is A** *[see I; V]*.

25. **The answer is A** *[see I; V]*.
The problem is easily solved by proportion. The question to be answered is if 1 g of drug is present in 1500 mL of a solution, what volume can be made with 4.8 g of drug?

$$\frac{1 \text{ g}}{4.8 \text{ g}} = \frac{1500 \text{ mL}}{x \text{ mL}}; x = 7200.0 \text{ mL}$$

(the volume of 1 to 1500 solution that can be prepared from 4.8 g of drug)

26. **The answer is A** *[see I; V]*.

27. The answer is C *[see VII.B]*.
Recalling the expression for ideal osmolar concentration:

$$\text{mOsmol/L} = \frac{100\ \text{g/L}}{147\ \text{g/mol}} \times 3 \times 1000$$
$$= \text{mOsmol/L} \times 0.147\ \text{L}$$
$$= 300\ \text{mOsmol}$$

28. The answer is A *[see VII.C]*.

29. The answer is D *[see VII.A]*.

30. The answer is B *[see IV.E]*.
Using dimensional analysis:

$$\frac{1000\ \text{mg}}{250\ \text{mL}} \times \frac{250\ \text{mL}}{2\ \text{hr}} \times \frac{1\ \text{hr}}{60\ \text{min}} = 8.33\ \text{mg/min}$$

Study Questions

Directions for questions 1–28: Each of the questions, statements, or incomplete statements in this section can be correctly answered or completed by one of the suggested answers or phrases. Choose the best answer.

1. Which substance is classified as a weak electrolyte?

(A) glucose
(B) urea
(C) ephedrine
(D) sodium chloride
(E) sucrose

2. The pH value is calculated mathematically as the

(A) log of the hydroxyl ion (OH^-) concentration.
(B) negative log of the OH^- concentration.
(C) log of the hydrogen ion (H^+) concentration.
(D) negative log of the H^+ concentration.
(E) ratio of H^+/OH^- concentration.

3. Which property is classified as colligative?

(A) solubility of a solute
(B) osmotic pressure
(C) hydrogen ion (H^+) concentration
(D) dissociation of a solute
(E) miscibility of the liquids

4. The colligative properties of a solution are related to the

(A) pH of the solution.
(B) number of ions in the solution.
(C) total number of solute particles in the solution.
(D) number of un-ionized molecules in the solution.
(E) pK_a of the solution.

5. The pH of a buffer system can be calculated with the

(A) Noyes–Whitney equation.
(B) Henderson–Hasselbalch equation.
(C) Michaelis–Menten equation.
(D) Young equation.
(E) Stokes equation.

6. Which mechanism is most often responsible for chemical degradation?

(A) racemization
(B) photolysis
(C) hydrolysis
(D) decarboxylation
(E) oxidation

7. Which equation is used to predict the stability of a drug product at room temperature from experiments at accelerated temperatures?

(A) Stokes equation
(B) Young equation
(C) Arrhenius equation
(D) Michaelis–Menten equation
(E) Hixson–Crowell equation

8. Based on the relation between the degree of ionization and the solubility of a weak acid, the drug aspirin ($pK_a = 3.49$) will be most soluble at

(A) pH 1.0.
(B) pH 2.0.
(C) pH 3.0.
(D) pH 4.0.
(E) pH 6.0.

9. Which solution is used as an astringent?

(A) strong iodine solution *USP*
(B) aluminum acetate topical solution *USP*
(C) acetic acid *NF*
(D) aromatic ammonia spirit *USP*
(E) benzalkonium chloride solution *NF*

10. The particle size of the dispersed solid in a suspension is usually greater than

(A) 0.5 μm.
(B) 0.4 μm.
(C) 0.3 μm.
(D) 0.2 μm.
(E) 0.1 μm.

11. In the extemporaneous preparation of a suspension, levigation is used to

(A) reduce the zeta potential.
(B) avoid bacterial growth.
(C) reduce particle size.
(D) enhance viscosity.
(E) reduce viscosity.

12. Which compound is a natural emulsifying agent?

(A) acacia
(B) lactose
(C) polysorbate 20
(D) polysorbate 80
(E) sorbitan monopalmitate

13. Vanishing cream is an ointment that may be classified as

(A) a water-soluble base.
(B) an oleaginous base.
(C) an absorption base.
(D) an emulsion base.
(E) an oleic base.

14. Rectal suppositories intended for adult use usually weigh approximately

(A) 1 g.
(B) 2 g.
(C) 3 g.
(D) 4 g.
(E) 5 g.

15. In the fusion method of making cocoa butter suppositories, which substance is most likely to be used to lubricate the mold?

(A) mineral oil
(B) propylene glycol
(C) cetyl alcohol
(D) stearic acid
(E) magnesium silicate

16. A very fine powdered chemical is defined as one that

(A) completely passes through a #80 sieve.
(B) completely passes through a #120 sieve.
(C) completely passes through a #20 sieve.
(D) passes through a #60 sieve and not more than 40% through a #100 sieve.
(E) passes through a #40 sieve and not more than 60% through a #60 sieve.

17. Which technique is typically used to mill camphor?

(A) trituration
(B) levigation
(C) pulverization by intervention
(D) geometric dilution
(E) attrition

18. The dispensing pharmacist usually blends potent powders with a large amount of diluent by

(A) spatulation.
(B) sifting.
(C) trituration.
(D) geometric dilution.
(E) levigation.

19. Which type of paper best protects a divided hygroscopic powder?

(A) waxed paper
(B) glassine
(C) white bond
(D) blue bond
(E) vegetable parchment

20. Which capsule size has the smallest capacity?

(A) 5
(B) 4
(C) 1
(D) 0
(E) 000

21. The shells of soft gelatin capsules may be made elastic or plastic-like by the addition of

(A) sorbitol.
(B) povidone.
(C) polyethylene glycol (PEG).
(D) lactose.
(E) hydroxypropyl methylcellulose.

22. The *United States Pharmacopeia* (*USP*) content uniformity test for tablets is used to ensure which quality?

(A) bioequivalency
(B) dissolution
(C) potency
(D) purity
(E) toxicity

23. All of the following statements about chemical degradation are true *except*

(A) as temperature increases, degradation decreases.
(B) most drugs degrade by a first-order process.
(C) chemical degradation may produce a toxic product.
(D) chemical degradation may result in a loss of active ingredients.
(E) chemical degradation may affect the therapeutic activity of a drug.

24. All of the following statements concerning zero-order degradation are true *except*

(A) its rate is independent of the concentration.
(B) a plot of concentration versus time yields a straight line on rectilinear paper.
(C) its half-life is a changing parameter.
(D) its concentration remains unchanged with respect to time.
(E) the slope of a plot of concentration versus time yields a rate constant.

25. All of the following statements about first-order degradation are true *except*

(A) its rate is dependent on the concentration.
(B) its half-life is a changing parameter.
(C) a plot of the logarithm of concentration versus time yields a straight line.
(D) its $t_{90\%}$ is independent of the concentration.
(E) a plot of the logarithm of concentration versus time allows the rate constant to be determined.

26. A satisfactory suppository base must meet all of the following criteria *except*

(A) it should have a narrow melting range.
(B) it should be nonirritating and nonsensitizing.
(C) it should dissolve or disintegrate rapidly in the body cavity.
(D) it should melt $< 30°C$.
(E) it should be inert.

27. Cocoa butter (theobroma oil) exhibits all of the following properties *except*

(A) it melts at temperatures between 33°C and 35°C.
(B) it is a mixture of glycerides.
(C) it is a polymorph.
(D) it is useful in formulating rectal suppositories.
(E) it is soluble in water.

28. *United States Pharmacopeia* (*USP*) tests to ensure the quality of drug products in tablet form include all of the following *except*

(A) disintegration.
(B) dissolution.
(C) hardness and friability.
(D) content uniformity.
(E) weight variation.

Directions for questions 29–42: The questions and incomplete statements in this section can be correctly answered or completed by **one or more** of the suggested answers. Choose the answer, **A–E.**

A if **I only** is correct
B if **III only** is correct
C if **I** and **II** are correct
D if **II** and **III** are correct
E if **I**, **II**, and **III** are correct

29. Forms of water that are suitable for use in parenteral preparations include

I. purified water *USP*.
II. water for injection *USP*.
III. sterile water for injection *USP*.

30. The particles in an ideal suspension should satisfy which of the following criteria?

I. Their size should be uniform.
II. They should be stationary or move randomly.
III. They should remain discrete.

31. The sedimentation of particles in a suspension can be minimized by

I. adding sodium benzoate.
II. increasing the viscosity of the suspension.
III. reducing the particle size of the active ingredient.

32. Ingredients that may be used as suspending agents include

I. methylcellulose.
II. acacia.
III. talc.

33. Mechanisms that are thought to provide stable emulsifications include the

I. formation of interfacial film.
II. lowering of interfacial tension.
III. presence of charge on the ions.

34. Nonionic surface-active agents used as synthetic emulsifiers include

I. tragacanth.
II. sodium lauryl sulfate.
III. sorbitan esters (Spans).

35. Advantages of systemic drug administration by rectal suppositories include

I. avoidance of first-pass effects.
II. suitability when the oral route is not feasible.
III. predictable drug release and absorption.

36. True statements about the milling of powders include

I. a fine particle size is essential if the lubricant is to function properly.
II. an increased surface area may enhance the dissolution rate.
III. milling may cause degradation of thermolabile drugs.

37. Substances used to insulate powder components that liquefy when mixed include

I. talc.
II. kaolin.
III. light magnesium oxide.

38. A ceramic mortar may be preferable to a glass mortar when

I. a volatile oil is added to a powder mixture.
II. colored substances (dyes) are mixed into a powder.
III. comminution is desired in addition to mixing.

39. Divided powders may be dispensed in

I. individual-dose packets.
II. a bulk container.
III. a perforated, sifter-type container.

40. True statements about the function of excipients used in tablet formulations include

I. binders promote granulation during the wet granulation process.
II. glidants help promote the flow of the tablet granulation during manufacture.
III. lubricants help the patient swallow the tablets.

41. Which manufacturing variables would be likely to affect the dissolution of a prednisone tablet in the body?

I. the amount and type of binder added
II. the amount and type of disintegrant added
III. the force of compression used during tableting

42. Agents that may be used to coat enteric-coated tablets include

I. hydroxypropyl methylcellulose.
II. carboxymethylcellulose.
III. cellulose acetate phthalate.

Directions for questions 43–46: Each of the following tablet-processing problems can be the result of one of the following reasons. The processing problems may be used more than once or not at all. Choose the **best** answer, **A–E**.

A excessive moisture in the granulation
B entrapment of air
C tablet friability
D degraded drug
E tablet hardness

43. Picking

44. Mottling

45. Capping

46. Sticking

Directions for questions 47–49: Each of the following processes can be described by one of the following comminution procedures. The processes may be used more than once or not at all. Choose the **best** answer, **A–E**.

A trituration
B spatulation
C levigation
D pulverization by intervention
E tumbling

47. Rubbing or grinding a substance in a mortar that has a rough inner surface

48. Reducing and subdividing a substance by adding an easily removed solvent

49. Adding a suitable agent to form a paste and then rubbing or grinding the paste in a mortar

Directions for questions 50–53: Each of the following controlled-release dosage forms is represented by one of the following drug products. The dosage forms may be used more than once or not at all. Choose the **best** answer, **A–E**.

A matrix formulations
B ion-exchange resin complex
C drug complexes
D osmotic system
E coated beads or granules

50. Ionamin capsules

51. Thorazine Spansule capsules

52. Rynatan pediatric suspension

53. Procardia XL

Answers and Explanations

1. **The answer is C** *[see IV.A.1.a; IV.A.3.d].*
Glucose, urea, and sucrose are nonelectrolytes. Sodium chloride is a strong electrolyte. Electrolytes are substances that form ions when dissolved in water. Thus, they can conduct an electric current through the solution. Ions are particles that bear electrical charges: Cations are positively charged, and anions are negatively charged. Strong electrolytes are completely ionized in water at all concentrations. Weak electrolytes (e.g., ephedrine) are only partially ionized at most concentrations. Because nonelectrolytes do not form ions when in solution, they are nonconductors.

2. **The answer is D** *[see IV.A.3.b].*
The pH is a measure of the acidity, or hydrogen ion concentration, of an aqueous solution. The pH is the logarithm of the reciprocal of the hydrogen ion (H^+) concentration expressed in moles per liter. Because the logarithm of a reciprocal equals the negative logarithm of the number, the pH is the negative logarithm of the H^+ concentration. A pH of 7.0 indicates neutrality. As the pH decreases, the acidity increases. The pH of arterial blood is 7.35 to 7.45; of urine, 4.8 to 7.5; of gastric juice, approximately 1.4; and of cerebrospinal fluid, 7.35 to 7.40. The concept of pH was introduced by Sörensen in the early 1900s. Alkalinity is the negative logarithm of $[OH^-]$ and is inversely related to acidity.

3. **The answer is B** *[see IV.A.2.d].*
Osmotic pressure is an example of a colligative property. The osmotic pressure is the magnitude of pressure needed to stop osmosis across a semipermeable membrane between a solution and a pure solvent. The colligative properties of a solution depend on the total number of dissociated and undissociated solute particles. These properties are independent of the size of the solute. Other colligative properties of solutes are reduction in the vapor pressure of the solution, elevation of its boiling point, and depression of its freezing point.

4. **The answer is C** *[see IV.A.1.b].*
The colligative properties of a solution are related to the total number of solute particles that it contains. Examples of colligative properties are the osmotic pressure, lowering of the vapor pressure, elevation of the boiling point, and depression of the freezing or melting point.

5. **The answer is B** *[see IV.A.3.e].*
The Henderson–Hasselbalch equation for a weak acid and its salt is as follows:

$$pH = pK_a + \log \frac{[salt]}{[acid]}$$

where pK_a is the negative log of the dissociation constant of a weak acid and [salt]/[acid] is the ratio of the molar concentration of salt and acid used to prepare a buffer.

6. **The answer is C** *[see V.D.1].*
Although all of the mechanisms listed can be responsible, the chemical degradation of medicinal compounds, particularly esters in liquid formulations, is usually caused by hydrolysis. For this reason, drugs that have ester functional groups are formulated in dry form whenever possible. Oxidation is another common mode of degradation and is minimized by including antioxidants (e.g., ascorbic acid) in drug formulations. Photolysis is reduced by packaging susceptible products in amber or opaque containers. Decarboxylation, which is the removal of COOH groups, affects compounds that include carboxylic acid. Racemization neutralizes the effects of an optically active compound by converting half of its molecules into their mirror-image configuration. As a result, the dextrorotatory and levorotatory forms cancel each other out. This type of degradation affects only drugs that are characterized by optical isomerism.

7. **The answer is C** *[see V.E.3.d].*
Testing of a drug formulation to determine its shelf life can be accelerated by applying the Arrhenius equation to data obtained at higher temperatures. The method involves determining the rate constant (k) values for the degradation of a drug at various elevated temperatures. The log of k is plotted against the reciprocal of the absolute temperature, and the k value for degradation at room temperature is obtained by extrapolation.

8. **The answer is E** *[see IV.A.3.g].*
The solubility of a weak acid varies as a function of pH. Because pH and pK_a (the dissociation constant) are related, solubility is also related to the degree of ionization. Aspirin is a weak acid that is completely ionized at a pH that is two units greater than its pK_a. Therefore, it is most soluble at pH 6.0.

9. **The answer is B** *[see VI.B.7].*
Aluminum acetate and aluminum subacetate solutions are astringents that are used as antiperspirants and as wet dressings for contact dermatitis. Strong iodine solution and benzalkonium chloride are topical antibacterial solutions. Acetic acid is added to products as an acidifier. Aromatic ammonia spirit is a respiratory stimulant.

10. **The answer is A** *[see IV.B.1.a].*
A suspension is a two-phase system that consists of a finely powdered solid dispersed in a liquid vehicle. The particle size of the suspended solid should be as small as possible to minimize sedimentation, but it is usually > 0.5 μm.

11. **The answer is C** *[see VI.E.3.a].*
Levigation is the process of blending and grinding a substance to separate the particles, reduce their size, and form a paste. Levigation is performed by adding a small amount of suitable levigating agent (e.g., glycerin) to the solid and blending the mixture with a mortar and pestle.

12. **The answer is A** *[see VI.D.3].*
Acacia, or gum arabic, is the exudate obtained from the stems and branches of various species of *Acacia*, a woody plant native to Africa. Acacia is a natural emulsifying agent that provides a stable emulsion of low viscosity. Emulsions are droplets of one or more immiscible liquids dispersed in another liquid. Emulsions are inherently unstable: The droplets tend to coalesce into larger and larger drops. The purpose of an emulsifying agent is to keep the droplets dispersed and prevent them from coalescing. Polysorbate 20, polysorbate 80, and sorbitan monopalmitate are also emulsifiers, but are synthetic, not natural, substances.

13. **The answer is D** *[see VI.E.2].*
Ointments are typically used as emollients to soften the skin, as protective barriers, or as vehicles for medication. A variety of ointment bases are available. Vanishing cream, an emulsion type of ointment base, is an oil-in-water emulsion that contains a high percentage of water. Stearic acid is used to create a thin film on the skin when the water evaporates.

14. **The answer is B** *[see VI.F.2.a].*
By convention, a rectal suppository for an adult weighs approximately 2 g. Suppositories for infants and children are smaller. Vaginal suppositories typically weigh approximately 5 g. Rectal suppositories are usually shaped like an elongated bullet (cylindrical and tapered at one end). Vaginal suppositories are usually ovoid.

15. **The answer is A** *[see VI.F.4.c].*
In the fusion method of making suppositories, molds made of aluminum, brass, or nickel–copper alloys are used. Finely powdered drug mixed with melted cocoa butter is poured into a mold that is lubricated very lightly with mineral oil.

16. **The answer is B** *[see VI.G; Table 2-8].*
The *USP* defines a very fine chemical powder as one that completely passes through a standard #120 sieve, which has 125-μm openings. The *USP* classification for powdered vegetable and animal drugs differs from that for powdered chemicals. To be classified as very fine, powdered vegetable and animal drugs must pass completely through a #80 sieve, which has 180-μm openings.

17. **The answer is C** *[see VI.G.1.c.(3.(b)].*
Pulverization by intervention is the milling technique that is used for drug substances that are gummy and tend to reagglomerate or resist grinding (e.g., camphor, iodine). In this sense, intervention is the addition of a small amount of material that aids milling and can be removed easily after pulverization is complete. For example, camphor can be reduced readily if a small amount of volatile solvent (e.g., alcohol) is added. The solvent is then allowed to evaporate.

18. **The answer is D** *[see VI.G.2.c].*
The pharmacist uses geometric dilution to mix potent substances with a large amount of diluent. The potent drug and an equal amount of diluent are first mixed in a mortar by trituration. A volume of diluent equal to the mixture in the mortar is added, and the mix is again triturated. The procedure is repeated, and each time, diluent equal in volume to the mixture then in the mortar is added, until all of the diluent is incorporated.

19. The answer is A *[see VI.G.3.b.(4)].*
Hygroscopic and volatile drugs are best protected by waxed paper, which is waterproof. The packet may be double-wrapped with a bond paper to improve the appearance of the completed powder.

20. The answer is A *[see VI.H.2.c.(1)].*
Hard capsules are numbered from 000 (largest) to 5 (smallest). Their approximate capacity ranges from 600 to 30 mg; however, the capacity of the capsule depends on the density of the contents.

21. The answer is A *[see VI.H.3.a–b].*
The shells of soft gelatin capsules are plasticized by the addition of a polyhydric alcohol (polyol), such as glycerin or sorbitol. An antifungal preservative can also be added. Both hard and soft gelatin capsules can be filled with a powder or another dry substance. Soft gelatin capsules are also useful dosage forms for fluids or semisolids.

22. The answer is C *[see VI.H.4.a].*
A content uniformity test is a test of potency. To ensure that each tablet or capsule contains the intended amount of drug substance, the *USP* provides two tests: weight variation and content uniformity. The content uniformity test can be used for any dosage unit but is required for coated tablets, for tablets in which the active ingredient makes up $<$ 50% of the tablet, for suspensions in single-unit containers or in soft capsules, and for many solids that contain added substances. The weight variation test can be used for liquid-filled soft capsules, for any dosage form unit that contains at least 50 mg of a single drug if the drug makes up at least 50% of the bulk, for solids that do not contain added substances, and for freeze-dried solutions.

23. The answer is A *[see V.A and V.B].*
The reaction velocity, or degradation rate, of a pharmaceutical product is affected by several factors, including temperature, solvents, and light. The degradation rate increases two to three times with each 10°C increase in temperature. The effect of temperature on reaction rate is given by the Arrhenius equation:

$$k = Ae^{-Ea/RT}$$

where k is the reaction rate constant, A is the frequency factor, Ea is the energy of activation, R is the gas constant, and T is the absolute temperature.

24. The answer is D *[see V.B.2.a].*
In zero-order degradation, the concentration of a drug decreases over time. However, the change of concentration with respect to time is unchanged. In the equation

$$-\frac{dC}{dt} = k$$

the fact that dC/dt is negative signifies that the concentration is decreasing. However, the velocity of the concentration change is constant.

25. The answer is B *[see V.B.2.b.(2)].*
The half-life ($t_{½}$) is the time required for the concentration of a drug to decrease by one-half. For a first-order degradation:

$$t_{½} = \frac{0.693}{k}$$

Because both k and 0.693 are constants, $t_{½}$ is a constant.

26. The answer is D *[see VI.F.3].*
A satisfactory suppository base should remain firm at room temperature. Preferably, it should not melt $<$ 30°C to avoid premature softening during storage and insertion. It should also be inert, nonsensitizing, nonirritating, and compatible with a variety of drugs. Moreover, it should melt just below body temperature and should dissolve or disintegrate rapidly in the fluid of the body cavity into which it is inserted.

27. The answer is E *[see VI.F.3.c.(1)].*
Cocoa butter is a fat that is obtained from the seed of *Theobroma cacao*. Chemically, it is a mixture of stearin, palmitin, and other glycerides that are insoluble in water and freely soluble in ether and chloroform. Depending on the fusion temperature, cocoa butter can crystallize into any one of four crystal forms. Cocoa butter is a good base for rectal suppositories, although it is less than ideal for vaginal or urethral suppositories.

28. The answer is C *[see VI.I.5].*
To satisfy the *USP* standards, tablets are required to pass one of two tests. A weight variation test is used if the active ingredient makes up the bulk of the tablet. A content uniformity test is used if the tablet is coated or if the active ingredient makes up $<$ 50% of the bulk of the tablet. Many tablets for oral administration are required to meet a disintegration test. Disintegration times are specified in the individual monographs. A dissolution test may be required instead if the active component of the tablet has limited water solubility. Hardness and friability would affect the disintegration and dissolution rates, but hardness and friability tests are in-house quality control tests, not official *USP* tests.

29. The answer is D (II, III) *[see VI.A.1].*
Water for injection *USP* is water that has been purified by distillation or by reverse osmosis. This water is used to prepare parenteral solutions that are subject to final sterilization. For parenteral solutions that are prepared aseptically and not subsequently sterilized, sterile water for injection *USP* is used. Sterile water for injection *USP* is water for injection *USP* that has been sterilized and suitably packaged. This water meets the *USP* requirements for sterility. Bacteriostatic water for injection *USP* is sterile water for injection *USP* that contains one or more antimicrobial agents. It can be used in parenteral solutions if the antimicrobial additives are compatible with the other ingredients in the solution, but it cannot be used in newborns. Purified water *USP* is not used in parenteral preparations.

30. The answer is E (I, II, III) *[see IV.B.2].*
An ideal suspension would have particles of uniform size, minimal sedimentation, and no interaction between particles. Although these ideal criteria are rarely met, they can be approximated by keeping the particle size as small as possible, the densities of the solid and the dispersion medium as similar as possible, and the dispersion medium as viscous as possible.

31. The answer is D (II, III) *[see IV.B.2].*
As Stokes's law indicates, the sedimentation rate of a suspension is slowed by reducing its density, reducing the size of the suspended particles, or increasing its viscosity by incorporating a thickening agent. Sodium benzoate is an antifungal agent and would not reduce the sedimentation rate of a suspension.

32. The answer is C (I, II) *[see VI.C.3].*
Acacia and methylcellulose are common suspending agents. Acacia is a natural product, and methylcellulose is a synthetic polymer. By increasing the viscosity of the liquid, these agents enable particles to remain suspended for a longer period.

33. The answer is E (I, II, III) *[see VI.D.3].*
Emulsifying agents provide a mechanical barrier to coalescence. They also reduce the natural tendency of the droplets in the internal phase (oil or water) of the emulsion to coalesce. Three mechanisms appear to be involved. Some emulsifiers promote stability by forming strong, pliable interfacial films around the droplets. Emulsifying agents also reduce interfacial tension. Finally, ions (from the emulsifier) in the interfacial film can lead to charge repulsion that causes droplets to repel one another, thereby preventing coalescence.

34. The answer is B (III) *[see VI.D.3].*
All of the substances listed are emulsifying agents, but only sorbitan esters are nonionic synthetic agents. Tragacanth, like acacia, is a natural emulsifying agent. Sodium lauryl sulfate is an anionic surfactant. Sorbitan esters (known colloquially as Spans because of their trade names) are hydrophobic and form water-in-oil emulsions. The polysorbates (known colloquially as Tweens) are also nonionic, synthetic sorbitan derivatives. However, they are hydrophilic and therefore form oil-in-water emulsions. Sodium lauryl sulfate, as alkali soap, is also hydrophilic and thus forms oil-in-water emulsions.

35. The answer is C (I, II) *[see VI.F.1–2].*
Rectal suppositories are useful for delivering systemic medication under certain circumstances. Absorption of a drug from a rectal suppository involves release of the drug from the suppository vehicle, diffusion through the rectal mucosa, and transport to the circulation through the rectal veins. The rectal veins bypass the liver, so this route avoids rapid hepatic degradation of certain drugs (first-pass effect). The rectal route is also useful when a drug cannot be given orally (e.g., because of vomiting). However, the extent of drug release and absorption is variable. It depends on the properties of the drug, the suppository base, and the environment in the rectum.

36. The answer is E (I, II, III) *[see VI.G.1.c].*
Milling is the process of mechanically reducing the particle size of solids before they are formulated into a final product. To work effectively, a lubricant must coat the surface of the granulation or powder. Hence, fine particle size is essential. Decreasing the particle size increases the surface area and can enhance the dissolution rate. Thermolabile drugs may undergo degradation because of the buildup of heat during milling.

37. The answer is D (II, III) *[see VI.G.2.a.(2)].*
Some solid substances (e.g., aspirin, phenylsalicylate, phenacetin, thymol, camphor) liquefy or form eutectic mixtures when in close, prolonged contact with one another. These substances are best insulated by the addition of light magnesium oxide or magnesium carbonate. Other inert diluents that can be used are kaolin, starch, and bentonite.

38. The answer is B (III) *[see VI.G.2.b].*
When powders are mixed, if comminution is especially important, a porcelain or ceramic mortar that has a rough inner surface is preferred over the smooth working surface of a glass mortar. Because a glass mortar cleans more easily after use, it is preferred for chemicals that may stain a porcelain or ceramic mortar as well as for simple mixing of substances that do not require comminution.

39. The answer is A (I) *[see VI.G.3.a–b].*
Powders for oral use can be dispensed by the pharmacist in bulk form or divided into premeasured doses (divided powders). Divided powders are traditionally dispensed in folded paper packets (chartulae) made of parchment, bond paper, glassine, or waxed paper. However, individual doses can be packaged in metal foil or small plastic bags if the powder needs greater protection from humidity or evaporation.

40. The answer is C (I, II) *[see VI.I.2.b].*
Tablets for oral ingestion usually contain excipients that are added to the formulation for their special functions. Binders and adhesives are added to promote granulation or compaction. Diluents are fillers that are added to make up the required tablet bulk. They can also aid in the manufacturing process. Disintegrants aid in tablet disintegration in gastrointestinal fluids. Lubricants, antiadherents, and glidants aid in reducing friction or adhesion between particles or between tablet and die. For example, lubricants are used in the manufacture of tablets to reduce friction when the tablet is ejected from the die cavity. Lubricants are usually hydrophobic substances that can affect the dissolution rate of the active ingredient.

41. The answer is E (I, II, III) *[see VI.2.b.(3)].*
Disintegrants are added to tablet formulations to facilitate disintegration in gastrointestinal fluids. Disintegration of the tablet in the body is critical to its dissolution and subsequent absorption and bioavailability. The binder and the compression force used during tablet manufacturing affect the hardness of the tablet as well as tablet disintegration and drug dissolution.

42. The answer is B (III) *[see VI.I.3.a.(4)].*
An enteric-coated tablet has a coating that remains intact in the stomach, but dissolves in the intestines to yield the tablet ingredients there. Enteric coatings include various fats, fatty acids, waxes, and shellacs. Cellulose acetate phthalate remains intact in the stomach because it dissolves only when the pH $>$ 6. Other enteric-coating materials include povidone (polyvinylpyrrolidone), polyvinyl acetate phthalate, and hydroxypropyl methylcellulose phthalate.

43. The answer is A *[see VI.I.4].*

44. The answer is D *[see VI.I.4].*

45. The answer is B *[see VI.I.4].*

46. The answer is A *[see VI.I.4].*
Sticking is adhesion of tablet material to a die wall. It may be caused by excessive moisture or by the use of ingredients that have low melting temperatures. Mottling is uneven color distribution. It is most often caused by poor mixing of the tablet granulation but may also occur when a degraded drug produces a colored metabolite. Capping is separation of the top or bottom crown of a tablet from the main body. Capping implies that compressed powder is not cohesive. Reasons for capping include excessive force of compression, use of insufficient binder, worn tablet tooling equipment, and entrapment of air during processing. Picking is adherence of tablet surface material to a punch. It can be caused by a granulation that is too damp, by a scratched punch, by static charges on the powder, and particularly by the use of a punch tip that is engraved or embossed.

47. The answer is A *[see VI.G.1.c; VI.G.2].*

48. The answer is D *[see VI.G.1.c; VI.G.2].*

49. The answer is C *[see VI.G.1.c; VI.G.2].*
Comminution is the process of reducing the particle size of a powder to increase its fineness. Several comminution techniques are suitable for small-scale use in a pharmacy. Trituration is used both to comminute and to mix dry powders. If comminution is desired, the substance is rubbed in a mortar that has a rough inner surface. Pulverization by intervention is often used for substances that tend to agglomerate or resist grinding. A small amount of easily removed (e.g., volatile) solvent is added. After the substance is pulverized, the solvent is allowed to evaporate or is otherwise removed. Levigation is often used to prepare pastes or ointments. The powder is reduced by adding a suitable nonsolvent (levigating agent) to form a paste and then either rubbing the paste in a mortar with a pestle or rubbing it on an ointment slab with a spatula. Spatulation and tumbling are techniques that are used to mix or blend powders, not to reduce them. Spatulation is blending small amounts of powders by stirring them with a spatula on a sheet of paper or a pill tile. Tumbling is blending large amounts of powder in a large rotating container.

50. The answer is B *[see VI.K.3.e].*

51. The answer is E *[see VI.K.3.a].*

52. The answer is C *[see VI.K.3.f].*

53. The answer is D *[see VI.K.3.d].*

Controlled-release dosage forms are designed to release a drug slowly for prolonged action in the body. A variety of pharmaceutical mechanisms are used to provide the controlled release. Ion-exchange resins may be complexed to drugs by passing a cationic drug solution through a column that contains the resin. The drug is complexed to the resin by replacement of hydrogen atoms. Release of drug from the complex depends on the ionic environment within the gastrointestinal tract and on the properties of the resin. Coated beads (e.g., Thorazine Spansule capsules) or granules produce blood levels similar to those obtained with multiple dosing. The various coating thicknesses produce a sustained-release effect.

Matrix devices may use insoluble plastics, hydrophilic polymers, or fatty compounds. These components are mixed with the drug and compressed into a tablet. The primary dose, or the portion of the drug to be released immediately, is placed on the tablet as a layer or coat. The remainder of the dose is released slowly from the matrix. Relatively insoluble tannate–amine complexes provide for a prolonged gastrointestinal absorption phase and sustained systemic concentrations of the weak bases. Osmotic systems employ osmotic pressure to control the release of the active ingredient from the formulation. Osmotic tablet formulations provide a semipermeable membrane as a coating that surrounds the osmotically active core. The coating allows water to diffuse into the core but does not allow drug to diffuse out. As water flows into the tablet, the drug dissolves. The laser-drilled hole in the coating allows the drug solution within the tablet to flow to the outside at a rate that is equivalent to the rate of water flow into the tablet. The osmotic pressure gradient and a zero-order drug-release rate will be maintained as long as excess osmotically active solute (e.g., electrolyte) remains in the tablet core.

Study Questions

Directions: Each question, statement, or incomplete statement in this section can be correctly answered or completed by **one** of the suggested answers or phrases. Choose the **best** answer.

1. Which statement best describes bioavailability?

(A) relation between the physical and the chemical properties of a drug and its systemic absorption
(B) measurement of the rate and amount of therapeutically active drug that reaches the systemic circulation
(C) movement of the drug into body tissues over time
(D) dissolution of the drug in the gastrointestinal tract
(E) amount of drug destroyed by the liver before systemic absorption from the gastrointestinal tract occurs

2. The route of drug administration that gives the most rapid onset of the pharmacologic effect is

(A) intramuscular injection.
(B) intravenous injection.
(C) intradermal injection.
(D) peroral administration.
(E) subcutaneous injection.

3. The route of drug administration that provides complete (100%) bioavailability is

(A) intramuscular injection.
(B) intravenous injection.
(C) intradermal injection.
(D) peroral administration.
(E) subcutaneous injection.

4. After peroral administration, drugs generally are absorbed best from the

(A) buccal cavity.
(B) stomach.
(C) duodenum.
(D) ileum.
(E) rectum.

5. The characteristics of an active transport process include all of the following *except* for which one?

(A) Active transport moves drug molecules against a concentration gradient.
(B) Active transport follows Fick's law of diffusion.
(C) Active transport is a carrier-mediated transport system.
(D) Active transport requires energy.
(E) Active transport of drug molecules may be saturated at high drug concentrations.

6. The passage of drug molecules from a region of high drug concentration to a region of low drug concentration is known as

(A) active transport.
(B) bioavailability.
(C) biopharmaceutics.
(D) simple diffusion.
(E) pinocytosis.

7. Which equation describes the rate of drug dissolution from a tablet?

(A) Fick's law
(B) Henderson–Hasselbalch equation
(C) Law of mass action
(D) Michaelis–Menten equation
(E) Noyes–Whitney equation

8. Which condition usually increases the rate of drug dissolution from a tablet?

(A) increase in the particle size of the drug
(B) decrease in the surface area of the drug
(C) use of the free acid or free base form of the drug
(D) use of the ionized, or salt, form of the drug
(E) use of sugar coating around the tablet

9. Dose dumping is a problem in the formulation of

(A) compressed tablets.
(B) modified-release drug products.
(C) hard gelatin capsules.
(D) soft gelatin capsules.
(E) suppositories.

10. The rate-limiting step in the bioavailability of a lipid-soluble drug formulated as an immediate-release compressed tablet is the rate of

(A) disintegration of the tablet and release of the drug.
(B) dissolution of the drug.
(C) transport of the drug molecules across the intestinal mucosal cells.
(D) blood flow to the gastrointestinal tract.
(E) biotransformation, or metabolism, of the drug by the liver before systemic absorption occurs.

11. The extent of ionization of a weak electrolyte drug depends on the

(A) pH of the media and pK_a of the drug.
(B) oil to water partition coefficient of the drug.
(C) particle size and surface area of the drug.
(D) Noyes–Whitney equation for the drug.
(E) polymorphic form of the drug.

12. The rate of drug bioavailability is most rapid when the drug is formulated as a

(A) controlled-release product.
(B) hard gelatin capsule.
(C) compressed tablet.
(D) solution.
(E) suspension.

13. The amount of drug that a transdermal patch (i.e., transdermal drug delivery system) delivers within a 24-hrs period depends on the

(A) patch composition, which includes an occlusive backing and an adhesive film in contact with the skin.
(B) affinity of the drug for the formulation matrix relative to its affinity for the stratum corneum.
(C) rate of drug partitioning and/or diffusion through the patch to the skin surface.
(D) surface area of the patch.
(E) All of the above

Answers and Explanations

1. The answer is B *[see I.A.3]***.**
Bioavailability is the measurement of the rate and extent (amount) of therapeutically active drug that reaches the systemic circulation. The relation of the physical and the chemical properties of a drug to its systemic absorption (i.e., bioavailability) is known as its biopharmaceutics. The movement of a drug into body tissues is an aspect of pharmacokinetics, which is the study of drug movement in the body over time. The dissolution of a drug in the gastrointestinal tract is a physicochemical process that affects bioavailability. Significant destruction of a drug by the liver before it is systemically absorbed (known as the first-pass effect because it occurs during the first passage of the drug through the liver) decreases bioavailability.

2. The answer is B *[see II.B.1.a]***.**
When the active form of the drug is given intravenously, it enters the systemic circulation directly. The drug is delivered rapidly to all tissues, including the drug receptor sites. For all other routes of drug administration, except intra-arterial injection, the drug must be systemically absorbed before it is distributed to the drug receptor sites. For this reason, the onset of pharmacologic effects is slower. If the drug is a prodrug that must be converted to an active drug, oral administration, not intravenous injection, may not provide the most rapid onset of activity if conversion to the active form takes place in the gastrointestinal tract or liver.

3. The answer is B *[see II.C.2]***.**
When a drug is given by intravenous injection, the entire dose enters the systemic circulation. With other routes of administration, the drug may be lost before it reaches the systemic circulation. For example, with first-pass effects, a portion of an orally administered drug is eliminated, usually through degradation by liver enzymes, before the drug reaches its receptor sites.

4. The answer is C *[see II.B.2.b.(4)]***.**
Drugs given orally are well absorbed from the duodenum. The duodenum has a large surface area because of the presence of villi and microvilli. In addition, because the duodenum is well perfused by the mesenteric blood vessels, a concentration gradient is maintained between the lumen of the duodenum and the blood.

5. **The answer is B** *[see II.A.2–3]***.**
Fick's law of diffusion describes passive diffusion of drug molecules moving from a high concentration to a low concentration. This process is not saturable and does not require energy.

6. **The answer is D** *[see II.A.2]***.**
The transport of a drug across a cell membrane by passive diffusion follows Fick's law of diffusion: The drug moves with a concentration gradient (i.e., from an area of high concentration to an area of low concentration). In contrast, drugs that are actively transported move against a concentration gradient.

7. **The answer is E** *[see III.A.1]***.**
The Noyes–Whitney equation describes the rate at which a solid drug dissolves. Fick's law is similar to the Noyes–Whitney equation in that both equations describe drug movement caused by a concentration gradient. Fick's law generally refers to passive diffusion, or passive transport, of drugs. The law of mass action describes the rate of a chemical reaction, the Michaelis–Menten equation involves enzyme kinetics, and the Henderson–Hasselbalch equation gives the pH of a buffer solution.

8. **The answer is D** *[see III.A.1–3]***.**
The ionized, or salt, form of a drug has a charge and is generally more water soluble and therefore dissolves more rapidly than the nonionized (free acid or free base) form of the drug. The dissolution rate is directly proportional to the surface area and inversely proportional to the particle size. An increase in the particle size or a decrease in the surface area slows the dissolution rate.

9. **The answer is B** *[see III.B.6]***.**
A modified-release, or controlled-release, drug product contains two or more conventional doses of the drug. An abrupt release of the drug, known as dose dumping, may cause intoxication.

10. **The answer is B** *[see III.B.1.c]***.**
For lipid-soluble drugs, the rate of dissolution is the slowest (i.e., rate-limiting) step in drug absorption and thus in bioavailability. The disintegration rate of an immediate-release or conventional compressed tablet is usually more rapid than the rate of drug dissolution. Because the cell membrane is a lipoprotein structure, transport of a lipid-soluble drug across the cell membrane is usually rapid.

11. **The answer is A** *[see III.A.4.b]***.**
The extent of ionization of a weak electrolyte is described by the Henderson–Hasselbalch equation, which relates the pH of the solution to the pK_a of the drug.

12. **The answer is D** *[see III.B.2.a]***.**
Because a drug in solution is already dissolved, no dissolution is needed before absorption. Consequently, compared with other drug formulations, a drug in solution has a high rate of bioavailability. A drug in aqueous solution has the highest bioavailability rate and is often used as the reference preparation for other formulations. Drugs in hydroalcoholic solution (e.g., elixirs) also have good bioavailability. The rate of drug bioavailability from a hard gelatin capsule, compressed tablet, or suspension may be equal to that of a solution if an optimal formulation is manufactured and the drug is inherently rapidly absorbed.

13. **The answer is E** *[see III.B.7]***.**
Drug delivery from a transdermal drug delivery system depends on all of the factors cited—that is, on the presence of an occlusive backing (to maintain skin hydration and elevate skin temperature slightly) and an adhesive film to maintain contact of the formulation matrix with the skin to enable drug transfer from the patch into the skin. If the drug's affinity for the formulation matrix is greater than its affinity for the stratum corneum, the drug's escaping tendency from the patch will be reduced, minimizing the gradient for drug transfer into the skin. The microviscosity of the formulation matrix, the presence of a membrane between the drug reservoir in the patch and the skin surface, and the interaction of the drug with the formulation matrix affect the rate and extent of diffusion and/or partitioning of the drug through the patch to the skin surface. Finally, the extent of drug delivery from the patch is directly proportional to the surface area of the patch in contact with the skin surface.

$$\frac{2000\ \mu g}{50\ \mu g/mL} = 40\ mL \text{ of fentanyl injection}$$

Bupivacaine hydrochloride 0.5% injection contains 500 mg/100 mL; therefore,

$$\frac{500}{100} = 125/x \qquad x = 25\ mL$$

If 40 mL of fentanyl injection is used, and 25 mL of bupivacaine hydrochloride injection is used, then 40 + 25 = 65 mL; the quantity of 0.9% sodium chloride injection required is 100 mL − 65 mL = 35 mL. Note: **If the order is to be filled in a 20-mL pump with delivery for 30 days, what is the delivery rate in microliter per hour?**

$$\frac{20\ mL}{30\ d} = 0.667\ mL/d$$

$$\frac{0.667\ mL}{day/24\ hrs} = 0.0277\ mL/hr$$

$$0.0277\ mL \times 1000\ \mu L/mL = 27.7\ \mu L/hr$$

c. Compounding procedure. Using commercially available injections, accurately measure the volume of each and fill into a sterile ambulatory pump reservoir. An air bubble can be injected and used to thoroughly mix the solution. Remove the air from the reservoir, and tightly seal/close the outlet. Label.

3. Example 3

a. Medication order

Morphine sulfate	5 g
Citric acid	100 mg
Sodium chloride, q.s. to isotonic	
Methylparaben	150 mg
Sterile water for injection, q.s.	100 mL

b. Calculations. Using a sodium chloride equivalent of 0.09 for a 5% morphine sulfate solution, 0.18 for citric acid, 1 for sodium chloride, and ignoring the methylparaben, the calculations can be made as follows:
5 g morphine sulfate is equivalent to 450 mg sodium chloride (5 g × 0.09 = 450 mg).
100 mg citric acid is equivalent to 18 mg sodium chloride (100 mg × 0.18 = 18 mg)

$$450\ mg + 18\ mg = 468\ mg$$

To be isotonic, the solution needs the equivalent of 900 mg of sodium chloride in the 100 mL: 900 mg − 468 mg = 432 mg sodium chloride needs to be added.

c. Compounding procedure. Dissolve the methylparaben in about 90 mL of sterile water for injection. A small amount of heat may be required. Cool the solution to room temperature, then add the morphine sulfate, citric acid, and sodium chloride. Add sufficient sterile water for injection to volume and mix well. Sterilize by filtration through a sterile 0.2-μm filter into a sterile vial or reservoir. Package and label.

4. Example 4

a. Medication order

Mefoxitin	1 g
Diluent to final concentration of 125 mg/mL	

b. Calculations. A 1-g vial of Mefoxin (cefoxitin for injection) is reconstituted with 10 mL of diluent to provide for approximate withdrawal of 10.5 mL and an approximate average concentration of 95 mg/mL. **What quantity of diluent should be added to provide an approximate average concentration of 125 mg/mL?**

$$10.5\ mL - 10\ mL = 0.5\ mL \text{ occupied by the powder}$$

$$\frac{1000\ mg}{125\ mg/mL} = 8\ mL \text{ total volume}$$

$$8\ mL - 0.5\ mL = 7.5\ mL \text{ diluent to be added}$$

c. Compounding procedure. Aseptically, withdraw 7.5 mL of diluent and inject into the vial to be reconstituted, using an appropriate vented needle. Gently swirl until dissolved.

Study Questions

Directions for questions 1–3: Each question or incomplete statement in this section can be correctly answered or completed by **one** of the suggested answers or phrases. Choose the **best** answer.

The following medication order is given to the pharmacist by the physician.

Olive oil	60 mL
Vitamin A	60,000 U
Water	120 mL
Sig:	15 mL t.i.d.

1. The final dosage form of this prescription will be

(A) a solution.
(B) an elixir.
(C) an emulsion.
(D) a suspension.
(E) a lotion.

2. When preparing this prescription, the pharmacist needs to add

(A) Tween 80.
(B) acacia.
(C) glycerin.
(D) alcohol.
(E) propylene glycol.

3. Which of the following caution labels should the pharmacist affix to the container when dispensing this preparation?

(A) Do not refrigerate.
(B) Shake well.
(C) For external use only.
(D) No preservatives added.

Directions for questions 4–9: Each question or statement in this section can be correctly answered or completed by one or more of the suggested answers or phrases. Choose the correct answer, A–E:

A if **I** only is correct
B if **III** only is correct
C if **I** and **II** are correct
D if **II** and **III** are correct
E if **I**, **II**, and **III** are correct

4. Which statements about the following prescription are correct?

Morphine	1 mg/mL
Flavored vehicle, q.s. a.d.	120 mL
Sig:	5 to 20 mg p.o. q 3 to 4 hrs p.r.n. pain

I. The amount of morphine needed is 240 mg.
II. Powdered morphine alkaloid should be used when compounding this prescription.
III. The final dosage form of this prescription is a solution.

5. When preparing the following prescription, the pharmacist should

Podophyllum	5%
Salicylic acid	10%
Acetone	20%
Flexible collodion, a.d.	30 mL
Sig:	Apply q h.s.

I. triturate 1.5 g of podophyllum with the 8 mL of acetone.
II. add 3 g of salicylic acid to the collodion with trituration.
III. affix an "external use only" label to the container.

6. Which statements about the following prescription are correct?

Sulfur	6 g
Purified water	
Camphor water, a.a. q.s. a.d.	60

I. Precipitated sulfur can be used to prepare this prescription.
II. The sulfur can be triturated with glycerin before mixing with other ingredients.
III. A "shake well" label should be affixed to the bottle.

7. Which statements about the following prescription are correct?

Starch	10%
Menthol	1%
Camphor	2%
Calamine, q.s. a.d.	120

I. The powders should be blended together in a mortar, using geometric dilution.
II. The prescription should be prepared by dissolving the camphor in a sufficient amount of 90% alcohol.
III. A eutectic mixture should be avoided.

8. When preparing the following prescription, the pharmacist should

Salicylic acid	3 g
Sulfur ppt	7 g
Lanolin	10 g
White petrolatum	10 g

I. reduce the particle size of the powders, using a mortar and pestle or using the pill tile with a spatula.

II. place on an ointment tile and levigate the ingredients, using geometric dilution.

III. package the ointment in an ointment jar or tube.

9. An equal volume of air is injected when removing drug solutions from

I. vials.

II. ampules.

III. syringes.

Answers and Explanations

1. The answer is C *[see V.B.1.]***.**

2. The answer is B *[see V.B.2; V.C.1]***.**

3. The answer is B *[see V.B.3]***.**
For 1–3: Because olive oil and water are two immiscible liquids, their incorporation requires a two-phase system in which one liquid is dispersed throughout another liquid in the form of small droplets. To accomplish this, an emulsifying agent is necessary. Acacia is the most suitable emulsifying agent when forming an oil-in-water emulsion that is intended for internal use. Emulsions are physically unstable, and they must be protected against the effects of microbial contamination and physical separation. Shaking before use redistributes the two layers of emulsion. Because light, air, and microorganisms also affect the stability of an emulsion, preservatives can be added.

4. The answer is B (III) *[see III.C.3]***.**
The concentration of morphine needed for the prescription described in the question is 1 mg/mL, and because 120 mL is the final volume, 120 mg of morphine is needed to compound this prescription. Morphine alkaloid has poor solubility; therefore, one of the salt forms should be used. Because morphine is dissolved in the vehicle, resulting in a liquid preparation, the final dosage form is a solution.

5. The answer is B (III) *[see III.C.1; III.C.5; III.D.3]***.**
Calculating for the amount of each ingredient of the prescription in the question requires 1.5 g of podophyllum, 3 g of salicylic acid, and 6 mL of acetone. The correct procedure would be to triturate the podophyllum with the acetone, then add the triturated salicylic acid to a calibrated bottle containing the podophyllum and acetone. Flexible collodion is then added up to the 30-mL calibration. An "external use only" label should be affixed to the container.

6. The answer is E (I, II, and III) *[see IV.B.2; IV.C.5; IV.D.1–2]***.**
Although precipitated sulfur can be used to prepare the prescription described in the question, it is difficult to triturate; therefore, it must first be levigated with a suitable levigating agent (e.g., glycerin). All suspensions, owing to their instability, require shaking before use to redistribute the insoluble ingredients.

7. The answer is A (I) *[see VI.C.3; VI.D.1]***.**
The proper procedure for compounding the prescription described in the question is to first form a liquid eutectic. This is done by triturating the menthol and camphor together in a mortar. This eutectic is then blended with the powdered starch and calamine, using geometric dilution.

8. The answer is E (I, II, and III) *[see IX.D.1–3; IX.E.1]***.**
The proper procedure for preparing the prescription given in the question is to reduce the particle size of each powder and mix them together, using geometric dilution. This ensures the proper blending of the powders. Next, this powdered mixture is incorporated, geometrically, with the petrolatum. Then, the lanolin is added geometrically.

9. The answer is A (I) *[see XI.E.2]***.**
An equal volume of air must be injected when removing a drug solution from a vial. This is done to prevent the formation of a vacuum within the vial. This problem does not occur with ampules and syringes containing drug solutions; therefore, it is unnecessary to inject any air when removing them.

Study Questions

Directions: Each question, statement, or incomplete statement in this section can be correctly answered or completed by **one** of the suggested answers or phrases. Choose the **best** answer.

1. Creatinine clearance is used as a measurement of

(A) renal excretion rate.
(B) glomerular filtration rate (GFR).
(C) active renal secretion.
(D) passive renal absorption.
(E) drug metabolism rate.

For questions 2–5: A new cephalosporin antibiotic was given at a dose of 5 mg/kg by a single intravenous bolus injection to a 58-year-old man who weighed 75 kg. The antibiotic follows the pharmacokinetics of a one-compartment model and has an elimination half-life of 2 hrs. The apparent volume of distribution is 0.28 L/kg, and the drug is 35% bound to plasma proteins.

2. What is the initial plasma drug concentration (C_p^0) in this patient?

(A) 0.24 mg/L
(B) 1.80 mg/L
(C) 17.9 mg/L
(D) 56.0 mg/L
(E) 1339 mg/L

3. What is the predicted plasma drug concentration (C_p) at 8 hr after the dose?
   (A) 0.73 mg/L
   (B) 1.11 mg/L
   (C) 2.64 mg/L
   (D) 4.02 mg/L
   (E) 15.10 mg/L

4. How much drug remains in the patient's body (D_B) 8 hrs after the dose?
   (A) 15.3 mg
   (B) 23.3 mg
   (C) 84.4 mg
   (D) 100.0 mg
   (E) 112.0 mg

5. How long after the dose is exactly 75% of the drug eliminated from the patient's body?
   (A) 2 hrs
   (B) 4 hrs
   (C) 6 hrs
   (D) 8 hrs
   (E) 10 hrs

For questions 6–11: A 35-year-old man who weighs 70 kg and has normal renal function needs an intravenous infusion of the antibiotic carbenicillin. The desired steady-state plasma drug concentration is 15 mg/dL. The physician wants the antibiotic to be infused into the patient for 10 hrs. Carbenicillin has an elimination half-life ($t_{½}$) of 1 hr and an apparent volume distribution (V_D) of 9 L in this patient.

6. Assuming that no loading dose was given, what rate of intravenous infusion is recommended for this patient?
   (A) 93.6 mg/hr
   (B) 135.0 mg/hr
   (C) 468.0 mg/hr
   (D) 936.0 mg/hr
   (E) 1350.0 mg/hr

7. Assuming that no loading intravenous dose was given, how long after the initiation of the intravenous infusion would the plasma drug concentration reach 95% of the theoretic steady-state drug concentration?
   (A) 1.0 hrs
   (B) 3.3 hrs
   (C) 4.3 hrs
   (D) 6.6 hrs
   (E) 10.0 hrs

8. What is the recommended loading dose?
   (A) 93.6 mg
   (B) 135.0 mg
   (C) 468.0 mg
   (D) 936.0 mg
   (E) 1350.0 mg

9. To infuse the antibiotic as a solution containing 10-g drug in 500 mL 5% dextrose, how many milliliters per hour of the solution would be infused into the patient?
   (A) 10.0 mL/hr
   (B) 46.8 mL/hr
   (C) 100.0 mL/hr
   (D) 936.0 mL/hr
   (E) 1141.0 mL/hr

10. What is the total body clearance rate for carbenicillin in this patient?
    (A) 100 mL/hr
    (B) 936 mL/hr
    (C) 4862 mL/hr
    (D) 6237 mL/hr
    (E) 9000 mL/hr

11. If the patient's renal clearance for carbenicillin is 86 mL/min, what is the hepatic clearance for carbenicillin?
    (A) 108 mL/hr
    (B) 1077 mL/hr
    (C) 3840 mL/hr
    (D) 5160 mL/hr
    (E) 6844 mL/hr

12. The earliest evidence that a drug is stored in tissue is
    (A) an increase in plasma protein binding.
    (B) a large apparent volume of distribution (V_D).
    (C) a decrease in the rate of formation of metabolites by the liver.
    (D) an increase in the number of side effects produced by the drug.
    (E) a decrease in the amount of free drug excreted in the urine.

13. The intensity of the pharmacologic action of a drug is most dependent on the
    (A) concentration of the drug at the receptor site.
    (B) elimination half-life ($t_{½}$) of the drug.
    (C) onset time of the drug after oral administration.
    (D) minimum toxic concentration (MTC) of the drug in plasma.
    (E) minimum effective concentration (MEC) of the drug in the body.

14. Drugs that show nonlinear pharmacokinetics have which property?
    (A) A constant ratio of drug metabolites is formed as the administered dose increases.
    (B) The elimination half-life ($t_{½}$) increases as the administered dose increases.
    (C) The area under the plasma drug concentration versus time curve (AUC) increases in direct proportion to an increase in the administered dose.
    (D) Both low and high doses follow first-order elimination kinetics.
    (E) The steady-state drug concentration increases in direct proportion to the dosing rate.

15. The loading dose (D_L) of a drug is usually based on the
- **(A)** total body clearance (Cl_T) of the drug.
- **(B)** percentage of drug bound to plasma proteins.
- **(C)** fraction of drug excreted unchanged in the urine.
- **(D)** apparent volume of distribution (V_D) and desired drug concentration in plasma.
- **(E)** area under the plasma drug concentration versus time curve (AUC).

16. The renal clearance of inulin is used as a measurement of
- **(A)** effective renal blood flow.
- **(B)** rate of renal drug excretion.
- **(C)** intrinsic enzyme activity.
- **(D)** active renal secretion.
- **(E)** GFR.

17. All of the following statements about plasma protein binding of a drug are true *except* which one?
- **(A)** Displacement of a drug from plasma protein binding sites results in a transient increased volume of distribution (V_D).
- **(B)** Displacement of a drug from plasma protein binding sites makes more free drug available for glomerular filtration.
- **(C)** Displacement of a potent drug that is normally $>$ 95% bound may cause toxicity.
- **(D)** Albumin is the major protein involved in protein binding of drugs.
- **(E)** Drugs that are highly bound to plasma proteins generally have a greater V_D compared with drugs that are highly bound to tissue proteins.

18. The onset time for a drug given orally is the time for the drug to
- **(A)** reach the peak plasma drug concentration.
- **(B)** reach the MEC.
- **(C)** reach the MTC.
- **(D)** begin to be eliminated from the body.
- **(E)** begin to be absorbed from the small intestine.

19. The initial distribution of a drug into tissue is determined chiefly by the
- **(A)** rate of blood flow to tissue.
- **(B)** GFR.
- **(C)** stomach emptying time.
- **(D)** affinity of the drug for tissue.
- **(E)** plasma protein binding of the drug.

20. Which tissue has the greatest capacity to biotransform drugs?
- **(A)** brain
- **(B)** kidney
- **(C)** liver
- **(D)** lung
- **(E)** skin

21. The principle of superposition in designing multiple-dose regimens assumes that
- **(A)** each dose affects the next subsequent dose, causing nonlinear elimination.
- **(B)** each dose of drug is eliminated by zero-order elimination.
- **(C)** steady-state plasma drug concentrations are reached at approximately 10 half-lives.
- **(D)** early doses of drug do not affect subsequent doses.
- **(E)** the fraction of drug absorbed is equal to the fraction of drug eliminated.

For questions 22–24: A new cardiac glycoside is developed for oral and intravenous administration. The drug has an elimination half-life ($t_{½}$) of 24 hrs and an apparent volume of distribution (V_D) of 3 L/kg. The effective drug concentration is 1.5 ng/mL. Toxic effects of the drug are observed at drug concentrations $>$ 4 ng/mL. The drug is bound to plasma proteins at approximately 25%. The drug is 75% bioavailable after an oral dose.

22. What is the oral maintenance dose, if given once a day, for a 68-year-old man who weighs 65 kg and has congestive heart failure (CHF) and normal renal function?
- **(A)** 0.125 mg
- **(B)** 0.180 mg
- **(C)** 0.203 mg
- **(D)** 0.270 mg
- **(E)** 0.333 mg

23. What is the loading dose (D_L) for this patient?
- **(A)** 0.270 mg
- **(B)** 0.293 mg
- **(C)** 0.450 mg
- **(D)** 0.498 mg
- **(E)** 0.540 mg

24. If the drug is available in tablets of 0.125 mg and 0.250 mg, what is the patient's plasma drug concentration if he has a dosage regimen of 0.125 mg every 12 hrs?
- **(A)** 1.39 ng/mL
- **(B)** 1.85 ng/mL
- **(C)** 2.78 ng/mL
- **(D)** 3.18 ng/mL
- **(E)** 6.94 ng/mL

25. If digoxin has a half-life of 35 hrs how long will it take for a toxic plasma concentration of 8 ng/mL to decline to a therapeutic plasma concentration of 2 ng/mL?
- **(A)** 17.5 hrs
- **(B)** 35 hrs
- **(C)** 70 hrs
- **(D)** 105 hrs
- **(E)** 140 hrs

Directions for question 26: The question in this section can be correctly answered by **one or more** of the suggested answers. Choose the correct answer, **A–E**.

A if **I only** is correct
B if **III only** is correct
C if **I** and **II** are correct
D if **II** and **III** are correct
E if **I**, **II**, and **III** are correct

26. Which equation is true for a zero-order reaction rate of a drug?

I. $\frac{dA}{dt} = -k$
II. $t_{½} = \frac{0.693}{k}$
III. $A = A_0 e^{-kt}$

Answers and Explanations

1. The answer is B *[see I.E.2.a]*.
A substance that is used to measure the GFR must be filtered but not reabsorbed or actively secreted. Although inulin clearance gives an accurate measurement of GFR, creatinine clearance is generally used because no exogenous drug must be given. However, creatinine formation depends on muscle mass and muscle metabolism, which may change with age and various disease conditions.

2. The answer is C *[see I.B.1.b.(2)]*.

3. The answer is B *[see I.A.3.b.(1); I.B.1]*.

4. The answer is B *[see I.B.1.a.(2)]*.

5. The answer is B *[see I.B.1.a.(2)]*.
Substituting the data for this patient in the equation for the initial plasma drug concentration (C_p^0) gives

$$C_p^0 = \frac{D_0}{V_D} = \frac{5 \text{ mg}}{0.28 \text{ L/kg}} = 17.9 \text{ mg/L}$$

To obtain the patient's plasma drug concentration (C_p) 8 hrs after the dose, the following calculation is performed:

$$C_p = C_p^0 \, e^{-kt}$$

$$k = \frac{0.693}{t_{½}} = \frac{0.963}{2} = 0.347 \text{ hr}^{-1}$$

$$C_p = 17.9e^{-(0.347)(8)}$$

$$C_p = (17.9)(0.0623) = 1.11 \text{ mg/L}$$

The amount of drug in the patient's body at 8 hrs is calculated as follows:

$$D_B = C_p V_D = (1.11)(0.28)(75) = 23.3 \text{ mg}$$

For any first-order elimination process, 50% of the initial amount of drug is eliminated at the end of the first half-life, and 50% of the remaining drug (i.e., 75% of the original amount) is eliminated at the end of the second half-life. Because the drug in the current case has an elimination half-life ($t_{½}$) of 2 hrs, 75% of the dose is eliminated in two half-lives or 4 hrs.

6. The answer is D *[see I.B.3.e.(3)]*.

7. The answer is C *[see I.B.3.c]*.

8. The answer is E *[see I.B.3.f.(2)]*.

9. The answer is B *[see I.B.3.e.(3)]*.

10. The answer is D *[see I.B.3.e.(3); I.E.1.a]*.

11. The answer is B *[see I.E.4.a]*.
The equation for the plasma concentration at steady state (C_{ss}) provides the formula for calculating the rate of an intravenous infusion (R). The equation is

$$C_{ss} = \frac{R}{kV_D}$$

where k is the first-order elimination rate constant and V_D is the apparent volume of distribution. Rearranging the equation and substituting the data for this patient give the following calculations:

$$R = C_{ss} k V_D = \frac{15 \text{ mg}}{100 \text{ mL}} \times \frac{0.693}{1 \text{ hr}} \times 9000 \text{ mL}$$

$$R = 936 \text{ mg/hr}$$

The time it takes for an infused drug to reach the C_{ss} depends on the elimination half-life of the drug. The time required to reach 95% of the C_{ss} is equal to 4.3 times the half-life, whereas the time required to reach 99% of the C_{ss} is equal to 6.6 times the half-life. Because the half-life in the current case is 1 hr, the time to reach 95% of the C_{ss} is 4.3 × 1 hr or 4.3 hrs.
The loading dose (D_L) is calculated as follows:

$$D_L = C_{ss} V_D = \frac{15 \text{ mg}}{100 \text{ mL}} \times 9000 \text{ mL} = 1350 \text{ mg}$$

The answer to question 6 shows that the infusion rate should be 936 mg/hr. Therefore, if a drug solution containing 10 g in 500 mL is used, the required infusion rate is

$$\frac{936 \text{ mg}}{1 \text{ hr}} \times \frac{500 \text{ mL}}{10000 \text{ mg}} = 46.8 \text{ mL/hrs}$$

The patient's total body clearance (Cl_T) is calculated as follows:

$$Cl_T = kV_D$$

$$Cl_T = \frac{0.693}{1} \times 9000 \text{ mL} = 6237 \text{ mL/hr}$$

The hepatic clearance (Cl_H) is the difference between total clearance (Cl_T) and renal clearance (Cl_R):

$$Cl_H = Cl_T - Cl_R$$

$$Cl_H = 6237 - (86 \text{ mL/min} \times 60 \text{ min/hr})$$

$$= 1077 \text{ mL/hr}$$

12. The answer is B *[see I.B.1.b.(1)]*.
A large apparent volume of distribution (V_D) is an early sign that a drug is not concentrated in the plasma but is distributed widely in tissue. An increase in plasma protein binding suggests that the drug is located in the plasma rather than in tissue. A decrease in hepatic metabolism, an increase in side effects, or a decrease in urinary excretion of free drug is caused by a decrease in drug elimination.

13. The answer is A *[see I.A.5.d.(3)]*.
As more drug is concentrated at the receptor site, more receptors interact with the drug to produce a pharmacologic effect. The intensity of the response increases until it reaches a maximum. When all of the available receptors are occupied by drug molecules, additional drug does not produce a more intense response.

14. The answer is B *[see I.D]*.
Nonlinear pharmacokinetics is a term used to indicate that first-order elimination of a drug does not occur at all drug concentrations. With some drugs, such as phenytoin, as the plasma drug concentration increases, the elimination pathway for metabolism of the drug becomes saturated and the half-life increases. The area under the plasma drug concentration versus time curve (AUC) of the drug is not proportional to the dose, neither is the rate of metabolite formation. The metabolic rate is related to the effects of the drug.

15. The answer is D *[see I.B.1.b.(2); I.B.5.g.(1)]*.
A loading dose (D_L) of a drug is given to obtain a therapeutic plasma drug level as rapidly as possible. The D_L is calculated based on the apparent volume of distribution (V_D) and the desired plasma level of the drug.

16. The answer is E *[see I.E.3.c]*.
Inulin is neither reabsorbed nor actively secreted. Therefore, it is excreted by glomerular filtration only. The inulin clearance rate is used as a standard measure of the GFR, a test that is useful both in a clinical situation and in the development of new drugs.

17. The answer is E *[see I.A.5.d]*.
Drugs that are highly bound to plasma proteins diffuse poorly into tissue and have a low apparent volume of distribution (V_D).

18. The answer is B *[see I.B.3.g]*.
The onset time is the time from the administration of the drug to the time when absorbed drug reaches the MEC. The MEC is the drug concentration in the plasma that is proportional, but not necessarily equal, to the minimum drug concentration at the receptor site that elicits a pharmacologic response.

19. The answer is A *[see I.A.5.a]*.
The initial distribution of a drug is chiefly determined by blood flow, whereas the affinity of the drug for tissue determines whether the drug concentrates at that site. The GFR affects the renal clearance of a drug, not its initial distribution. The gastric emptying time and degree of plasma protein binding affect drug distribution but are less important than the rate of blood flow to tissue.

20. The answer is C *[see I.E.4.b.(2)]*.
The kidney, lung, skin, and intestine all have some capacity to biotransform, or metabolize, drugs; but the brain has little capacity for drug metabolism. The liver has the highest capacity for drug metabolism.

21. The answer is D *[see I.B.5.c]*.
The superposition principle, which underlies the design of multiple-dose regimens, assumes that earlier drug doses do not affect subsequent doses. If the elimination rate constant or total body clearance of the drug changes during multiple dosing, then the superposition principle is no longer valid. Changes in the total body clearance (Cl_T) may be caused by enzyme induction, enzyme inhibition, or saturation of an elimination pathway. Any of these changes would cause nonlinear pharmacokinetics.

22. The answer is D *[see I.B.5.e.(3)]*.

23. The answer is E *[see I.B.5.g.(1)]*.

24. The answer is A *[see I.B.5.d.(2); I.B.5.e.(3)]*.
The oral maintenance dose (D_0) should maintain the patient's average drug concentration at the effective drug concentration. The bioavailability of the drug (F), the apparent volume of distribution (V_D), the dosage interval (τ), and the excretion rate constant (k) must be considered in calculating the dose. The equation used is

$$C_{Av}^{\infty} = FD_0 / kV_D\tau$$

For this drug, $F = 0.75$, $k = 0.693/24$ hrs, $V_D = 3$ L/kg $\times$ 65 kg, $\tau = 24$ hrs, and $C^{\infty}_{Av} = 1.5$ ng/mL, or 1.5 μg/L. Therefore, by substitution, $D_0 = 270$ μg, or 0.270 mg. When the maintenance dose is given at a dosage frequency equal to the half-life, then the loading dose is equal to twice the maintenance dose, in this case 540 μg, or 0.540 mg. To determine the plasma drug concentration for a dosage regimen of 0.125 mg every 12 hrs, the C^{∞}_{Av} formula is used. This time, $F = 0.75$, $D_0 = 0.125$ mg, $k = 0.693/24$ hrs, $V_D = 3$ L/kg $\times$ 65 kg, and $\tau = 12$ hrs. Therefore, $C^{\infty}_{Av} = 1.39$ ng/mL. For cardiac glycosides, the peak (C_{max}) and trough (C_{min}) concentrations are calculated, and plasma drug concentrations are monitored after dosing. The loading dose (D_L) may be given in small increments over a specified period, according to the dosage regimen suggested by the manufacturer.

25. The answer is C *[see I.A.3.b]*.
For first-order elimination, it takes two half-lives for plasma drug concentration of 8 ng/mL to decline to 2 ng/mL. The first half-life, the plasma drug concentration declines to 4 ng/mL, and the next half-life, the plasma drug concentration declines to 2 ng/mL.

26. The answer is A (I) *[see I.A.3.a]*.
The first equation in the question describes a zero-order reaction (dA/dt) in which the reaction rate increases or decreases at a constant rate (k). A zero-order reaction produces a graph of a straight line with the equation of $A = -kt + A_o$ when A is plotted against time (t). The other equations in the question represent first-order reactions.

Study Questions

Directions for questions 1–3: Each of the questions, statements, or incomplete statements in this section can be correctly answered or completed by one of the suggested answers or phrases. Choose the best answer.

1. The parameters used to describe bioavailability are

(A) C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$.
(B) C_{max}, AUC_{0-t}, $AUC_{0-\infty}$, and T_{max}.
(C) C_{max}, AUC_{0-t}, $AUC_{0-\infty}$, and $t_{½}$.
(D) C_{max} and AUC_{0-t}.
(E) C_{max}, AUC_{0-t}, $AUC_{0-\infty}$, T_{max}, and $t_{½}$.

2. To determine the absolute bioavailability of a drug given as an oral extended-release tablet, the bioavailability of the drug must be compared to the bioavailability of the drug from

(A) an immediate-release oral tablet containing the same amount of active ingredient.
(B) an oral solution of the drug in the same dose.
(C) a parenteral solution of the drug given by intravenous (IV) bolus or IV infusion.
(D) a reference (brand) extended-release tablet that is a pharmaceutical equivalent.
(E) an immediate-release hard gelatin capsule containing the same amount of active drug and lactose.

3. A single-dose, two-way crossover, fasting, comparative bioavailability study was performed in 24 healthy, adult male subjects. Plasma drug concentrations were obtained for each subject, and the results shown in *Table 6-Q3* were obtained. The relative bioavailability of the drug from the generic tablet compared to the reference tablet is

(A) 82.3%.
(B) 69.8%.
(C) 91.7%.
(D) 96.2%.
(E) 103.9%.

Table 6-Q3

Drug Product	Dose (mg)	C_{max} (μg/mL)	T_{max} (hr)	$AUC_{0-\infty}$ (μghr/mL)
IV bolus injection	100			1714
Oral solution	200	21.3	1.2	3143
Generic tablet	200	17.0	2.1	2822
Reference tablet	200	16.5	1.9	2715

IV, intravenous.

Directions for questions 4–6: The questions and incomplete statements in this section can be correctly answered or completed by **one or more** of the suggested answers. Choose the answer, A–E.

A if **I only** is correct
B if **III only** is correct
C if **I and II** are correct
D if **II and III** are correct
E if **I**, **II**, **and III** are correct

4. For two drug products, generic (test) and brand (reference), to be considered bioequivalent,

I. there should be no statistical difference between the extent of bioavailability of the drug from the test product compared to the reference product.
II. the 90% confidence interval about the ratio of the means of the C_{max} and AUC values for the test product to reference product must be within 80% to 125% of the reference product.
III. there should be no statistical differences between the mean C_{max} and AUC values for the test product compared to the reference product.

5. For which of the following products is measuring plasma drug concentrations not appropriate for estimating bioequivalence?

I. metered-dose inhaler containing a bronchodilator
II. antifungal agent for the treatment of a vaginal infection
III. enteric-coated tablet containing a nonsteroidal anti-inflammatory agent

6. Bioequivalence studies compare the bioavailability

I. of the generic drug product to the brand drug product.
II. of a reformulated brand drug product to the original formulation of the brand product.
III. of a to-be-marketed brand product to the drug product used in the clinical trials.

Answers and Explanations

1. The answer is B *[see III.B]***.**
AUC relates to the extent of drug absorption. C_{max} and T_{max} relate to the rate of drug absorption. The elimination $t_{½}$ of the drug is usually independent of the route of drug administration and is not used as a measure of bioavailability. For the FDA, only the C_{max} and AUC parameters must meet 90% confidence intervals of 80% to 125% of the reference (brand) product (*Table 6-1*).

2. The answer is C *[see IV.B]***.**
After an IV bolus injection or IV infusion, the entire dose is absorbed into the body. The ratio of the AUC of the drug given orally to the AUC of the drug given by IV injection is used to obtain the absolute bioavailability (F) of the drug.

3. The answer is E *[see IV.A]***.**
The relative bioavailability is determined from the ratio of the AUC of the generic (test) product to the AUC of the reference standard. Thus, the relative bioavailability can exceed 100%, whereas the absolute bioavailability cannot exceed 100%. $AUC_{generic}/AUC_{reference} = 2822/2715 = 1.039$ or 103.9%.

4. The answer is E (I, II, III) *[see V.C]***.**
Although T_{max} is an indication of rate of drug absorption, it is a discrete measurement and usually too variable to use for statistical comparisons in bioequivalence studies. Statistical comparisons use AUC and C_{max} values from test and reference drug products as the basis of bioequivalence.

5. The answer is C (I, II) *[see V.A]***.**
Although some systemic absorption may be demonstrated after administering a metered dose inhaler containing a bronchodilator or a vaginal antifungal agent, bioequivalence can be determined only by using a clinical response measurement.

6. The answer is E (I, II, III) *[see I.A–E]***.**
Bioequivalence studies compare the bioavailability of a drug from one drug product to another drug product containing the same active ingredient. Drug products such as capsules that are used in clinical trials should be bioequivalent to the marketed drug product, which may be a tablet. Generic drug products and the corresponding brand drug product must be bioequivalent. For any change in a formulation, the manufacturer (brand or generic) must demonstrate that the formulation change does not affect the bioavailability compared to the original product.

Study Questions

Directions: Choose the **best** answer to each of the following questions.

1. Most biologic drugs are sensitive to all of the following **except**
   (A) heat.
   (B) shaking.
   (C) stainless steel.
   (D) light.

2. Recombinant protein drugs are designed to replicate which of the following types of molecules?
   (A) Antibodies
   (B) Enzymes
   (C) Proteins in the plasma
   (D) All of the above
   (E) None of the above

3. Nucleic acid drugs or drug candidates include which of the following?
   (A) Gene therapy
   (B) Oligonucleotides
   (C) A and B
   (D) None of the above

4. Glycoprotein is a protein linked to _____.
   (A) a carbohydrate
   (B) a nucleotide
   (C) an amino acid
   (D) a lipid molecule
   (E) None of the above

5. Examples of monoclonal antibody drugs include all of the following **except**
   (A) infliximab.
   (B) Herceptin.
   (C) trypsin.
   (D) rituximab.

6. An example of a recombinant cytokine is _____.
   (A) muromonab
   (B) albumin
   (C) oligonucleotide
   (D) interferon
   (E) growth hormone

7. A recombinant protein will have the same in vivo properties if the genetic sequence is the same. This statement is _____.
   (A) always true
   (B) not necessarily true
   (C) always false

8. Monoclonal antibodies are most often used for what type of clinical indications?
   (A) Cancer
   (B) Correcting congenital deficiencies
   (C) Replacement therapy
   (D) Psychiatric disorders
   (E) None of the above

9. Gene therapy _____.
   (A) is a technology that is widely used in patient care
   (B) involves short nucleic acid sequences to inhibit gene expression
   (C) has not been tested in clinical trials
   (D) All of the above
   (E) None of the above

10. Which of the following statements is true for polyethylene glycol (PEG)?
    (A) It is a carbohydrate used to increase clearance of drugs.
    (B) It is conjugated only to recombinant hormones.
    (C) It blocks the renal filtration of drugs.
    (D) It is naturally occurring on many biologic molecules.

Answers and Explanations

1. **The answer is C** *[see I.E.]***.**
   Biologic drugs are sensitive to high (and very low) temperatures, agitation, and light.

2. **The answer is D** *[see IV; VI; VII.A.]***.**
   Protein drugs are used for protein replacement or for providing pharmacologic activity when used in therapeutic doses. Besides enzymes, plasma proteins, mAbs, and cytokines, hormones are also classes of proteins that have been made into recombinant drugs.

3. **The answer is C** *[see VIII]***.**
   Many macromolecular nucleic acid drugs are in clinical trials and preclinical development, such as miRNA, ribozymes, siRNA, and gene therapy, but only oligonucleotides have become approved drugs at this time. Nucleoside

drugs are small nucleic acid drug molecules and many are in use, especially for antiviral therapy.

4. **The answer is A** *[see II.K]***.**
Glycoproteins are made of a carbohydrate linked to a protein.

5. **The answer is C** *[see IV.B; Table 7-1]***.**
Trypsin is an enzyme that digests proteins. The other drugs listed are examples of mAbs.

6. **The answer is D** *[see V]***.**
Muromonab is an mAb, albumin is a plasma protein, oligonucleotides are nucleic acid drugs, and growth hormone is a hormone. Only interferon is considered a cytokine of this list.

7. **The answer is B** *[see I.B; VII.B.1; Table 7-2]***.**
Because product quality and even structure are dependent on the manufacturing process (including cell line, equipment, chemicals and their impurities, material handling, etc.), each biologic product is unique even if the original gene sequence used is identical. Therefore, generic versions of biologics are not available; rather, similar products that follow the innovator are called **biosimilars**.

8. **The answer is A** *[see IV.B; Table 7-1]***.**
mAbs bind to unique epitopes on specific antigens, which either act as an antagonist to the antigen or employ the immune system to elicit an immune response against the target. Congenital defects in the immune system would result in an overall lack of antibody defense instead of lacking a single antibody type.

9. **The answer is E** *[see VIII.C]***.**
Gene therapies are in clinical trials but have not yet been FDA approved. Gene therapy involves delivery of a gene (usually thousands of double-stranded nucleotides in size) compared to an oligonucleotide (15–30 single-stranded nucleotides).

10. **The answer is C** *[see Table 7-1; II.S; V.B.2; VII.A; VII.B.2; VIII.B.2]***.**
Polyethylene glycol (PEG) is a synthetic polymer that is conjugated to protein and nucleic acid drugs to increase the half-life and decrease the renal clearance of a drug by glomerular filtration. Many different protein drugs have employed this method to improve the pharmacokinetic properties of the compound, including filgrastim, adenosine deamidase, and anti-TNF antibody.

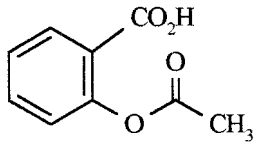
Study Questions

Directions: Each of the numbered items or incomplete statements in this section is followed by answers or by completions of the statement. Select the one lettered answer or completion that is **best** in each case.

1. Which of the following statements concerning drug metabolism is true?

(A) Generally, a single metabolite is excreted for each drug administered.
(B) Often, a drug may undergo a phase II reaction followed by a phase I reaction.
(C) Drug-metabolizing enzymes are found only in the liver.
(D) All metabolites are less active pharmacologically than their parent drugs.
(E) Phase I metabolites more likely are able to cross cellular membranes than phase II metabolites.

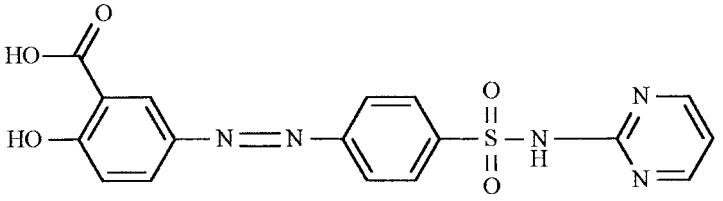
2. Which of the following metabolites would be the least likely excretion product of orally administered aspirin (see structure below)?



(A) Glycine conjugate
(B) Ester glucuronide
(C) Unchanged drug
(D) Ether glucuronide
(E) Hydroxylated metabolite

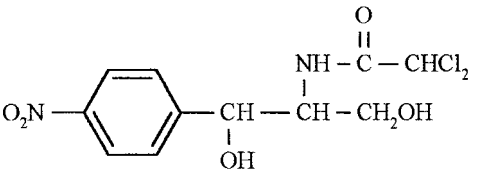
3. Sulfasalazine (see structure below) is a prodrug that is activated in the intestine by bacterial enzymes. The enzyme most likely responsible is

(A) azoreductase.
(B) pseudocholinesterase.
(C) *N*-acetyltransferase.
(D) β-glucuronidase.
(E) methyltransferase.



4. Chloramphenicol (see structure below) is considered to be toxic in infants (gray baby syndrome). This is due to tissue accumulation of unchanged chloramphenicol, resulting from an immature metabolic pathway. Which of the following enzymes would most likely be deficient?

(A) Pseudocholinesterase
(B) Glucuronyltransferase
(C) *N*-Acetyltransferase
(D) Azoreductase
(E) Methyltransferase



5. Which of the following therapeutic advantages cannot be obtained by the use of prodrugs?

(A) oral absorption
(B) water solubility
(C) duration of action
(D) potency
(E) palatability

6. Which of the following routes of administration would be subject to first-pass metabolism in the liver?
   (A) IV (intravenous)
   (B) Inhalation
   (C) Sublingual
   (D) IM (intramuscular)
   (E) Oral

7. A compound that slows the metabolism of a xenobiotic is called a(n)
   (A) inducer.
   (B) epimer.
   (C) reductase.
   (D) inhibitor.
   (E) object.

8. Which family of drug-metabolizing enzymes is characterized as a microsomal enzyme that contains a porphyrin prosthetic group?
   (A) Glucuronosyltransferases
   (B) Cytochrome P450s
   (C) Flavin-containing monooxygenases
   (D) Esterases
   (E) *N*-Acetyltransferases

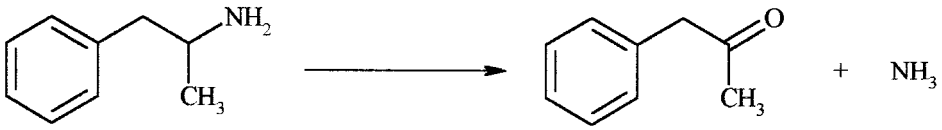
9. The most common type of genetic variation is a(n)
   (A) copy number variation.
   (B) insertion.
   (C) deletion.
   (D) frameshift.
   (E) single nucleotide polymorphism.

10. Which polymorphic enzyme is responsible for the conversion of codeine to morphine?
    (A) TPMT
    (B) *N*-Acetyltransferase
    (C) CYP2D6
    (D) CYP2C9
    (E) CCR5 coreceptor

Directions: Each question in this section contains three suggested answers, of which **one or more** is correct. Choose the answer.

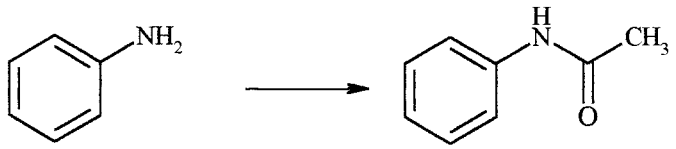
A if **I only** is correct
B if **III only** is correct
C if **I and II** are correct
D if **II and III** are correct
E if **I**, **II**, **and III** are correct

11. Terms that may be used to describe the following metabolic reaction include
    I. *N*-oxidation.
    II. oxidative deamination.
    III. phase I metabolism.

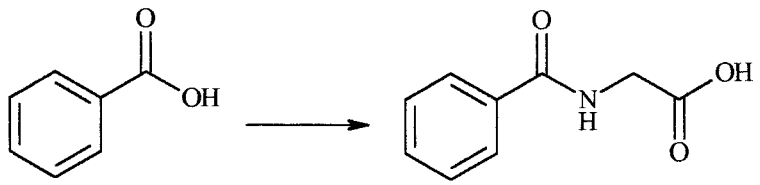


12. Which of the following reactions can be classified as phase II metabolism?

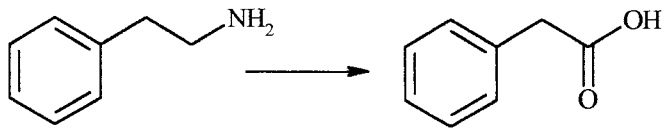
I.



II.



III.



13. Conditions that tend to increase the action of an orally administered drug that undergoes phase II metabolism include

- **I.** enterohepatic circulation.
- **II.** enzyme saturation.
- **III.** first-pass effect.

14. Which of the following statements concerning CYP450 are correct?

- **I.** The CYP7, CYP11, and CYP27 subfamilies are involved in steroid and bile acid synthesis and metabolism.
- **II.** A single drug may be metabolized by multiple isoforms of CYP450.
- **III.** The majority of xenobiotics, or drugs, are metabolized by the CYP4B and CYP1A subfamilies.

15. Which of the following are genetic contributors to variation in the therapeutic dose of warfarin among patients?

- **I.** CYP2C9
- **II.** VKORC1
- **III.** CYP2D6

16. Examples of phase II enzymes include

- **I.** CYP450.
- **II.** *N*-acetyltransferase.
- **III.** sulfotransferase.

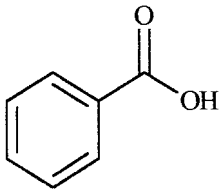
Directions: The group of items in this section consists of lettered options followed by a set of numbered items. For each item, select the **one** lettered option that is most closely associated with it. Each lettered option may be selected once, more than once, or not at all.

Questions 17–20

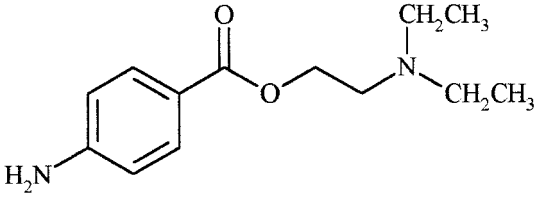
For each drug, select its most likely metabolic pathway.

(A) Ether glucuronidation
(B) Ester glucuronidation
(C) Nitroreduction
(D) Oxidative deamination
(E) Ester hydrolysis

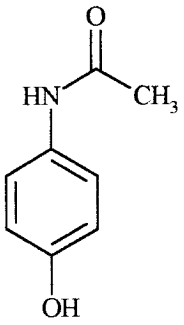
17. Benzoic acid



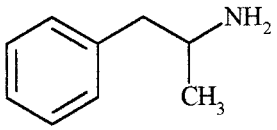
18. Procaine



19. Acetaminophen



20. Amphetamine



Answers and Explanations

1. The answer is E *[see III.A; III.B]*.
Phase I metabolites are often somewhat more polar than their parents. With the exception of acetylated and methylated metabolites, phase II metabolites are much more polar than their parents. Thus, phase I metabolites are more likely to retain some lipid solubility and are more likely to cross cellular membranes.

It is unusual for a single metabolite to be excreted for a given drug. Most drugs yield a mixture of metabolites. Because of the high polarity and subsequent high excretion of phase II metabolites, they are not likely to undergo further metabolism. Phase I metabolites, on the other hand, are less polar and are very likely to undergo further phase II metabolic reactions.

Whereas the major site of metabolism is the liver, there are many extrahepatic sites that secrete drug-metabolizing enzymes. Although many metabolites are less pharmacologically active than their parents, there are many drugs whose metabolites have equal or greater pharmacological activity and sometimes greater toxicity as well. Prodrugs (i.e., drugs inactive in the form administered) always form at least one active metabolite.

2. The answer is C *[see III.B.1; III.B.3; Table 8-1]*.
Because of the types of functional groups present, aspirin may undergo a number of different metabolic reactions. These include hydroxylation of the aromatic nucleus, conjugation of the carboxyl group with glycine,

conjugation of the carboxyl group with glucuronic acid with the formation of an ester glucuronide, hydrolysis of the acetate ester, and conjugation of the phenol group (resulting from hydrolysis of the acetate ester) with glucuronic acid to form an ether glucuronide.

Because the acetate ester is a simple ester, aspirin is susceptible to hydrolysis in the acid media of the stomach before absorption takes place. In addition, any acetylated molecules that are absorbed are subjected to hydrolysis and are catalyzed by the many esterases present in the circulation. Any acetylated molecules not hydrolyzed in the circulation are subject to hydrolysis in the liver. All of these processes occur before the drug reaches the glomerular filtrate; therefore, excretion of the unchanged acetylated drug is highly unlikely.

3. **The answer is A** *[see III.A.8.c; Table 8-2]***.**
Sulfasalazine has both anti-inflammatory and antibacterial activity when converted to aminosalicylic acid and sulfapyridine in the body. This reaction occurs by reductive cleavage of the "azo" linkage contained in the sulfasalazine molecule and is catalyzed in the intestine by bacterial azoreductase. This is a form of site-specific delivery because the intact drug is not absorbed from the stomach or upper intestine and reaches the colon, where it is metabolized. Sulfasalazine is one of a few drugs that are effective for the treatment of ulcerative colitis.

4. **The answer is B** *[see IV.D.1; Table 8-4]***.**
The chloramphenicol molecule contains an aromatic nucleus, which would be subject to hydroxylation; a nitro group that is subject to reduction; an amide group that is subject to liver hydrolysis; and alcohol groups that are subject to glucuronidation. Of all the enzyme systems responsible for these reactions, the system responsible for glucuronidation is developed poorly in premature infants and infants up to approximately 6 to 8 weeks of age.

5. **The answer is D** *[see V]***.**
By definition, prodrugs are inactive or very weakly active molecules that require in vivo activation to the parent molecule. Thus, conversion of a drug molecule to a prodrug does not increase potency because the original molecule, with whatever potency it contains, is produced after administration. A variety of advantages, including increased water solubility, duration of action, oral absorption, and palatability, can be obtained through the use of prodrugs, but none of these advantages results in an increase in potency of the parent molecule.

6. **The answer is E** *[see IV.I.1–2]***.**
First-pass metabolism in the liver refers to biotransformation of a xenobiotic after absorption from the GI tract before it reaches the systemic circulation. Orally administered drugs that are absorbed from the GI tract enter the portal circulation and pass through the liver where they are metabolized. Routes of administration that bypass the first-pass metabolism in the liver include IV, IM, sublingual, buccal, rectal, and inhalation. These routes of administration allow for absorption either outside of the GI tract or in regions of the GI tract that are not part of portal circulation.

7. **The answer is D** *[see IV.H.2]***.**
An inhibitor, also called the precipitant drug, is a substance that blocks the metabolism of another drug called the *object drug*. An inducer is a compound that increases the expression of drug-metabolizing enzymes. Both inhibitors and inducers alter drug metabolism that may cause toxicity or lack of efficacy depending on the metabolic consequence of the object drug.

8. **The answer is B** *[see II.A.2.a]***.**
The family of cytochrome P450 enzymes are microsomal proteins that contain a porphyrin prosthetic group. Glucuronosyltransferases and flavin-containing monooxygenases are both microsomal enzymes, but they do not contain the porphyrin group.

9. **The answer is E** *[see VII.C.1–3]***.**
The most common genetic variation is a single nucleotide polymorphism (SNP), which may be an insertion or deletion that causes a frameshift. These polymorphisms can be called a synonymous SNP if the amino acid expressed is not changed or a nonsynonymous SNP if the amino acid expressed is different. These polymorphisms may also influence the promoter region or the splicing sites for proteins that would not result differences in the amino acids expressed. Multiple copies of a gene, as reported with CYP2D6, are called copy number variations.

10. **The answer is C** *[see VII.D.2.a–c, e, & g]***.**
CYP2D6 is a highly polymorphic drug-metabolizing enzyme that is responsible for the conversion of codeine to morphine. TPMT, *N*-acetyltransferase, and CYP2C9 are polymorphic drug-metabolizing enzymes but are not responsible for the conversion codeine to morphine. The CCR5 coreceptor is not a drug-metabolizing enzyme but is involved in the cellular penetration of HIV.

11. The answer is D (II, III) *[see III.A; Table 8-1]***.**
The reaction shown in the question involves the conversion of one functional group to another (amine to carbonyl); thus, it is classified as a phase I reaction. The introduction of oxygen into the molecule indicates oxidation, and the loss of the amino group signifies deamination; thus, the reaction also can be classified as oxidative deamination. *N*-Oxidation reactions by CYP450 or FMO are observed but result in the addition of an oxygen to the nitrogen. In this case, no oxygen has been added to the nitrogen; therefore, this is not an *N*-oxidation reaction.

12. The answer is C (I, II) *[see III.A–B; Table 8-4]***.**
Phase II metabolic reactions involve masking an existing functional group with a natural endogenous constituent. The formulas shown in choices I and II represent this type of reaction, with choice I being an acetylation reaction and choice II a glycine conjugation reaction. Choice III represents a change in an existing functional group and, thus, represents a phase I reaction. It is an oxidative deamination reaction.

13. The answer is C (I, II) *[see III.C.2.b; IV.I.1; IV.J]***.**
Enterohepatic circulation refers to the process by which glucuronides, which are secreted into the intestine with the bile, are hydrolyzed by intestinal bacterial β-glucuronidase. The hydrolyzed free drug, which is no longer polar, becomes available for intestinal reabsorption into the system and subsequent penetration to its active site.

If an enzyme system becomes saturated, then the active drug cannot be inactivated by that pathway. If the drug cannot undergo an alternative pathway, the increased plasma levels of an unchanged active drug can result in increased activity or toxicity.

The first-pass effect results in metabolism of a drug by the liver before the drug reaches its site of action, resulting in an overall decrease in its activity. Drugs that undergo first-pass metabolism generally are effective in much smaller intravenous doses as compared to oral doses.

14. The answer is C (I, II) *[see I; III.A.2.b]***.**
There are six mammalian families involved in steroid and bile acid metabolism. These are CYP7, CYP11, CYP17, CYP19, CYP21, and CYP27. Because cholesterol is the common intermediate for the biosynthesis of all endogenous steroids, some of these enzymes are directly involved in cholesterol metabolism. The families listed, CYP7, CYP11, and CYP27, all metabolize cholesterol, whereas the other three families catalyze additional oxidations of the initial metabolites.

There are multiple enzymes and paths that are possible for a single xenobiotic, so it is common that multiple metabolites with varying properties are possible and observed. The cytochrome P450 subfamilies responsible for the majority of the biotransformations are CYP2C, CYP2D, and CYP3A.

15. The answer is C (I, II) *[see VII.D.2.a]***.**
Some of the individual variability in dosing is related to the metabolism of warfarin by CYP2C9 and by the level of expression of the warfarin target, VKORC1. With CYP2C9, the variability is related to differences in the metabolic efficiency of the different alleles, whereas differences in the promoter region of VKORC1 result in different levels of expression of the enzyme inhibited by warfarin. CYP2D6, although highly polymorphic, does not contribute to the variability of warfarin dosing.

16. The answer is D (II, III) *[see III.A.2; III.B.2 & 5]***.**
Phase II drug-metabolizing enzymes are commonly called transferase enzymes because they transfer a biomolecule from an activated cofactor to a target functional group. Phase II enzymes include glucuronosyltransferase, sulfotransferase, *N*-acyltransferase, glutathione-S-transferase, *N*-acetyltransferase, and methyltransferase. CYP450 is the most common phase I enzyme.

17–20. The answers are 17-B *[see III.B.1]***, 18-E** *[see III.A.9.a]***, 19-A** *[see III.B.1]***, 20-D** *[see Table 8-1]***.**
Benzoic acid contains a carboxylic acid, a functional group that commonly undergoes conjugation with glucuronic acid. The resulting conjugation produces an ester. Carboxylic acids can also undergo conjugation with the amino acids glycine and glutamine. Additionally, benzoic acid can undergo aromatic hydroxylation, a common phase I pathway for drugs containing unsubstituted aromatic rings. Of these options, ester glucuronidation is the only answer available here.

Procaine is an ester-containing local anesthetic. Due to the wide physiological distribution of esterase enzymes, it is extremely susceptible to in vivo hydrolysis. This susceptibility to hydrolysis is the major reason why ester-containing local anesthetics have shorter durations of action as compared to those in other chemical classes.

One of the principal functional groups in acetaminophen is the phenol group. Similar to the carboxylic acid in benzoic acid, the phenol commonly undergoes glucuronide conjugation. The one difference is that a phenol (or an alcohol) produces an **ether** glucuronide, whereas a carboxylic acid produces an **ester** glucuronide. Phenols also commonly undergo sulfate conjugation reactions and occasionally undergo O-methylation reactions.

The principal functional group in amphetamine is its primary amine. Oxidative deamination is a very common metabolic path for primary amines. Occasionally, primary amines undergo phase II acetylation; however, this is a less common pathway. Aromatic hydroxylation, similar to that discussed previously for benzoic acid, is also possible for amphetamine.

Study Questions

Directions for questions 1–14: Each of the questions, statements, or incomplete statements in this section can be correctly answered or completed by **one** of the suggested answers or phrases. Choose the **best** answer.

1. Which of the following drugs would most likely be used in the treatment of bronchospasm that is associated with chronic obstructive pulmonary disease?

(A) edrophonium (Tensilon)
(B) ipratropium (Atrovent)
(C) rocuronium (Zemuron)
(D) propantheline (Pro-Banthine)
(E) homatropine

2. All of the following adverse effects are manifestations of cholinergic agonists *except*

(A) bradycardia.
(B) bronchoconstriction.
(C) xerostomia.
(D) lacrimation.
(E) myopic accommodation.

3. Which of the following drugs is considered to be the agent of choice for anaphylactic reactions?

(A) clonidine (Catapres)
(B) isoproterenol (Inderal)
(C) epinephrine
(D) phenylephrine
(E) terbutaline (Brethine)

4. Which of the following neuromuscular blocking agents can cause muscarinic responses such as bradycardia and increased glandular secretions?

(A) tubocurarine
(B) succinylcholine (Anectine)
(C) pancuronium
(D) decamethonium
(E) gallamine

5. Which of the following agents would *not* be appropriate in the treatment of glaucoma?

(A) atropine
(B) pilocarpine
(C) physostigmine
(D) timolol (Timoptic)
(E) epinephrine

6. Adverse reactions to atropine include all of the following *except*

(A) photophobia.
(B) dry mouth.
(C) sedation.
(D) diarrhea.
(E) tachycardia.

7. Which of the following drugs is a volatile substance that is administered by inhalation?

(A) thiopental (Pentothal)
(B) halothane
(C) alprazolam (Xanax)
(D) buspirone (Buspar)
(E) phenytoin (Dilantin)

8. Which of the following agents is used to treat anxiety?

(A) chlordiazepoxide (Librium)
(B) thioridazine
(C) alprazolam (Xanax)
(D) buspirone (Buspar)
(E) pentobarbital

9. Which of the following best describes the mechanism of diazepam to cause a sedative effect?

(A) The drug blocks glutamate receptor to decrease neuronal excitability.
(B) The drug blocks the uptake of GABA into the nerve to increase its action at the receptor.
(C) It increases the ability of GABA to produce chloride conductance into neurons.
(D) It prevents the metabolism of catecholamines by blocking monoamine oxidases.
(E) It blocks inositol phosphate metabolism in neurons.

10. Which of the following mechanisms of action is true and most likely contributes to the treatment of parkinsonism?

(A) The direct-acting dopaminergic agonist bromocriptine (Parlodel) mimics the activity of striatal dopamine.
(B) The antimuscarinic activity of entacapone (Comtan) contributes to the restoration of striatal dopaminergic–cholinergic neurotransmitter balance.
(C) Striatal H_1-receptors are blocked by levodopa.
(D) The ergoline bromocriptine stimulates the release of striatal dopamine from intact terminals.
(E) The ability of dopamine to cross the blood–brain barrier allows it to restore striatal dopaminergic–cholinergic neurotransmitter balance.

11. All of the following adverse effects are associated with the use of levodopa *except*

(A) increased intraocular pressure.
(B) orthostatic hypotension.
(C) delusions and confusion.
(D) dyskinesia.
(E) agranulocytosis.

12. The activity of which of the following drugs depends on a *p*-phenyl-*N*-alkylpiperidine moiety?

(A) phenobarbital
(B) chlorpromazine
(C) diazepam (Valium)
(D) imipramine (Tofranil)
(E) meperidine (Demerol)

13. Opioids are used for all the following conditions *except*

(A) cough.
(B) severe chronic pain.
(C) arthritis.
(D) severe diarrhea.
(E) preanesthetic.

14. Which of the following agents would *not* be an alternative to phenytoin in the treatment of tonic-clonic seizure?

(A) levetiracetam (Keppra)
(B) gabapentin (Neurontin)
(C) ethosuximide (Zarontin)
(D) lamotrigine (Lamictal)
(E) carbamazepine (Tegretol)

Directions for questions 15–19: The questions and incomplete statements in this section can be correctly answered or completed by **one or more** of the suggested answers. Choose the answer, **A–E**.

A if **I only** is correct
B if **III only** is correct
C if **I and II** are correct
D if **II and III** are correct
E if **I, II, and III** are correct

15. Cholinesterase inhibitors can be used therapeutically

I. as miotic agents in the treatment of glaucoma.
II. to increase skeletal muscle tone in the treatment of myasthenia gravis.
III. to decrease gastrointestinal (GI) and urinary bladder smooth muscle tone.

16. Antimuscarinic agents are used in the treatment of Parkinson disease and in the control of some neuroleptic-induced extrapyramidal disorders. These agents include

I. ipratropium (Atrovent).
II. benztropine.
III. trihexyphenidyl.

17. Certain drugs are sometimes incorporated into local anesthetic solutions to prolong their activity and reduce their systemic toxicity. These drugs include

I. dobutamine.
II. phenoxybenzamine.
III. epinephrine.

18. Improper administration of local anesthetics can cause toxic plasma concentrations that may result in

I. seizures and central nervous system (CNS) depression.
II. respiratory and myocardial depression.
III. circulatory collapse.

19. In addition to their anxiolytic properties, benzodiazepines are indicated for use

I. as preanesthetic medications.
II. as anticonvulsants.
III. during acute withdrawal from alcohol.

For questions 20–23: A 58-year-old white male who has a history of essential hypertension and bronchial asthma has recently been diagnosed with prostatic hypertrophy. His medication history includes the following drugs:

(A) propranolol (Inderal), for hypertension
(B) ipratropium (Atrovent), for asthma
(C) metaproterenol, for asthma
(D) finasteride (Proscar), for prostatic hypertrophy
(E) prazosin (Minipress), for hypertension

Directions: The following questions can be answered by **one** of the listed drugs. Choose the **best** answer, **A–E**.

20. Tamsulosin (Flomax) may replace this agent on the list.

21. Which agent would be most likely to cause postural hypotension?

22. Which agent acts selectively at β_2-receptors?

23. Which of the agents on the list would be counterproductive or inappropriate in a patient taking metaproterenol?

For questions 24–27: A 55-year-old black female has a history of moderate hypertension, glaucoma, and mild osteoarthritis. Her medication history includes the following drugs:

(A) metoprolol (Lopressor), for hypertension
(B) pilocarpine gel, for glaucoma
(C) dipivefrin (Propine) drops, for glaucoma
(D) echothiophate, for glaucoma
(E) timolol (Timoptic), for glaucoma

Directions: The following questions can be answered by **one or more** of the listed drugs. Choose the **best** answers, **A–E**.

24. Which of her glaucoma medicines acts via an indirect mechanism?

25. Which two agents could have an additive effect to produce excessive bradycardia?

26. Which two glaucoma agents could lessen the effects of the other?

27. Which of the aforementioned agents is a prodrug that is metabolized to its active form?

Directions for questions 28–31: Each statement in this section describes **one** of the following drugs. Choose the **best** answer, **A–E**.

(A) tranylcypromine (Parnate)
(B) imipramine (Tofranil)
(C) buspirone (Buspar)
(D) fluoxetine (Prozac)
(E) phenelzine (Nardil)

28. An anxiolytic drug that does not possess either hypnotic or anticonvulsant properties.

29. A prototype tricyclic antidepressant with significant antimuscarinic properties.

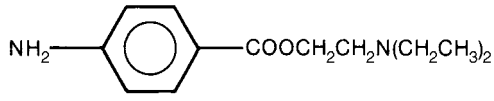
30. An antidepressant that inhibits serotonin reuptake and may cause adverse effects such as insomnia, sexual dysfunction, and GI distress.

31. Tyramine-containing foods may cause dangerous hypertension in patients on this agent.

Directions for questions 32–34: Each structure in this section can be described by **one** of the following pharmacological categories. Choose the **best** answer.

(A) general anesthetic
(B) local anesthetic
(C) antidepressant
(D) anxiolytic
(E) opioid antagonist

32.



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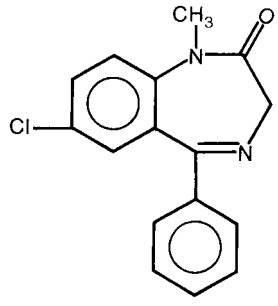

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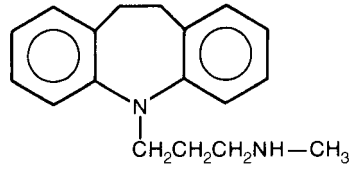


For questions 35–37: A 38-year-old man has a history of affective disorders, including schizophrenia, depression, obsessive–compulsive disorder, and situational anxiety. His past medications include thiothixene, chlorpromazine, amitriptyline, and diazepam. His current medication profile includes the following drugs:

(A) clozapine (Clozaril)
(B) fluoxetine (Prozac)
(C) buspirone (Buspar)
(D) amoxapine

Directions: The following questions can be answered by **one** of the listed drugs. Choose the **best** answer, **A–D.**

35. Which agent is most likely being used to treat his schizophrenic psychosis?

36. Which agent is most likely being used to treat depression and obsessive–compulsive disorder?

37. Which of these agents is able to selectively block the actions of the serotonin transporter?

Directions for questions 38–44: Each of the questions, statements, or incomplete statements in this section can be correctly answered or completed by **one** of the suggested answers or phrases. Choose the **best** answer.

38. Amphetamine exemplifies the pharmacologic mechanism of

(A) ganglionic blockade.
(B) inhibition of transmitter release.
(C) facilitation of transmitter release.
(D) interference with vesicular storage.
(E) blockade of transmitter reuptake.

39. Considering the general chemical structures of sympathomimetic amines, modification of the meta-hydroxyl group on the phenyl ring of norepinephrine would likely produce

(A) increased α-receptor potency.
(B) increased β-receptor potency.
(C) indirect sympathomimetic activity.
(D) decreased transport through the blood–brain barrier.
(E) loss of any biological activity in the nervous system.

40. Sometimes, combination treatment of Parkinson disease is warranted. Which of the following drug combinations could work cooperatively to enhance a clinical anti-parkinsonian response?

(A) amphetamine (Adderall) and reserpine
(B) levodopa and carbidopa
(C) carbidopa and tolcapone (Tasmar)
(D) amantadine (Symmetrel) and haloperidol (Haldol)
(E) dopamine and tyramine

41. Terazosin is able to facilitate micturition when used in the treatment of benign prostatic hypertrophy (BPH) because the drug

(A) relaxes the prostate gland.
(B) constricts the neck of the bladder.
(C) prevents penile erections associated with BPH.
(D) blocks seminal fluid production.
(E) blocks prostate cell growth.

42. BRL37344 is a β_3-agonist. It might be of interest to develop this agent into a clinically usable drug because of the expectation that β_3-agonists would

(A) constrict blood vessels and increase blood pressure in shock patients.
(B) induce lipolysis and decrease adipose cell mass in obese patients.
(C) increase glycogenolysis and prevent glycogen storage in liver cirrhosis.
(D) enhance renal vasodilation and increase urinary elimination of ethanol in alcoholics.
(E) cause bronchodilation and counteract the negative effects of asthma treatment agents.

43. The pharmacologic profile of carvedilol is most similar to that of

(A) esmolol.
(B) labetalol (Trandate).
(C) metoprolol (Lopressor).
(D) nadolol (Corgard).
(E) timolol (Timoptic).

44. The CNS and respiratory depression due to morphine overdose can be reversed by

(A) methadone (Dolophine).
(B) meperidine (Demerol).
(C) propranolol (Inderal).
(D) flumazenil (Romazicon).
(E) naloxone (Narcan).

Answers and Explanations

1. **The answer is B** *[see II.B.2.b]*.
Ipratropium is an approved antimuscarinic agent used to treat bronchospasm. Propantheline and homatropine are antimuscarinic agents used as a gastrointestinal (GI) antispasmodic and as a mydriatic, respectively. Edrophonium and ambenonium are indirect-acting cholinergic agonists and, as such, would be expected to induce bronchospasm.

2. **The answer is C** *[see II.B.1]*.
Xerostomia, or dry mouth, results from reduced salivary secretions and, therefore, is not a manifestation of cholinergic agonist activity. All of the other effects listed in the question are extensions of therapeutic effects of cholinergic agonists to the point of being adverse effects.

3. **The answer is C** *[see II.A.8.a]*.
Of the adrenergic agonists listed in the question, only epinephrine, because of its broad, nonselective α- and β-activity, is an agent of choice for anaphylactic reactions. Epinephrine improves circulatory and respiratory function and counteracts the vascular effects of histamine-related anaphylaxis.

4. **The answer is B** *[see II.C.1.f]*.
Neuromuscular blocking agents interact with nicotinic receptors at the skeletal neuromuscular junction. Succinylcholine is also capable of eliciting K^+ release from skeletal muscle due to muscle contractions.

5. **The answer is A** *[see II.B.1.a,b]*.
Both direct-acting (e.g., pilocarpine) and indirect-acting (e.g., physostigmine) cholinergics may be used in glaucoma to increase cholinergic activity and facilitate outflow of aqueous humor. Similarly, both β-agonists (e.g., epinephrine) and antagonists (e.g., timolol) may be used, respectively, to increase outflow and decrease production of aqueous humor. Atropine is contraindicated in glaucoma because its anticholinergic effects can block the outflow of aqueous humor and, consequently, increase intraocular pressure.

6. **The answer is D** *[see II.B.2.a]*.
Classic signs and symptoms of muscarinic blockade, as with atropine, include mydriasis, which may cause light sensitivity (photophobia); dry mouth and constipation by decreasing secretory activity and motility in the GI tract; and tachycardia by inhibiting the normal inhibitory cholinergic control of the cardiac system. Diarrhea is one of the common signs of cholinergic agonists (others signs include salivation, lacrimation and urination).

7. **The answer is B** *[see III.B.2.a]*.
The general anesthetics are divided into two major classes of drugs: those that are gases or volatile liquids, which are administered by inhalation, and those that are nonvolatile salts, which are administered as intravenous solutions. Halothane is a halogenated hydrocarbon, which belongs to the former class. It has the advantage over older volatile anesthetics (e.g., ethyl ether, cyclopropane) of being nonflammable. Thiopental sodium, alprazolam, buspirone, and phenytoin are all nonvolatile substances that are administered orally or parenterally. Thiopental is a general anesthetic and is sometimes referred to as a basal anesthetic because it does not produce significant third-stage surgical anesthesia. Alprazolam and buspirone are anxiolytics, whereas phenytoin is an anticonvulsant.

8. **The answer is B** *[see III.C]*.
Chlordiazepoxide, alprazolam, buspirone, and phenobarbital are all used as anxiolytic agents, whereas thioridazine is a phenothiazine antipsychotic.

9. **The answer is C** *[see III.C.1.c]*.
Benzodiazepines like diazepam enhance the actions of GABA on the $GABA_A$ receptor to enhance chloride influx into neurons. Topiramate and valproate are able to decrease epileptic activity by blocking glutamate receptors, whereas tiagabine prevents GABA uptake into the nerve terminal. Diazepam is not a MAOI and does not block the metabolism of inositol phosphates like lithium.

10. **The answer is A** *[see III.G.1.d]*.
Entacapone blocks peripheral COMT to enhance CNS penetration of levodopa, which is metabolized to dopamine but has no H_1-receptor activity. Bromocriptine directly stimulates dopamine receptors in the striatum to restore the balance between GABA-ergic and cholinergic neurons in Parkinson disease.

11. **The answer is E** *[see III.G.1.c]*.
Levodopa is not associated with agranulocytosis.

12. **The answer is E** *[see III.H.1; Figure 9-17]*.
The *p*-phenyl-*N*-alkylpiperidine moiety is common to the structurally specific opioid analgesics. Meperidine is an opioid analgesic and is an *N*-methyl-*p*-phenylpiperidine derivative. Its chemical name is ethyl 1-methyl-4-phenylpiperidine-4-carboxylate. Phenobarbital is a barbiturate sedative. Chlorpromazine is a phenothiazine antipsychotic. Diazepam is a benzodiazepine anxiolytic. Imipramine is a tricyclic dibenzazepine antidepressant.

13. **The answer is C** *[see III.H.2]*.
Opioids are used to treat all the following conditions except arthritis, which is often treated with nonsteroidal anti-inflammatory drugs (NSAIDs) and immunosuppressants, depending on the type of disease and severity.

14. **The answer is C** *[see III.F.1]*.
All these agents are used to treat partial or generalized tonic-clonic seizures except ethosuximide, which is more effective against absence seizures.

15. **The answer is C** *[see II.B.2.b]*.
Cholinesterase inhibitors are indirect-acting cholinergic agonists useful in treating myasthenia gravis and glaucoma. Their effects on GI and urinary bladder smooth muscle would be to increase smooth-muscle tone, not decrease it.

16. **The answer is D** *[see II.B.2]*.
All three compounds listed in the question are antimuscarinic agents; however, only benztropine and trihexyphenidyl are used to control parkinsonism and some neuroleptic-induced extrapyramidal disorders. Ipratropium is an approved agent for the treatment of bronchospasm.

17. **The answer is B** *[see II.A.8.c]*.
Dobutamine is a β_1-selective adrenergic agonist. It would be inappropriate to use dobutamine to decrease blood flow at the site of local anesthetic administration. Epinephrine is a nonselective α- and β-agonist that can be used to limit the systemic absorption of local anesthetics and prolong their activity. Phenoxybenzamine is an α-selective antagonist that will only enhance the loss of the local anesthetic away from the site of application.

18. **The answer is E** *[see III.A.4]*.
Careful administration of a local anesthetic by a knowledgeable practitioner is essential to prevent systemic absorption and consequent toxicity. This is especially important when the patient has cardiovascular disease, poorly controlled diabetes, thyrotoxicosis, or peripheral vascular disease.

19. **The answer is E** *[see III.C.1.c]*.
Benzodiazepines can serve as induction agents for general anesthesia; they also have anxiolytic properties. In addition, intravenous diazepam is used to treat status epilepticus, whereas clonazepam is used orally for myoclonic and absence (petit mal) seizures. Benzodiazepines also diminish alcohol withdrawal symptoms.

20. **The answer is D** *[see II.A.9.a]*.
Tamsulosin is an α_{1A}-selective antagonist that may be used in place of finasteride to treat benign prostatic hypertrophy (BPH).

21. **The answer is E** *[see II.A.9.a]*.
Due to venodilatory actions, prazosin is associated with postural or orthostatic hypotension.

22. **The answer is C** *[see II.A.8.c]*.
Of all of the agents, only metaproterenol is an agonist at the β_2-receptors.

23. **The answer is A** *[see II.A.9.b]*.
The administration of propranolol, a nonselective antagonist of β-receptors, will antagonize β_2-receptors in the bronchioles of the patient to prevent the ability of metaproterenol to dilate the airways.

24. **The answer is D** *[see II.B.2.a]*.
Pilocarpine acts directly at the muscarinic receptor, whereas dipivefrin eventually activates α_2-receptors. Timolol blocks β-receptors. Echothiophate inhibits the metabolism of ACh, indirectly increasing levels of the endogenous neurotransmitter.

25. **The answers are A and E** *[see II.A.9.b]*.
Metoprolol, a β_1-selective agent, can cause bradycardia alone. The addition of topical timolol, while limiting systemic absorption, could have an additive β-blocking effect to decrease heart rate (negative chronotropy) and hypotension.

26. **The answers are C and E** *[see II.A.9.b; II.B.1.a,b]*.
Pilocarpine and echothiophate cause the stimulation of muscarinic receptors (pilocarpine directly and echothiophate indirectly), so applying them together would not produce any additional benefit. However, dipivefrin (once activated, below) can compete with timolol for β-receptors on the ciliary body, reducing the effectiveness of timolol.

27. **The answer is C** *[see II.A.8.a]*.
Dipivefrin is diacetylated epinephrine, which is readily metabolized to epinephrine to activate α_2-receptors on the ciliary body to reduce the production of aqueous humor.

28–31. **The answers are: 28-C** *[see III.C.3]*, **29-B** *[see III.E.2.e]*, **30-D** *[see III.E.1.d]*, **31-E** *[see III.E.3.d]*.
Buspirone's mechanism of anxiolytic action is unknown. Unlike the benzodiazepines, buspirone lacks hypnotic and anticonvulsant properties. The tricyclic antidepressant imipramine is useful in the treatment of enuresis because the compound blocks muscarinic receptors mediating micturition. Fluoxetine is the serotonin uptake blocker and has the adverse effects listed. Phenelzine is a MAOI that enhances catecholamine content in the nerve terminal, and foods containing tyramine (e.g., cheese) would elicit greater catecholamine release to potentially cause hypertension.

32–34. The answers are: 32-B *[see Figure 9-8]***, 33-D** *[see Figure 9-10]***, 34-C** *[see Figure 9-15]***.**
The structure shown in question 29 is that of procaine, which is a diethylaminoethyl *p*-aminobenzoate ester. It contains a hydrophilic amino group in the alcohol portion of the molecule and a lipophilic aromatic acid connected by the ester linkage. The procaine molecule is typical of ester-type local anesthetics.
The structure in question 30 is that of diazepam, which has a benzo-1,4-diazepine as its base nucleus. The widely used benzo-1,4-diazepine derivatives have significant anxiolytic, hypnotic, and anticonvulsant activities.
The structure in question 31 is that of desipramine, which has a dibenzazepine as its base nucleus. Dibenzazepine derivatives that have a methyl- or dimethylaminopropyl group attached to the ring nitrogen have significant antidepressant activity. Similarly, substituted dibenzocycloheptadienes also have antidepressant activity. Together, these two chemical classes make up most of the tricyclic antidepressants.

35. The answer is A *[see III.D.4]***.**
Clozapine, although therapeutically defined as a general antipsychotic, is used almost exclusively in the treatment of schizophrenia.

36. The answer is B *[see III.E.1]***.**
Fluoxetine is most likely being used in this patient in an attempt to treat depression and obsessive–compulsive disorder with the same drug. Clinical trials have shown fluoxetine to improve both conditions. The use of a single agent for both conditions will minimize the risk of drug–drug interactions, as well as reduce the chances of adverse effects.

37. The answer is B *[see III.E.1]***.**
Fluoxetine produces its antidepressant actions by selectively blocking the SERT to enhance serotonin levels in the synapse.

38. The answer is C *[see II.A.8.d]***.**
Amphetamine is an indirectly acting sympathomimetic that enters the nerve terminal and displaces norepinephrine from the storage vesicles, thus increasing the quanta of the transmitter released.

39. The answer is A *[see II.A.8.b]***.**
Both aromatic hydroxyl functions are important for both α- and β-receptor binding; however, modification of the meta-hydroxyl to a methoxy derivative increases α- versus β-receptor selectivity.

40. The answer is B *[see III.G.1.a]***.**
Although levodopa can cross the blood–brain barrier to gain access into the brain, a significant portion of an orally administered dose is converted into dopamine and norepinephrine at peripheral sites, leading to peripheral side effects and decreased brain bioavailability. Carbidopa, a dopa decarboxylase inhibitor that does not cross the blood–brain barrier, is coadministered with levodopa to decrease its peripheral conversion and increase central delivery of the drug and, hence, the therapeutic response.

41. The answer is A *[see II.A.9.a]***.**
Terazosin blocks α-receptors on the prostate gland to cause a relaxant effect, which reduces the pressure exerted by the prostate on the urethra, thus easing urinary voidance.

42. The answer is B *[see Table 9-1]***.**
Stimulation of β_3-receptors induces the metabolic breakdown of fat stores into free fatty acids that can be further catabolized by the body. The hope is that this category of pharmacologic agents could, with repeated use, lead to a decrease in the content and number of fat cells, and, hence, an antiobesity effect.

43. The answer is B *[see II.A.9.b; Table 9-2]***.**
Like labetalol, carvedilol is a nonselective α- and β-receptor antagonist used in the treatment of hypertension. Blockade of vascular α (alpha-1)-receptors would cause vasodilatation and decreased peripheral vascular resistance, whereas blockade of myocardial β (beta-1)-receptors would decrease cardiac contractility. The resultant decrease in cardiac output would produce a fall in blood pressure (blood pressure = cardiac output × peripheral resistance).

44. The answer is E *[see III.H.1.b]***.**
Only naloxone is able to effectively compete with morphine binding to central μ-opioid receptors to reverse the depressant effects of the opiate. Meperidine may have additive suppressive effects in this condition.

Study Questions

Directions for questions 1–19: Each of the questions, statements, or incomplete statements in this section can be correctly answered or completed by **one** of the suggested answers or phrases. Choose the **best** answer.

1. Calcium-channel blockers can have all of the following characteristics *except*

(A) they block the slow inward current carried by calcium during phase 2 of the cardiac action potential.
(B) they dilate peripheral arterioles and reduce total peripheral resistance.
(C) they constrict coronary arteries and arterioles and decrease oxygen delivery to the myocardium.
(D) they are useful in treating vasospastic angina.
(E) adverse effects include bradycardia and edema.

2. The termination of heparin activity by protamine sulfate is the result of

(A) a chelating action.
(B) the inhibition of gastrointestinal absorption of heparin.
(C) the displacement of heparin–plasma protein binding.
(D) an acid–base interaction.
(E) the prothrombin-like activity of protamine.

3. Which of the following agents is composed of a steroid nucleus, unsaturated lactone, and saccharide units?

(A) nifedipine
(B) digoxin
(C) flecainide
(D) cholestyramine
(E) warfarin

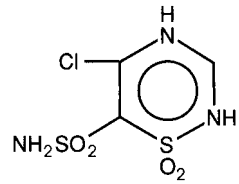
4. Digoxin may be useful in treating one of the following conditions:

(A) AV block
(B) torsades de pointes
(C) congestive heart failure
(D) ventricular tachycardia
(E) bradycardia

5. Which of the following antiarrhythmic agents is most likely to cause pulmonary fibrosis during therapy?

(A) procainamide
(B) sotalol
(C) amiodarone
(D) lidocaine
(E) quinidine

6. The structure shown is characteristic of which of the following agents?



(A) osmotic diuretics
(B) carbonic anhydrase inhibitors
(C) thiazides
(D) loop diuretics
(E) potassium-sparing diuretics

7. Much of the reduction in circulating LDL-cholesterol during treatment with simvastatin may be due to

(A) enhanced uptake of LDL by the liver.
(B) upregulation of HMG-CoA reductase.
(C) decreased GI absorption of cholesterol.
(D) decreased bile acid production.
(E) decreased VLDL levels.

8. Valsartan is used to treat all the following conditions *except*

(A) hypertension.
(B) diabetic nephropathy.
(C) heart failure.
(D) post-MI patient.
(E) supraventricular arrhythmias.

9. Diuretics such as hydrochlorothiazide are first-line therapy for essential hypertension. Which of the following statements best explains the actions of these drugs?

(A) Loss of sodium in the renal filtrate causes hyponatremia that reduces blood osmolarity.
(B) Water loss in the urine decreases blood volume that lowers systemic blood pressure.
(C) Loss of potassium causes water loss to decrease blood pressure.
(D) They are prominent vasodilators.
(E) They produce a decrease in heart rate to lower cardiac output and blood pressure.

10. Sildenafil, when used to treat pulmonary arterial hypertension, can cause all of the following adverse effects *except*

(A) hepatotoxicity.
(B) priapism.
(C) visual disturbances.
(D) headache.
(E) flushing of the skin.

11. Which of the following agents is not used to treat angina symptoms?

(A) propranolol
(B) nitroglycerin
(C) ranolazine
(D) digoxin
(E) verapamil

12. Spontaneous depolarization of the SA node can be reduced by

(A) verapamil.
(B) lidocaine.
(C) milrinone.
(D) digoxin.
(E) flecainide.

13. All of the following agents can be used to manage atrial fibrillation *except*

(A) verapamil.
(B) lidocaine.
(C) dronedarone.
(D) propranolol.
(E) quinidine.

14. Which of the following is a likely adverse event of heparin therapy?

(A) purple toe syndrome
(B) thrombocytopenia
(C) dry cough
(D) skin necrosis
(E) hypertension

15. A major use of dabigatran is in

(A) thrombocytopenia.
(B) stroke prophylaxis in atrial fibrillation.
(C) decreasing clotting after stent placement.
(D) breaking down clots that have formed during myocardial infarction.
(E) intermittent claudication.

16. Bile acid reabsorption from the GI tract is reduced by

(A) ezetimibe.
(B) cholestyramine.
(C) pravastatin.
(D) niacin.
(E) fenofibrate.

17. Alteplase is less likely to cause systemic bleeding than urokinase because

(A) it only activates thrombin that is associated with a clot.
(B) it has more specific effects on platelets.
(C) it is a recombinant protein.
(D) it only activates plasminogen associated with a clot.
(E) urokinase is extracted from hemolytic streptococcus that causes bleeding.

18. All of the following agents have actions on blood platelets to modify clot formation *except*

(A) eptifibatide.
(B) dabigatran.
(C) clopidogrel.
(D) dipyridamole.
(E) tirofiban.

19. The amount of dietary cholesterol absorbed from the GI tract is reduced by

(A) niacin.
(B) rosuvastatin.
(C) ezetimibe.
(D) clofibrate.
(E) colestipol.

Directions for questions 20–25: The questions and incomplete statements in this section can be correctly answered or completed by **one or more** of the suggested answers. Choose the answer, **A–E**.

A if **I only** is correct
B if **III only** is correct
C if **I** and **II** are correct
D if **II** and **III** are correct
E if **I**, **II**, and **III** are correct

20. The use of milrinone in the treatment of acute heart failure

I. increases intracellular calcium.
II. activates protein kinase A.
III. increases myocardial contractility.

21. Warfarin

I. increases hepatic vitamin K epoxide.
II. decreases reduced hepatic vitamin K.
III. decreases the absorption of dietary vitamin K.

22. Ms. Jane M. was being treated with atorvastatin calcium (20 mg/d) and this produced a lowering in LDL-C, but this effect was not maintained beyond 3 months. Her physician wants to increase the dose of the drug to 40 mg/d and asks you if this strategy will be successful. Which of the following would be part of an appropriate answer?

I. The patient is becoming desensitized to the 20 mg dose so doubling it will not have any additional benefit.
II. The patient must have increased her dietary intake of cholesterol and increasing the dose of drug will only cause her to eat more cholesterol-containing foods.
III. The patient's liver may have upregulated the amount of HMG-CoA reductase and so increasing the drug dose can produce further lowering in LDL-C.

23. The use of lepirudin in heparin-induced thrombocytopenia would indicate that

I. thrombin is activated during this condition.
II. increased clotting may occur during this condition.
III. this is caused by leech saliva.

24. Nitroglycerin, when used to treat stable angina,

I. decreases myocardial oxygen demand by reducing the tension on the ventricular walls.
II. increases oxygen supply by allowing ventricular arterioles to remain open for longer periods by reducing ventricular filling.
III. reduces the amount of blood returning to the heart by causing a venodilation.

25. Which of the following is required for heparin's action on factor Xa?

I. Antithrombin III
II. Fibrinogen
III. Thrombin

Directions for questions 26–30: Each group of adverse effects in this section is most closely related to **one** of the following drug classes. The drug classes may be used more than once or not at all. Choose the **best** answer, **A–E**.

A Cardiac glycosides
B Calcium-channel blockers
C Angiotensin-converting enzyme inhibitors
D β-Adrenergic antagonists
E Nitrites and nitrates

26. Bradycardia, hypotension, increased airway resistance, and congestive heart failure

27. Visual disturbances (yellow or green vision), confusion, anorexia, vomiting, atrioventricular (AV) block, and ventricular tachycardia

28. Hypotension, acute renal failure, dry cough, and angioedema

29. Birth defects if women take them during early pregnancy

30. Produce a vasodilation by reducing the influx of a cation necessary for contraction

Directions for questions 31–34: Each statement in this group is most closely characterized by **one** of the following drugs. The drugs may be used more than once or not at all. Choose the **best** answer, **A–E**.

A Furosemide
B Hydrochlorothiazide
C Spironolactone
D Mannitol
E Acetazolamide

31. It interferes with collecting tubular aldosterone-mediated sodium–potassium exchange and may cause hyperkalemia, gynecomastia, and menstrual irregularities.

32. Freely filtered, this drug limits tubular reabsorption of water and is useful in reducing cerebral edema and intracranial pressure.

33. The principal site of action of this drug is on the thick ascending limb of the loop of Henle; it is useful in treating pulmonary edema and ascites.

34. This agent is used to treat mountain or altitude sickness.

Directions for questions 35–38: Each of the questions, statements, or incomplete statements in this section can be correctly answered or completed by **one** of the suggested answers or phrases. Choose the **best** answer.

35. Angiotensin-converting enzyme inhibitors (ACEIs) such as enalapril (Vasotec) are prodrugs. What is the purpose of the prodrug formulation of enalapril?

(A) enhance potency
(B) enhance oral activity
(C) mask taste
(D) enhance water solubility
(E) increase stability

36. Angiotensin receptor antagonists or blockers (ARBs) are less likely to cause angioedema and cough than the angiotensin-converting enzyme inhibitors (ACEI) because

(A) ARBs do not contain a sulfhydryl functional group.
(B) ARBs are not administered as prodrugs.
(C) ACEIs are more specific for inhibiting the production of angiotensin II.
(D) ARBs are pseudo-irreversible antagonists.
(E) ARBs do not inhibit the breakdown of bradykinin.

37. Which of the following diuretics does NOT contain a sulfonamide substituent?

(A) furosemide (Lasix)
(B) ethacrynic acid (Edecrin)
(C) torsemide (Demadex)
(D) hydrochlorothiazide (HydroDIURIL)
(E) bumetanide (Bumex)

38. Which of the following anticoagulant agent's dose is influenced by genetic polymorphisms in CYP2C9 and vitamin K reductase?

(A) enoxaparin (Lovenox)
(B) fondaparinux (Arixtra)
(C) warfarin (Coumadin)
(D) lepirudin (Refludan)
(E) bivalirudin (Angiomax)

Answers and Explanations

1. The answer is C *[see II.B]*.
By blocking the influx of calcium into vascular smooth muscle (via L-type channels), these agents decrease rather than increase the contractile response of various arterial beds.

2. The answer is D *[see VII.G.2]*.
Heparin is a highly acidic mucopolysaccharide, whereas protamine is a highly basic protein. When administered after heparin, protamine chemically combines with it (presumably by an acid–base interaction) and inactivates its anticoagulant effect. Hence, it is an effective antidote for heparin. Caution must be employed when using protamine because an excess of protamine can cause an anticoagulant effect.

3. The answer is B *[see IV.A.1*; *Figure 10-10]*.
Digoxin is composed of a steroid nucleus, unsaturated lactone ring, and three sugars attached via a glycosidic bond.

4. The answer is C *[see IV.A.1]*.
Low doses of digoxin activate the vagal reflex to cause AV block and bradycardia, and this action can be beneficial in preventing atrial fibrillations from causing ventricular tachycardias, but the more common use of cardiac glycosides is to increase cardiac contractility in heart failure.

5. The answer is C *[see V.C.3]*.
Of all the drugs on the list, amiodarone is most likely to cause life-threatening pulmonary fibrosis.

6. The answer is C *[see II.B.2*; *Figure 10-5]*.
The structure is a benzothiadiazine (or thiazide) derivative and, more specifically, it is the diuretic hydrochlorothiazide. Only this class of diuretics contains the benzothiadiazine nucleus even though the sulfonamide moiety is common to others such as the loop diuretics and carbonic anhydrase inhibitors.

7. The answer is A *[see VI.H.2]*.
The HMG-CoA reductase inhibitors such as simvastatin reduce hepatic cholesterol synthesis, but the lipid lowering effects more often occur as hepatocytes increase their expression of the LDL receptor to scavenge LDL-C from the circulation.

8. The answer is E *[see II.A.6]*.
Valsartan has no antiarrhythmic activity and would not be useful in supraventricular arrhythmias, but it is used to treat all the other listed conditions.

9. The answer is D *[see II.B.2]*.
Like all diuretics, hydrochlorothiazide increases Na^+ loss in the renal filtrate, which osmotically draws water with it to cause a diuresis. The water loss decreases blood volume to reduce systemic blood pressure.

10. The answer is A *[see II.D.2]*.
Sildenafil is not associated with hepatotoxicity, although all the other adverse events have been reported with use.

11. The answer is D *[see III]*.
Digoxin would worsen angina symptoms by increasing cardiac contractility and thereby increasing myocardial oxygen demand.

12. The answer is A *[see V.A.2; V.E]*.
SA nodal cells are highly dependent on L-type calcium channels for their spontaneous depolarization and initiation of pacemaker activity. This allows verapamil to have a significant bradycardia effect by blocking these channel activities. The relative specificity of lidocaine and flecainide for Na^+ channels prevents them from having significant effects at the SA node. Milrinone tends to increase heart rate by increasing intracellular cAMP to enhance spontaneous depolarization of the SA node, whereas digoxin has greater effects on the AV node via vagal inputs.

13. The answer is B *[see V.B.1–2; V.C]*.
The relative specificity of lidocaine for Na^+ channels results in little nodal inhibition, so fibrillation due to SA or AV nodal activity would be unaffected. Lidocaine also has little effect on atrial myocardial cell depolarization because its Na^+ channels are only in the inactive state for very brief periods and so would not be effective against ectopic atrial arrhythmias. Overall, lidocaine is not effective in the management of supraventricular arrhythmias, unlike the other agents on the list.

14. The answer is E *[see VII.G.2]*.
All the adverse events listed except for hypertension have been reported with heparin use. However, heparin needs to be used cautiously in uncontrolled hypertension in order to prevent the occurrence of strokes.

15. The answer is B *[see VII.G.3]*.
By virtue of its direct inhibition of thrombin (not requiring antithrombin III), dabigatran is able to reduce the clot formation in patients with atrial fibrillation. It is not approved for decreasing clots after stent placement or in intermittent claudication.

16. The answer is B *[see VI.G]*.
Only the bile acid–binding resins such as cholestyramine reduce the reabsorption of bile acid from the GI tract to reduce plasma LDL-C levels.

17. The answer is D *[see VII.I.1]*.
Alteplase is a recombinant form of tissue plasminogen activator that requires plasminogen to be bound to the fibrin of clots before it can cleave to plasmin. Urokinase is able to catalytically activate free plasminogen to plasmin, which can lead to generalized dissolving of clots and a systemic bleeding or lytic state.

18. The answer is B *[see VII.G.3]*.
Dabigatran does not interact with platelets but rather inhibits thrombin directly to reduce clot formation.

19. The answer is C *[see VI.J]*.
Ezetimibe specifically interacts with the sterol transporter on GI epithelial cells to reduce the absorption of dietary cholesterol.

20. The answer is E (I, II, and III) *[see IV.A.3]*.
Milrinone is a type 3 phosphodiesterase inhibitor that increases cAMP to increase PKA activity. PKA phosphorylates L-type channels to increase calcium influx into myocardial cells to increase contractility.

21. The answer is C (I and II) *[see VII.G.1; Figure 10-22]*.
Warfarin competes with vitamin K epoxide for access to the reductase that converts the epoxide back to the reduced (active) form. This leads to elevation of the epoxide form and a reduction in the reduced form of vitamin K in hepatocytes. Warfarin does not affect the absorption of dietary vitamin K from the GI tract, and in fact, this intake can oppose the activity of warfarin by supplying fresh reduced vitamin K for carboxylation of nascent clotting factors.

22. The answer is B (III) *[see VI.H.3]*.
Inhibition of HMG-CoA reductase activity by statins increases hepatic expression of the enzyme that may require further increases in the dose of the statins to maintain the suppression of the enzyme and low LDL-C.

23. The answer is C (I and II) *[see VII.G.3]*.
HIT appears to be due to an immune reaction following heparin administration and is often accompanied by marked platelet activation and destruction as well as thrombin activation to cause disseminated clotting. Direct thrombin inhibitors such as lepirudin can be used to control thrombin-induced coagulation without perpetuating the immune reaction.

24. The answer is E (I, II, and III) *[see III.A.4]*.
Nitroglycerin liberates NO in venous smooth muscle, leading to venous pooling and reduced blood returning to the heart (preload). Thus, ventricular filling is reduced and this decreases the tension on the ventricular walls to reduce oxygen demand. Reduced wall tension, especially during diastole, also allows subendocardial arteries to remain patent for longer periods to increase blood flow to the heart muscle.

25. The answer is A (I) *[see VII.G.2]*.
Both UFH and LMWHs require antithrombin III as an intermediate to inhibit the actions of factor Xa or II (thrombin).

26. The answer is D *[see chapter 9.I.A.1.b]*.
Nonselective β-adrenergic blockers (e.g., propranolol) produce adverse effects associated with their mechanism of action on the autonomic nervous system. Thus, bronchospasm, lowering of blood pressure, and reduced heart rate result from blockade of autonomic β-adrenergic receptors.

27. The answer is A *[see IV.A.1]*.
Visual disturbances (yellow or green vision) are peculiar to cardiac glycoside overdose. AV dissociation and ventricular tachycardia are obviously more significant adverse effects.

28. The answer is C *[see II.A.5]*.
ACE inhibitors may cause dry cough, angioedema, hypotension, and acute renal failure.

29. The answer is C *[see II.A.5]*.
ACE inhibitors will cause birth defects and fetal demise if taken during the second and third trimesters of pregnancy.

30. The answer is B *[see II.C]*.
Calcium influx during arterial smooth muscle contraction is blocked by L-type channel blockers resulting in a rapid vasodilation.

31. The answer is C *[see II.A.7]*.
Spironolactone interferes with aldosterone-mediated sodium–potassium exchange, reducing the amount of potassium excreted and is often used with other diuretics that promote the excretion of potassium, such as the benzothiadiazines.

32. The answer is D *[see II.B.4]*.
Mannitol increases the osmolarity of the glomerular filtrate because it is reabsorbed poorly. By increasing the osmolarity of the glomerular filtrate, mannitol limits tubular reabsorption of water, thus promoting diuresis. In this way, it reduces cerebral edema and decreases intracranial pressure.

33. The answer is A *[see II.B.1]*.
Furosemide is a diuretic of choice for treating acute congestive heart failure and ascites because it promotes a significant, rapid excretion of water and sodium. This is accomplished by inhibiting the actions of the $Na^+/K^+/2Cl^-$ transporter in the thick ascending loop of Henle.

34. The answer is E *[see II.B.4]*.
This is one of the few unique uses of carbonic anhydrase inhibitors such as acetazolamide.

35. The answer is B *[II.A.5.b]*.
Enalapril has an ethyl ester that covers a required carboxylic acid. After ester hydrolysis, the active drug enalaprilat is released to inhibit ACE. By covering the ionic carboxylic acid functional group with the more lipophilic ethyl ester, the oral bioavailability of enalapril is enhanced. Prodrugs can also be used to mask a foul-tasting drug, enhance water solubility, or increase the stability of a drug, but this is not the case with enalapril.

36. The answer is E *[II.A.6.e; II.A.5.d]*.
ACEIs inhibit not only the conversion of angiotensin I to angiotensin II but also inhibit the metabolism of bradykinin. The accumulation of bradykinin has been associated with the side effects of nonproductive cough and angioedema observed with the ACEI. The ARBs do not interfere with bradykinin metabolism and therefore have a much lower incidence of these effects than observed with the ACEI. Although the other choices are sometimes true statements, they do not address the question related to the side effects.

37. The answer is B *[II.B.1.a; II.B.2.a; Figure 10-5]*.
Ethacrynic acid, an aryloxyacetic acid derivative, is the only loop diuretic that does not have a sulfonamide substituent. Furosemide, torsemide, and bumetanide are loop diuretics. The thiazide and thiazide-like diuretics also have a sulfonamide, including hydrochlorothiazide, and also contain a sulfonamide substituent. This may be important in patients with a hypersensitivity to sulfonamides, although cross-reactivity with sulfonamide antibiotics is not always apparent.

38. The answer is C *[VII.G.1.d]*.
Polymorphisms of the CYP2C9 gene can result in variant forms of the enzyme with markedly altered capacity for warfarin metabolism. The reduced metabolic capacity of the variants can increase the likelihood of bleeding with usual doses. Specific polymorphisms in the vitamin K reductase gene can lead to altered hepatic levels of the enzyme such that patients with low expression can be more susceptible to anticoagulant effects of standard warfarin doses, again increasing the potential for bleeding.

Study Questions

Directions: Each of the questions, statements, or incomplete statements in this section can be correctly answered or completed by **one** of the suggested answers or phrases. Choose the **best** answer.

1. A 45-year-old long-haul trucker suffers from seasonal allergies. He asks advice on which over-the counter product is best to relieve his symptoms. Which of the following choices is the best recommendation for this patient?

(A) diphenhydramine
(B) promethazine
(C) clemastine
(D) chlorpheniramine
(E) loratadine

2. Which of the following choices would be most appropriate in treating nausea and vomiting associated with motion sickness?

(A) diphenhydramine
(B) brompheniramine
(C) ondansetron
(D) omeprazole
(E) ranitidine

3. Omeprazole would *not* be effective in the treatment of

(A) gastroesophageal reflux disease.
(B) peptic ulcer disease.
(C) Zollinger-Ellison syndrome.
(D) heartburn.
(E) urticaria.

4. Which of the following antiulcer medications is most likely to cause drug interactions and endocrine side effects?

(A) ranitidine
(B) omeprazole
(C) lansoprazole
(D) cimetidine
(E) famotidine

5. A patient has just been diagnosed with recurrent migraine headaches. Which of the following preexisting conditions would preclude the use of sumatriptan for this patient?

(A) liver disease
(B) renal failure
(C) ischemic heart disease
(D) irritable bowel syndrome (IBS)
(E) gouty arthritis

6. Aspirin is best described as a(n)

(A) acetyl ester of salicylic acid.
(B) acetic acid derivative.
(C) propionic acid derivative.
(D) *N*-arylanthranilic acid derivative.
(E) enolic acid derivative.

7. Which of the following prostaglandin analogs is used specifically for the treatment of glaucoma?

(A) alprostadil
(B) latanoprost
(C) carboprost
(D) dinoprostone
(E) epoprostenol

8. The use of misoprostol to prevent nonsteroidal anti-inflammatory drug–induced ulcers could cause all of the following side effects *except*

(A) fever.
(B) gastrointestinal cramping.
(C) hypertension.
(D) headache/pain.
(E) diarrhea.

9. Which of the following asthma therapies has been associated with an acute vascular syndrome that is associated with sudden withdrawal of corticosteroid anti-inflammatory drugs?

(A) zafirlukast
(B) zileuton
(C) montelukast
(D) cetirizine
(E) ranitidine

10. Which of the following asthma therapies is effective by decreasing the amounts of released leukotrienes?

(A) zafirlukast
(B) zileuton
(C) montelukast
(D) alprostadil
(E) bimatoprost

11. Rizatriptan is effective in treating migraine headache by all of the following *except*

(A) directly vasoconstricting involved blood vessels.
(B) inhibiting the roles of inflammatory neurotransmitters.
(C) directly blocking pain transmission.
(D) inhibiting platelet aggregation.
(E) inhibiting the release of vasodilating substances.

12. Which of the following drugs, based on its mechanism of action, is effective in treating diarrhea-predominant irritable bowel syndrome (IBS)?

(A) misoprostol
(B) naratriptan
(C) alosetron
(D) cetirizine
(E) rabeprazole

13. The second-generation antihistamines (H_1-receptor antagonists) are generally considered nonsedating because they

(A) are more selective for H_1 receptors than the first-generation agents.
(B) are metabolized faster than the first-generation agents.
(C) actually function as H_1 receptor inverse agonists.
(D) do not cross the blood–brain barrier as easily as the first-generation agents.
(E) are only applied topically and therefore do not enter the systemic circulation.

14. Aspirin exerts its antiplatelet effect by inhibiting

(A) cyclooxygenase (COX) 1.
(B) COX-2.
(C) COX-3.
(D) prostaglandin synthesis.
(E) leukotriene synthesis.

15. Acetaminophen has advantages over aspirin or other nonsteroidal anti-inflammatory drugs by virtue of all of the following *except*

(A) relative lack of antiplatelet effects.
(B) relative lack of gastrointestinal ulcerative effects.
(C) being a safe alternative for children with viral infections.
(D) no hepatotoxicity.
(E) absence of adverse cardiovascular effects.

16. Acetaminophen toxicity is characterized by

(A) profound vasoconstriction and pain.
(B) severe abdominal cramping and diarrhea.
(C) central nervous system stimulation and seizures.
(D) profound liver damage and failure.
(E) tinnitus.

17. Which of the following antigout medications is specifically used in acute attacks?

(A) colchicine
(B) allopurinol
(C) probenecid
(D) pegloticase
(E) febuxostat

18. Which of the following antigout medications acts by decreasing serum levels but increasing urine levels of uric acid, thus increasing the risk of kidney stone development?

(A) colchicine
(B) allopurinol
(C) probenecid
(D) rasburicase
(E) pegloticase

19. The nonsteroidal anti-inflammatory drugs, as a class, are anti-inflammatory primarily through their ability to inhibit

(A) cyclooxygenase (COX) 1.
(B) COX-2.
(C) COX-3.
(D) leukotriene synthesis.
(E) thromboxane synthesis.

20. The selective cyclooxygenase (COX) 2 inhibitors have been associated with which of the following adverse drug reactions?

(A) severe ischemic colitis
(B) torsades de pointes
(C) cardiovascular thrombotic events
(D) acute liver failure
(E) Churg-Strauss syndrome

21. Which of the following antihistamines is used for the treatment of emesis?

(A) fexofenadine
(B) doxylamine
(C) chlorpheniramine
(D) promethazine
(E) desloratadine

22. Which of the following agents would produce a long-term inhibition of reduced gastric acid secretion through an irreversible mechanism?

(A) rabeprazole
(B) cimetidine
(C) famotidine
(D) nizatidine
(E) nedocromil

23. Which of the following is an indole derivative that antagonizes the 5-HT_1-receptor?

(A) ergotamine
(B) sumatriptan
(C) granisetron
(D) buspirone
(E) methylergonovine

24. Each of the following is classified as an NSAID *except*

(A) piroxicam
(B) ketorolac
(C) oxaprozin
(D) acetaminophen
(E) indomethacin

25. Which one of the following side effects is the topic of a black box warning on all NSAIDs?

(A) liver failure
(B) asthma
(C) cardiovascular events
(D) nephrotoxicity
(E) CNS depression

Answers and Explanations

1. The answer is E *[see VIII.C.1.b]*.
Diphenhydramine, promethazine, and clemastine all possess moderate to strong anticholinergic activity. This will increase the risk of sedation, which could prove dangerous in this patient. Chlorpheniramine, although the least sedating of the first-generation drugs, still may cross the blood–brain barrier and cause some sedation. Loratadine, as a second-generation drug that has minimal anticholinergic activity and does not cross the blood–brain barrier (thus producing no central effects), is least likely to cause sedation and thus affect his job.

2. The answer is A *[see VIII.C.1.b.(2)]*.
Although ondansetron is used for nausea associated with chemotherapy and anesthetics, it is not typically used for nausea associated with motion or vertigo. Diphenhydramine, which possesses a high degree of anticholinergic activity, is effective in reducing nausea and vomiting associated with vestibulocochlear activity, vertigo, and motion sickness. None of the other choices directly reduces nausea or vomiting; therefore, diphenhydramine is the best choice.

3. The answer is E *[see IX.A]*.
Because choices A–D are all disease states that represent some action of excessive acid secretion, omeprazole, which also blocks the proton or acid pump, would be effective in reducing the acid-induced pain and damage associated with gastroesophageal reflux disease (GERD), peptic ulcer disease (PUD), Zollinger-Ellison syndrome, and heartburn. Urticaria is best treated with a H_1-receptor antagonist.

4. The answer is D *[see VIII.C.2.c]*.
Of the drugs listed, and specifically, of the H_2 antagonists, cimetidine is the only drug that inhibits the hepatic microsomal metabolizing system (specifically, the 3A4 isozyme) and the only drug that exhibits weak androgenic activity. The former is responsible for numerous drug interactions and some side effects, whereas the latter is responsible for endocrine (specifically, androgen-like) side effects.

5. The answer is C *[see VII.C.2]*.
Sumatriptan (and other drugs in the class) specifically causes vasoconstriction. This effect, when present in coronary vessels, can cause chest tightness or pain as a normal side effect of the drug. However, in patients with ischemic heart disease, angina, or a risk for coronary artery disease, this action could precipitate attacks of angina or potentially cause myocardial infarction and should not be used in those patients.

6. The answer is A *[see III.B.1–5]*.
Aspirin is the acetyl ester of salicylic acid or a salicylate member of the NSAIDs. Diclofenac is an example of an acetic acid derivative, whereas ibuprofen is an example of a propionic acid. Meclofenamate sodium is an example of an *N*-arylanthranilic acid or fenamic acid. Meloxicam is an example of an enolic acid derivative or an oxicam.

7. The answer is B *[see II.D.3.b]*.
Although most prostaglandin analogs are nonspecific in their sites of action and may produce similar physiological effects, latanoprost is specifically formulated and marketed for use in the treatment of glaucoma. The relative selectivity of latanoprost for the $PGF_2\alpha$ receptor is responsible for its ability to lower intraocular pressure and therefore its benefit in treating glaucoma.

8. The answer is C *[see II.D.1.c]*.
As noted in the answer to question 7, most prostaglandin analogs have activity at receptors throughout the body, causing a prostaglandin-like effect on numerous organ systems. Misoprostol, as a relatively nonselective agonist, would cause contraction of gastrointestinal smooth muscle, stimulate pain fibers, and reset the thermoregulatory center of the CNS, thus causing all the potential side effects listed except hypertension. Hypotension is more commonly observed.

9. The answer is A *[see VI.D.2]*.
Zafirlukast is the only drug that has been associated with Churg-Strauss syndrome, a condition of eosinophilic vasculitis that occurs when a patient who is on both zafirlukast and corticosteroid therapy suddenly discontinues the corticosteroid. This effect has not been observed with the pharmacologically similar drug montelukast. Note that slow withdrawal of the corticosteroid (which should be done anyway, to minimize acute adrenal insufficiency) will prevent this adverse drug reaction. Neither ranitidine nor cetirizine are indicated for the treatment of asthma.

10. The correct answer is B *[see VI.C.1]*.
Zafirlukast and montelukast exert their effect by blocking leukotrienes at their receptor. Zileuton, which acts by inhibiting lipo-oxygenase, will decrease the synthesis of these inflammatory mediators. Therefore, it is the only drug listed that will decrease the synthesis and, consequently, the release of leukotrienes. Alprostadil and bimatoprost are both prostaglandin analogs.

11. The answer is D *[see VII.C.1; II.C.3]*.
Rizatriptan (and other drugs in the class) are 5-HT_1-agonists. This mechanism results in three distinct and beneficial pharmacodynamic effects. First, it causes direct vasoconstriction, which returns the blood vessel to its preheadache diameter. Second, by acting on neuronal receptors, it inhibits the release of additional vasodilating and pain-transmitting substances, such as neurokinin A and substance P. Third, this action has been shown to have a direct antinociceptive action, preventing the firing of pain neurons directly. Therefore A, B, C, and E are correct answers that describe the benefit of rizatriptan. Platelet aggregation is inhibited by PGI and its analogs along with some of the NSAIDs but not by the 5-HT_1-agonists.

12. The correct answer is C *[see VII.E.2; II.D.1.b; VIII.C.1.a and b.(2)]*.
Alosetron is the agent useful in treating diarrhea-predominant IBS. By blocking the 5-HT_3-receptor, it inhibits the serotonin-induced increase in intestinal motility, thus slowing peristalsis and gut movement. Naratriptan, acting as a 5-HT_1-agonist, has little effect on GI motility. Misoprostol is a PGE_1 analog that causes diarrhea. Cetirizine is a second-generation antihistamine with minimal anticholinergic activity or effects on GI motility. Rabeprazole is a proton pump inhibitor used to decrease gastric acid secretion that has little effect on GI motility.

13. The correct answer is D *[see VIII.C.1.b; VIII.C.1.b.(4)]*.
The division between first- and second-generation antihistamines is the sedating properties of the first-generation agents that are a result of the antagonism of histamine receptors in the CNS. The second-generation agents do not access the CNS as easily as the first-generation agents. The second-generation agents are more selective for the H_1 receptor that reduces the anticholinergic side effects but does not affect sedation.

14. The correct answer is A *[see III.A]*.
Recall that in prostaglandin and thromboxane synthesis, COX-1 is responsible for much of the daily production of maintenance eicosanoids. COX-2, while also contributing to daily production of prostaglandins and thromboxanes, is more important in inflammation. COX-3 is the debated splice variant that may be the central source of prostaglandins that contributes to CNS function of the eicosanoids. Also recall that it is thromboxane that specifically has platelet-aggregating ability. Therefore, it is through inhibition of COX-1 and the subsequent decrease in thromboxane (not prostaglandin or leukotriene) synthesis that the antiplatelet effect of aspirin is effected.

15. The correct answer is D *[see III.D; IV.D.4]*.
Acetaminophen does not possess any antiplatelet activity or reduce the synthesis of gastric cytoprotective prostaglandins, so it does not interfere with platelet function or other antiplatelet therapies, and it would not be prone to cause gastric ulceration. In addition, the relationship between aspirin and Reye syndrome in children with viral infections does not apparently exist with acetaminophen, making it a safe antipyretic to use in those patients. Acetaminophen does have a significant risk of hepatotoxicity with overdose or chronic use, but, to date, no correlation to increased risk of cardiovascular disease has been identified.

16. The correct answer is D *[see IV.D.4]*.
Acetaminophen toxicity is characterized by a profound hepatotoxicity, which is mediated by a reactive intermediary formed on saturation and depletion of the normal metabolic pathways. This does not affect the vasculature (as with the ergot derivatives), thus no vasoconstriction is observed. Neither is severe GI upset evident (although mild GI upset may occur early in toxicity), nor does profound CNS stimulation occur, as it does with aspirin toxicity. Tinnitus is a sign of salicylate overdose. Therefore, answer D is correct.

17. The correct answer is A *[see V.B.2]*.
Allopurinol, probenecid, pegloticase, and febuxostat, although effective in preventing attacks of gouty arthritis by lowering circulating levels of uric acid, are not effective in treating the acute inflammatory situation that characterizes an acute attack. Colchicine, by inhibiting the migration of proinflammatory cells into the affected joint, will reduce the inflammatory process, thus alleviating the pain and edema associated with acute attacks of gouty arthritis.

18. The correct answer is C *[see V.C.3, D, and E]*.
Probenecid, as a uricosuric and promoting the excretion of uric acid, will effectively lower plasma concentration of urate. However, it also increases the urinary levels of uric acid. If this concentration exceeds the solubility constant of uric acid in the urine, then it may crystallize and precipitate out, causing stone formation or urinary lithiasis. For this reason, patients taking probenecid should always be counseled to drink copious amounts of water. Pegloticase and rasburicase are recombinant uricase enzymes that metabolize uric acid to allantoin, which is more water soluble.

19. The correct answer is B *[see III.A.2]*.
The roles of COX-1, -2, and -3 are reviewed in the answer to question 14. It is through their inhibition of inflammatory prostaglandin synthesis by inhibiting COX-2 that the NSAIDs exert their anti-inflammatory actions.

20. The correct answer is C *[see III.E.4]*.
The primary side effects that have been associated with the COX-2–specific inhibitors are gastrointestinal bleeding and, more recently, potentially fatal thrombotic events. The latter is thought to reflect a toxicodynamic effect that results from inhibition of vascular COX-2, which contributes to the daily control of platelet and/or vascular function. Severe ischemic colitis has been reported with alosetron; torsades de pointes, with older second-generation antihistaminics and cisapride, which is no longer available for use; acute liver failure, with acetaminophen overdose; and Churg-Strauss syndrome, with zafirlukast and corticosteroid withdrawal. None of these adverse drug reactions has been associated with the COX-2–specific inhibitors.

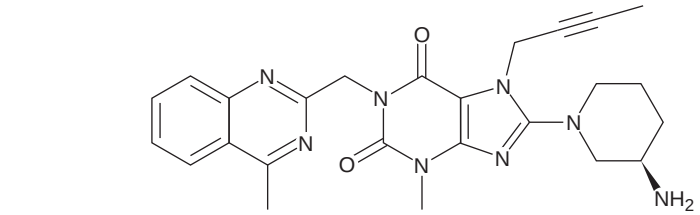
21. The correct answer is D *[see VIII.C.1.b.(2)]*.
Promethazine (Phenergan) is an H_1-receptor antagonist, which is useful as an antiemetic. Diphenhydramine, marketed as Dramamine, is also used as an antiemetic. Other antihistamines do not have significant antiemetic effects.

22. The correct answer is A *[see IX.A; VIII.C.2.a]*.
Rabeprazole is a proton pump inhibitor that works by covalently binding to the proton pump for an irreversible inhibition of acid secretion. This irreversible inhibition of the proton pump produces a longer term inhibition of gastric acid secretion compared to the H_2-receptor antagonists (i.e., cimetidine, ranitidine, famotidine, and nizatidine). Nedocromil is a mast cell stabilizer used ophthalmically for the treatment of allergic conjunctivitis, not acid reduction.

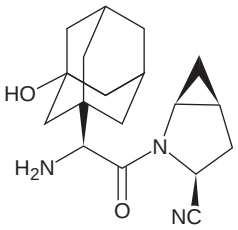
23. The correct answer is B *[see VII.C.1]*.
Sumatriptan (Imitrex) is a 5-HT_1-receptor agonist and indole derivative that causes direct vasoconstriction and decrease in the release of inflammatory and vasodilating substances that contributes to the efficacy of sumatriptan as a migraine headache medication. Both ergotamine and methylergonovine are ergot alkaloids that have 5-HT_1-receptor agonist activity as a contributor to its mechanism of action, but the ergotamine derivatives are not indoles. Granisetron (Kytril) is a 5-HT_3-receptor antagonist used to manage nausea and vomiting. Buspar is an anxiolytic agent that modulates the CNS serotonergic system but lacks efficacy in the treatment of migraine headaches.

24. The answer is D *[see IV; III.B]*.
Acetaminophen is not an NSAID because it has no anti-inflammatory properties. Acetaminophen does have antipyretic and analgesic activities similar to aspirin, the prototypical NSAID. Each of the other drugs listed are anti-inflammatory agents.

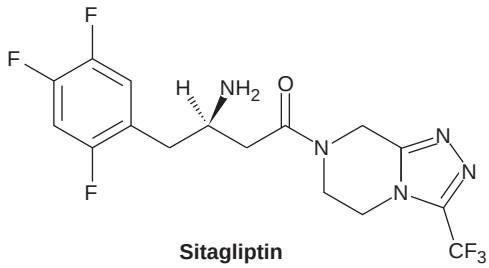
25. The answer is C *[see III.D.1–6; III.E.4]*.
There is an increased risk of cardiovascular events, which may include thrombotic events, myocardial infarction, or stroke, with the use of NSAIDs. This was also observed with the COX-2–specific NSAIDs. Adverse GI effects are also included in a black box warning in the NSAIDs. Each of the other side effects listed are associated with NSAID use but are not specifically addressed in a black box warning.



Linagliptin



Saxagliptin



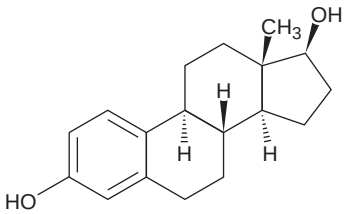
Sitagliptin

Figure 12-24. Dipeptidyl peptidase-IV (DPP-4) inhibitors linagliptin, saxagliptin, and sitagliptin.

Study Questions

Directions for questions 1–10: Each of the questions, statements, or incomplete statements in this section can be correctly answered or completed by **one** of the suggested answers or phrases. Choose the **best** answer.

1. The following structure is a hormone. It would be classified best as



(A) an estrogen.
(B) a progestin.
(C) an androgen.
(D) a gonadotropin.
(E) an adrenocorticosteroid.

2. All of the following substances are endogenous tropic hormones secreted by the pituitary gland *except*

(A) somatotropin.
(B) human chorionic gonadotropin (hCG).
(C) follicle-stimulating hormone (FSH).
(D) thyroid-stimulating hormone (TSH).
(E) adrenocorticotropic hormone (ACTH).

3. Which of the following substances, when present in urine, is the most likely positive sign of pregnancy?

(A) thyroid-stimulating hormone (TSH)
(B) adrenocorticotropic hormone (ACTH)
(C) human chorionic gonadotropin (hCG)
(D) interstitial cell-stimulating hormone (ICSH)
(E) isophane insulin (neutral protamine Hagedorn [NPH])

4. All of the following hormonal drugs possess a steroidal nucleus *except*

(A) ethinyl estradiol.
(B) norethindrone.
(C) liothyronine.
(D) prednisolone.
(E) fluoxymesterone.

5. Which of the following glucocorticoids produces the least sodium retention?

(A) cortisone
(B) hydrocortisone
(C) prednisolone
(D) dexamethasone
(E) fludrocortisone

6. Which of the following insulins can be administered intravenously?

(A) regular insulin (Humulin R)
(B) isophane insulin (neutral protamine Hagedorn; NPH; Humulin N)
(C) insulin lispromix (Humalog Mix 75/25)
(D) insulin glargine (Lantus)
(E) insulin glulisine (Levemir)

7. In comparing levothyroxine to liothyronine, which of the following statements is *not* correct?
   (A) Both levothyroxine and liothyronine are naturally occurring thyroid hormones.
   (B) Liothyronine can be converted in the peripheral circulation to levothyroxine.
   (C) Liothyronine is more potent than levothyroxine.
   (D) The plasma concentration of liothyronine is less than that of levothyroxine.
   (E) Liothyronine has a shorter duration of action than levothyroxine.

8. Which of the following classes of compounds directly stimulates the release of insulin from pancreatic β-cells?
   (A) progestins
   (B) biguanides
   (C) α-glucosidase inhibitors
   (D) DPP-4 inhibitors
   (E) sulfonylureas

9. Which of the following compounds is incorrectly matched with its mechanism of action?
   (A) flutamide: competitively blocks the binding of androgens to their receptor
   (B) finasteride: inhibits 5α-reductase
   (C) miglitol: inhibits α-glucosidase
   (D) pioglitazone: competitively blocks the binding of estrogens to their receptor
   (E) anastrozole: inhibits aromatase

10. Which of the following compounds is incorrectly matched with one of its therapeutic uses?
    (A) raloxifene: ovulation induction
    (B) metformin: type 2 diabetes mellitus
    (C) finasteride: benign prostatic hyperplasia
    (D) propylthiouracil: hyperthyroidism
    (E) tamoxifen: estrogen-dependent breast cancer

11. Which of the following compounds would be most likely to cause hypoglycemia?
    (A) miglitol (Glyset)
    (B) metformin (Glucophage)
    (C) pioglitazone (Actos)
    (D) sitagliptin (Januvia)
    (E) glipizide (Glucotrol)

12. Which of the following compounds has a mechanism of action most similar to exenatide (Byetta)?
    (A) insulin (Humulin R)
    (B) saxagliptin (Onglyza)
    (C) pramlintide (Symlin)
    (D) repaglinide (Prandin)
    (E) metformin (Glucophage)

13. Anastrozole (Arimidex) as to aromatase as _____ is to 5α-reductase.
    (A) flutamide (Eulexin)
    (B) tamoxifen (Nolvadex)
    (C) mifepristone (Mifeprex)
    (D) finasteride (Proscar)
    (E) testosterone

14. All of the following can be used to treat hypothyroid *except*
    (A) thyroid USP (Armour Thyroid).
    (B) liotrix (Thyrolar).
    (C) methimazole (Tapazole).
    (D) levothyroxine (Synthroid).
    (E) liothyronine (Cytomel).

Directions for questions 15–17: The questions and incomplete statements in this section can be correctly answered or completed by **one or more** of the suggested answers. Choose the answer, **A–E.**

A if **I only** is correct
B if **III only** is correct
C if **I and II** are correct
D if **II and III** are correct
E if **I, II, and III** are correct

15. Hormones that form lipophilic esters without prior structural modifications include
    I. hydrocortisone.
    II. testosterone.
    III. progesterone.

16. Insulin preparations that contain a modifying protein include
    I. insulin glargine.
    II. regular insulin.
    III. isophane insulin (neutral protamine Hagedorn [NPH]).

17. Agents used to treat hypercalcemia include
    I vitamin D.
    II calcitonin.
    III aledronate.

Directions for questions 18–20: Each statement in this section is most closely related to **one** of the following hormones. The hormones may be used more than once or not at all. Choose the **best** answer, **A–E.**

A Testosterone
B Insulin
C Corticotropin
D Estradiol
E Vasopressin

18. Secreted by pancreatic β-cells to facilitate glucose and amino acid transport for normal cellular metabolic processes.

19. Initiates and controls male sexual development and maintains the integrity of the male reproductive system.

20. Promotes the reabsorption of water at the renal collecting tubule.

Directions for questions 21–23: Each statement in this section is most closely related to **one** of the following drug classes. The drug classes may be used more than once or not at all. Choose the **best** answer, **A–E.**

A Antithyroid agents
B Sulfonylureas
C Adrenocorticosteroids
D Progestins
E Androgens

21. Peptic ulceration and gastrointestinal hemorrhage; hyperglycemia, hypertension, and edema; "buffalo hump" and "moon face"; psychological disturbances; and increased susceptibility to infection

22. Agranulocytosis and other blood dyscrasias, cholestatic jaundice, nausea and vomiting, hypoglycemia, and hypersensitivity reactions

23. Rare adverse effects include drug fever, hepatitis, nephritis, and systemic lupus erythematosus–like syndrome.

Answers and Explanations

1. The answer is A *[see III.A.1; Figure 12-2]***.**
Ring A is aromatic. Because the only type of steroidal hormone that has an aromatic A-ring is an estrogen, this structure represents an estrogen. Other structural characteristics of estrogens include the fact that the structure contains 18 carbon atoms; thus it is an estrane and contains a β-alcohol group in position 17.

2. The answer is B *[see II.B.1–4]***.**
hCG is produced by placental tissue and serves to stimulate the secretion of progesterone during pregnancy. Growth hormone (somatotropin), FSH, TSH, and ACTH are all secreted by the anterior pituitary gland.

3. The answer is C *[see II.B.4.c]***.**
hCG is a proteinaceous tropic hormone that is secreted by chorionic (e.g., placental) tissue. Thus, hCG is present in the urine only after conception has occurred.

4. The answer is C *[see III.A.1; III.D.1; III.F.2; IV.B.1.b.(2); Figures 12-12, 12-17, and 12-18]***.**
Liothyronine is a thyroid hormone. Thyroid hormones consist of iodinated aromatic amino acids and are not steroidal in nature. Ethinyl estradiol is a steroidal estrogen, norethindrone is a steroidal 19-norprogestin, prednisolone is an adrenocorticosteroid, and fluoxymesterone is a steroidal androgen.

5. The answer is D *[see IV.B.1.b.(4); Figure 12-17]***.**
Glucocorticoids have varying degrees of mineralocorticoid activity. This mineralocorticoid activity, which can result in sodium and fluid retention, can be blocked by the introduction of a methyl or hydroxyl group in position 16 of the steroidal nucleus. Dexamethasone has a 16α-methyl substituent.

6. The answer is A *[see VII.A.1.a.(2)]***.**
Most insulin preparations are suspensions; thus, they contain particulate matter. Only clear solutions may be administered intravenously. Regular insulin, which consists of water-soluble crystalline zinc insulin, is therefore suitable for intravenous administration. Insulin aspart (Novolog) is also approved for intravenous administration. All other insulin preparations are normally injected subcutaneously.

7. The answer is B *[see V.A.1]***.**
The thyroid gland produces both levothyroxine (T_4) and liothyronine (T_3). The natural ratio of these compounds is 4:1 in favor of levothyroxine; therefore, liothyronine is normally present at a lower concentration than levothyroxine. Liothyronine is more potent than levothyroxine, but has a shorter duration of action. Peripheral conversion involves deiodination; thus, levothyroxine is converted to liothyronine. The reverse process is not possible.

8. The answer is E *[see VII.B.1.a; VII.B.3.a; VII.B.5.a; VII.B.6.a]***.**
Of the five classes of compounds listed, only biguanides, α-glucosidase inhibitors, and sulfonylureas are used in the treatment of type 2 diabetes mellitus. These classes provide their beneficial effects through different mechanisms of action. Biguanides enhance the peripheral use of insulin, suppress gluconeogenesis, and are often referred to as antihyperglycemic agents. α-Glucosidase inhibitors decrease the absorption of glucose. Sulfonylureas and the structurally unrelated compounds, repaglinide and nateglinide, stimulate the secretion of insulin from pancreatic β-cells.

9. **The answer is D** *[see III.C.1; III.G.2; III.H.1; VII.B.4.a; VII.B.5]*.
Pioglitazone does not interact with estrogen receptors. It is an oral antidiabetic agent that produces its effects by binding to nuclear PPARs involved in transcription of insulin-responsive genes and in regulation of adipocyte differentiation and lipid metabolism. The other four agents are correctly matched to their mechanisms.

10. **The answer is A** *[see III.B.2.a–c; III.H.1; V.G.3; VI.F.4; VII.B.3.a–b]*.
Raloxifene is a SERM and is not used to treat ovulation induction. Clomiphene is currently the only antiestrogen that is approved for the induction of ovulation in women who have ovulation failure. Instead, because of its ability to reduce bone resorption and decrease bone turnover, it is used for the prevention of osteoporosis. All of the other four compounds are correctly matched to their therapeutic use. Finasteride is also used to treat androgenic alopecia.

11. **The answer is E** *[see VII.B.1.c, 3.c, 4.c, 5.b, and 6.b]*.
Of all the oral antidiabetics listed, only glipizide, a sulfonylurea, directly stimulates the release of insulin to cause hypoglycemia. The other agents are frequently classified as euglycemic agents (i.e., miglitol, sitagliptin) or insulin sensitizers (i.e., metformin, pioglitazone) that do not frequently cause hypoglycemia.

12. **The answer is B** *[see VII.A.2.a; VII.B.6]*.
Exenatide (Byetta) is an analog of the incretin GLP-1, whereas saxagliptin (Onglyza) is an inhibitor of DDP4 that is responsible for the metabolism of endogenous GLP-1. Each of the other agents has a mechanism of action that does not directly influence the activity or duration of action of the incretins.

13. **The answer is D** *[see III.C.1; III.H.1]*.
Anastrozole inhibits the enzyme aromatase responsible for the synthesis of estrogen. Finasteride inhibits the enzyme 5α-reductase, which is responsible for the conversion of testosterone to DHT. The other agents are receptor antagonists (flutamide, tamoxifen, and mifepristone) or natural agonists (testosterone).

14. **The answer is C** *[see V.B.1–4; V.G.3.a]*.
Methimazole is a thioamide that inhibits the synthesis of thyroid hormones and therefore would not be useful in the treatment of hypothyroid. Thyroid USP, litrix, levothyroxine, and liothyronine are various forms of the two thyroid hormones (T_4 and T_3) that can decrease the symptoms of hypothyroid.

15. **The answer is C (I, II)** *[see Figures 12-7, 12-12, and 12-17]*.
Hydrocortisone has a 21-hydroxyl group, and testosterone has a 17-hydroxyl group; therefore, both of these agents can form esters (e.g., hydrocortisone acetate, testosterone propionate). Progesterone does not have any alcohol groups in its molecule; therefore, it cannot directly form any esters.

16. **The answer is B (III)** *[see VII.A.1.a.(3)]*.
Regular insulin, which is a rapid-acting insulin preparation, contains only zinc insulin crystals. Insulin glargine is a synthetic insulin that has been structurally altered at two sites. The structural alterations cause a decreased solubility and an increased duration of action; however, no protein modifiers are added to this preparation. NPH insulin contains protamine, a strongly basic protein. The protamine reduces the water solubility of zinc insulin and lengthens its duration of action. Isophane insulin is classified as an intermediate-acting insulin preparation, having a duration of action of about 24 hrs.

17. **The answer is D (II, III)** *[see VI.C.3; VI.D; VI.E.1]*.
A common side effect of vitamin D is hypercalcemia due to increased calcium absorption from the GI track and increased calcium retention from the kidney. Calcitonin can be used to treat hypercalcemia because it increases the renal excretion of calcium. Aledronate decreases the resorption of bone calcium, which is useful in the treatment of hypercalcemia.

18. **The answer is B** *[see VI.A.1]*.

19. **The answer is A** *[see III.F]*.

20. **The answer is E** *[see II.A.2]*.
Insulin is required for the proper use of glucose and the transport of glucose and amino acids across cell membranes. Testosterone, which is produced principally from the Leydig cells of the testes, is responsible for male sexual characteristics. Vasopressin is secreted from the posterior pituitary and is sometimes referred to as an antidiuretic hormone.

21. **The answer is C** *[see IV.B.3]*.

22. **The answer is B** *[see VII.B.1.c]*.

23. **The answer is A** *[see V.G.3.b]*.
Exogenously administered adrenocorticosteroids are effective anti-inflammatory agents but give rise to a wide range of metabolic and immunosuppressive effects that result in severe adverse effects. Sulfonylureas are oral antidiabetic agents and can cause blood dyscrasias, impaired liver function, nausea/vomiting, hypoglycemia, and hypersensitivity reactions. The antithyroid agents are associated with rare adverse effects, including drug fever, hepatitis, nephritis, and systemic lupus erythematosus–like syndrome.

Study Questions

Directions for questions 1–2: Each question contains three suggested answers, of which **one** or more is correct. Choose the answer, **A–E**.

A **I only** is correct
B **III only** is correct
C **I and II** are correct
D **II and III** are correct
E **I, II, and III** are correct

1. Drug interactions may be classed as

I. pharmacokinetic interactions
II. pharmacodynamic interactions
III. pharmaceutical interactions

2. Situations that can potentially lead to drug interactions include

I. multiple-drug therapy
II. multiple prescribers
III. patient compliance

Directions for questions 3–10: Each question is followed by four suggested answers. Select the **one** lettered answer that is the **best** response to the question.

3. Which of the following statements regarding drug interactions is true?

(A) All drug interactions can potentially cause an adverse response in the patient.
(B) The clinical significance for each potential drug interaction must be considered individually.
(C) A precipitant drug that inhibits the metabolism of the object drug causes a more serious drug interaction compared to a precipitant drug causing an increase in the bioavailability of the object drug.
(D) If the patient is prescribed drugs that can potentially interact, the prescriber should be called, and a different precipitant drug should be suggested.

4. A patient on indinavir antiretroviral therapy (ART) begins taking St. John's wort for depression and suffers unexpected reduction in CD4 count. This is most likely due to

(A) pharmacodynamic interaction producing additive toxicity.
(B) pharmacodynamic interaction producing antagonistic therapeutic effect.
(C) enzyme induction by St. John's wort causing increased metabolism of ART.
(D) enzyme inhibition by St. John's wort causing toxic levels of ART.

5. Which of the following is a valid therapeutic use of a drug interaction?

(A) The use of probenecid with penicillin G to prolong high penicillin levels to treat a sexually transmitted disease
(B) Giving aspirin with warfarin to enhance anticoagulation
(C) Instructing the patient to take levofloxacin with milk or antacid to decrease GI intolerance to oral therapy
(D) The treatment of depression with a combination of citalopram and a MAOI

6. Which of the following is not a harmful food–drug interaction?

(A) Raw green salads for patients on warfarin deep vein thrombosis (DVT) prophylaxis
(B) Grapefruit juice and cyclosporine to prevent graft-versus-host rejection of a transplanted kidney
(C) Omeprazole beads in applesauce for a patient with problems swallowing capsules secondary to gastroesophageal reflux disease (GERD)
(D) Milk with doxycycline to treat *Helicobacter pylori*

7. Which of the following statements regarding pharmacogenetic polymorphisms is not true?

(A) An EM taking metoprolol for hypertension begins to take OTC Tagamet® regularly for heartburn. He or she is at increased risk for bradycardia and cardiac arrhythmias.
(B) An EM taking methadone begins taking Tegretol® for neuropathic pain. He or she is at risk for treatment failure and pain crisis.
(C) A PM taking atorvastatin for hyperlipidemia is placed on ketoconazole for a fungal infection. He or she is at increased risk for myalgia and rhabdomyolysis.
(D) A PM taking metoprolol for tachycardia begins taking Benadryl® for sleep. He or she is not at risk for significant bradycardia and cardiac block.

8. Asians are at greatest risk of all racial groups for genetic polymorphism in which one of the following CYP450 isoenzymes?

(A) CYP2D6
(B) CYP3A4
(C) CYP2C19
(D) CYP1A2

9. Which of the following statements regarding pharmacogenetics is false?
   (A) Polymorphisms occur only in the CYP450 hepatic enzymes.
   (B) Polymorphisms result in many variations of an isoenzyme.
   (C) The overall expression of the combined alleles is the phenotype of the enzyme.
   (D) Single-nucleotide polymorphisms (SNPs) can occur as errors of transcription, defective splicing, start and stop codones, and amino acid changes.

10. Which of the following statements regarding allele polymorphisms is false?
   (A) Wild-type alleles encode for "normal" metabolism.
   (B) Ultra-rapid metabolizers (UMs) have two or more amplified alleles.
   (C) Poor metabolizers (PMs) carry one defective allele and one amplified allele.
   (D) Extensive metabolizers (EMs) with heterozygous alleles have slower metabolism than metabolizers with homozygous alleles.

Answers and Explanations

1. **The answer is E** *[see I.B]*.
Most drug interactions in vivo are caused by pharmacokinetic and pharmacodynamic interactions. Pharmaceutical interactions can occur during extemporaneous compounding, preparation of IV admixtures, and improper dosing, as in the case of giving aspirin with acidic juices (e.g., orange, cranberry).

2. **The answer is E** *[see IV.A.1–3]*.
Patient profiles might not contain all the drug history information of the patient. Patients who take nonprescription (OTC) medications and who go to several different physicians or purchase drugs at various pharmacies may neglect to inform the pharmacist of all the medications being taken.

3. **The answer is B** *[see IV.B]*.
Not all drug interactions are clinically significant. Some potential clinically significant drug interactions can be prevented by proper patient instruction and compliance. The potential for a clinically significant drug interaction should be documented before calling a physician concerning the prescribed medication.

4. **The answer is C** *[see II.E.1.c; Table 13-3]*.
St. John's wort induces CYP3A4 isoenzymes, increasing the metabolism of the indinavir and resulting in low indinavir levels and therapeutic failure of ART. St. John's wort itself has no direct effect on CD4.

5. **The answer is A** *[see II.E.2; Table 13-4]*.
Probenecid is given with penicillin and some cephalosporins in the treatment of some sexually transmitted diseases. Probenecid competes with penicillins for renal elimination, prolonging the half-life of the penicillin. Aspirin and warfarin cause additive anticoagulation, leading to bleeding. Levofloxacin taken with milk to decrease GI irritation causes complexation of the levofloxacin with the calcium in the milk and results in decreased levofloxacin to be available. Concomitant treatment of depression of citalopram and MAOI results in serotonin syndrome, an additive toxicity.

6. **The answer is C** *[see V.B]*.
Omeprazole beads are enteric coated. Giving an enteric-coated bead with an acidic food such as applesauce preserves the enteric coating and allows the drug to pass intact through the acidic stomach environment and into the basic duodenum environment where it is absorbed. The result is improved drug absorption and decreased drug destruction in the acidic stomach than if the beads were not in an acidic food.

7. **The answer is C** *[see VII.C.2]*.
The PM already has inhibited metabolism of atorvastatin. Additional inhibition will not significantly increase the blood levels of atorvastatin. Therefore, dose-related toxicity is unlikely. The EM taking metoprolol and Tagamet® (cimetidine) will show a greater increase in the metoprolol levels due to the exaggerated effect of the inhibitor in EM. The EM taking methadone and Tegretol® (carbamazepine) will have increased enzyme induction and metabolism of the methadone, lowering methadone levels and putting the patient at risk for treatment failure of his pain. The PM taking metoprolol and Benadryl® (diphenhydramine) will show inhibition of the metabolism of the metoprolol and increased levels of metoprolol, leading to a higher risk of bradycardia and cardiac block.

8. **The answer is A** *[see VII.A.3]*.
Polymorphism is highest in the CYP2D6 isoenzyme in Asians, reaching incidence of greater than 50%.

9. **The answer is A** *[see VII.A.2]*.
Polymorphisms can occur in any enzyme system including mixed oxidase and *N*-acetyl transferase systems as well as the CYP450 hepatic enzyme system.

10. **The answer is C** *[see VII.B.3.a]*.
PMs carry a normal allele combined with a defective or deleted allele.

Study Questions

Directions: Each of the numbered items or incomplete statements in this section is followed by answers or completions of the statement. Select the **one** lettered answer or completion that is **best** in each case.

1. Primary literature includes which of the following?

(A) Original clinical trials
(B) Letters to the editor
(C) Systematic reviews
(D) Special reports

2. Which of the following statements is TRUE regarding tertiary resources?

(A) Tertiary resources include textbooks and computer databases.
(B) Textbooks typically include the most recent literature and/or information.
(C) Tertiary resources do not typically include a bibliography.
(D) The credentials of the editor of a tertiary resource are not considered important.

3. Which of the following should NOT be done when developing an effective search strategy?

(A) Determine if the question is clinical or research-related
(B) Identify appropriate search terms
(C) Disregard other medications the patient may be taking
(D) Ascertain if the inquirer is a health care professional

4. Which of the following resources would be appropriate for identifying a drug manufactured in a foreign country?

(A) *Martindale: The Complete Drug Reference*
(B) *Clinical Pharmacology*
(C) *Trissel's Stability of Compounded Formulations*
(D) *AHFS*

5. Which of the following resources would be appropriate for identifying the capsule with the imprint code of Watson 405?

I. *Facts and Comparison E Answers*
II. *Lexi-Drugs ID (Lexicomp Online)*
III. *Myler's Side Effects of Drugs*

(A) **I** and **II** only
(B) **I** and **III** only
(C) **II** and **III** only

6. Which of the following resources would be appropriate for determining the adverse effects of ginkgo biloba?

I. *Natural Medicines Comprehensive Database*
II. *Facts and Comparisons E Answers*
III. *Natural Standards*
IV. *Handbook on Injectable Drugs*

(A) **I** and **II** only
(B) **II** and **III** only
(C) **I**, **II**, and **III** only
(D) **II** and **IV** only

7. Which of the following resources would be appropriate for determining if Levaquin is compatible or stable in D_5W?

(A) *Evaluations of Drug Interactions (EDI)*
(B) *Trissel's Handbook on Injectable Drugs*
(C) *Red Book*
(D) *Nonprescription Products Therapeutics*

8. Which of the following resources can be used to determine unapproved uses of drugs?

(A) *Clinical Pharmacology*
(B) *PDR*
(C) *Index Nominum*
(D) *King's Guide to Parenteral Admixtures*

9. Which of the following is *not* important when evaluating a clinical study?

(A) Study objective
(B) Patient demographics
(C) Drug administration
(D) Number of authors

10. Which of the following statements is TRUE?

(A) Prospective studies evaluate events that have already occurred.
(B) Retrospective studies are useful for evaluating rare diseases.
(C) A run-in phase typically increases variation.
(D) Crossover design allows patients to undergo only one type of treatment.

11. Which of the following resources would be appropriate in evaluating the drug interaction between tramadol and citalopram?

I. *Evaluations of Drug Interactions (EDI)*
II. *Lexi-Interact (Lexicomp Online)*
III. *Trissel's Stability of Compounded Formulations*

A. **I** and **II** only
B. **I** and **III** only
C. **II** and **III** only
D. **I**, **II**, and **III**

12. Which of the following resources would be appropriate for determining whether ranitidine causes edema?

I. *Red Book*
II. *PDR*
III. *Myler's Side Effects of Drugs*

A. **I** and **II**
B. **I** and **III** only
C. **II** and **III** only
D. **I**, **II**, and **III**

13. What resource should be used when searching for the most current clinical trials on the use of atenolol for hypertension?

A. *King's Guide to Parenteral Admixture*
B. Medline
C. *American Hospital Formulary Service (AHFS)*
D. *The American Drug Index*

14. Which of the following resources would be appropriate for evaluating information on orphan drugs?

I. *Drug Facts and Comparisons/Facts and Comparison E Answers*
II. The FDA Office of Orphan Products Development (OOPD)
III. The National Institutes of Health (NIH) Office of Rare Diseases

A. **I** and **II** only
B. **I** and **III** only
C. **II** and **III** only
D. **I**, **II**, and **III**

15. Which of the following control methods are used in clinical trials to reduce bias?

I. Random allocation
II. Double-blind trial design
III. Matching dummies

A. **I** and **II** only
B. **I** and **III** only
C. **II** and **III** only
D. **I**, **II**, and **III**

Answers and Explanations

1. The answer is A *[see II.A.3]***.**
All material included in a journal is not considered a primary resource. Original clinical trials are considered primary literature; however, review articles, articles of opinion, correspondence, and special reports are not.

2. The answer is A *[see II, II.C]***.**
Tertiary resources include both textbooks and databases. Information available in textbooks may not include the most recent data because it could take several years to publish. A bibliography and reference citations should be present in both textbooks and databases so that the reader may refer to a specific reference if desired. Additionally, the areas of expertise for the author and/or publisher should be evaluated when using a tertiary resource.

3. The answer is C *[see V.A; V.C; VII.B; VII.D]***.**
One should determine whether the question is related to a clinical scenario or is research related to develop an effective search strategy. Appropriate index terms should be identified to assist in the literature search. Other medications, including herbal products, and disease states should be taken into consideration. The background of the inquirer should be determined so that the response can be tailored to the specific inquirer.

4. The answer is A *[see IV.B.2.a]***.**
Martindale: The Complete Drug Reference is one resource that may be used to identify a drug manufactured in a foreign country. Other resources for identifying drugs manufactured in a foreign country include *Index Nominum, Lexi-Drugs International Online (Lexicomp Online)*, and the *USP Dictionary of United States Adopted Names (USAN) and International Drug Names*. *Clinical Pharmacology, Trissel's Stability of Compounded Formulations,* and *AHFS* do not contain this type of information.

5. The answer is A *[see IV.B.5]***.**
For an unknown drug, the physical characteristics, including an imprint code, may be used to identify the drug. Several resources, including *Facts and Comparison E Answers* and *Lexi-Drugs Online (Lexicomp Online)* may be used.

6. **The answer is C** *[see IV.B.6]*.
For a natural product, the following resources are available: *Facts and Comparison E Answers*, *Natural Medicines Comprehensive Database*, *Natural Standards*, and *Natural Products Database (Lexicomp Online)*.

7. **The answer is B** *[see V.C.12]*.
The stability of a drug, the compatibility of a drug with other drugs and/or appropriate containers, and proper administration techniques are included in *Trissel's Handbook on Injectable Drugs*, *King's Guide to Parenteral Admixtures*, and *Trissel's Stability of Compounded Formulations*. Databases such as *Clinical Pharmacology*, *Micromedex*, *Lexicomp Online*, and *Facts and Comparison E Answers* may also be used for these types of questions.

8. **The answer is A** *[see V.C.2.b]*.
Unapproved uses of drugs can be found in *Clinical Pharmacology*. This information is not available in the *PDR*, *Index Nominum*, or *King's Guide to Parenteral Admixtures*.

9. **The answer is D** *[see VI.A; VI.B; VI.C]*.
A critical assessment of available information is important in developing an appropriate response. The study objective, the study subjects (via demographics and inclusion and exclusion criteria), and drug administration should be evaluated.

10. **The answer is B** *[see VI.E]*.
Retrospective studies evaluate events that have already occurred and are useful for studying rare diseases. Prospective studies follow identified patients forward in time to answer a specific question. Crossover design allows for each patient group to undergo each type of treatment. A run-in phase is a control measure used to reduce variation.

11. **The answer is A** *[see V.C.8.f]*.
The following resources may be helpful when evaluating drug–drug interactions: *Drug Interaction Facts*, *Hansten's Drug Interaction Analysis and Management*, *Evaluations of Drug Interactions (EDI)*, and a general drug reference such as the *PDR*. Medline may also be useful in identifying reports of drug interactions documented in the primary literature.

12. **The answer is C** *[see V.C.7.d]*.
Adverse drug reactions are documented in the *PDR*/package insert, *Myler's Side Effects of Drugs*, and in databases such as *Clinical Pharmacology*, *Micromedex*, *Facts and Comparison E Answers*, and *Lexicomp Online*. Additionally, Medline may be used to search the primary literature for case reports of adverse drug reactions.

13. **The answer is B** *[see II.B; Table 14-1]*.
Indexing and abstracting services, such as Medline, are helpful tools for searching the primary literature for specific information, data, citations, and articles. It is important to remember, however, that each indexing or abstracting service reviews a finite number of journals. Thus, multiple services must be used to conduct a thorough search of the available literature.

14. **The answer is D** *[see IV.B.4]*.
Orphan drugs are used to prevent or treat rare diseases. The following resources can be used for information on these drugs: *Drug Facts and Comparisons/Facts and Comparison E Answers*, The FDA Office of Orphan Products Development (OOPD), and The National Institutes of Health Office of Rare Disorders.

15. **The answer is D** *[see VI.E]*.
The methods used when completing a study are important when determining whether the results of the study are reliable and valid. Controls that are often used to reduce bias include blind assessment, patient blinding, random allocation, matching placebos, and controlled comparisons.

Study Questions*

1. Which measure(s) of central tendency is/are sensitive to outliers?

(A) Mean
(B) Median
(C) Mode

2. For what type of data can standard deviation (SD) be used?

(A) Parametric data
(B) Ordinal data
(C) Nominal data

3. Which of the following is correct regarding measures of variability?

(A) Range can be both descriptive and inferential.
(B) Standard error of the mean (SEM) is always larger than SD.
(C) All values contained in a confidence interval (CI) are statistically possible.
(D) CI is a descriptive measure only.

4. A study was performed to determine the effect of a new antipsychotic agent (Drug A) on psychosis in patients with underlying schizophrenia as compared to placebo. A sample size of 300 patients was calculated to be needed based on an α of 0.05 and a β of 0.2. The double-blind, parallel, superiority trial was performed in 350 patients for 8 weeks. At the end of the 8-week period, the new antipsychotic agent was found to induce remission in 20% of patients as compared to 19% in the placebo group ($P = 0.04$). Which of the following statements is true based on the results of the study?

(A) Drug A was found to have a statistically significant and clinically significant difference on remission of psychosis as compared to placebo.
(B) Drug A was found to have a statistically significant difference but not a clinically significant difference on remission of psychosis as compared to placebo.
(C) Drug A was found to have a clinically significant difference but not a statistically significant difference on remission of psychosis as compared to placebo.
(D) Drug A was not found to have a clinically or statistically significant difference on remission of psychosis as compared to placebo.

(For the next two questions) A study of the effects of bupropion (Zyban) versus nicotine gum (Nicorette) on the primary end point of change in the number of cigarettes smoked per day in a parallel, randomized trial. The investigators plan to include 450 subjects (150 in each arm) to reach statistical significance based on a β of 0.2 and α of 0.05.

5. Which of the following statistical tests would be the most appropriate? (Hint: assume no confounders)

(A) One-way ANOVA
(B) Chi-square (χ^2)
(C) Fisher exact test
(D) Friedman test
(E) *t* test

6. Which of the following statistical tests would be the most appropriate if the study had evaluated three groups instead of only two? (i.e., bupropion [Zyban] vs. nicotine patches [Nicoderm CQ] vs. nicotine gum [Nicorette])

(A) One-way ANOVA
(B) Chi-square (χ^2)
(C) Fisher exact test
(D) Friedman test
(E) Student's *t* test

7. A study is designed to evaluate the change in blood pressure lowering between metoprolol tartrate (Lopressor®) and metoprolol succinate (Toprol XL®). The investigators decide to perform a parallel trial in 200 patients. There were significant baseline differences between the groups in diet and exercise. Which of the following statistical tests would be most appropriate?

(A) One-way ANOVA
(B) Chi-square (χ^2)
(C) Fisher exact test
(D) ANCOVA
(E) Student's *t* test

* These study questions were composed by Melanie Pound, PharmD, BCPS and Rebekah Grube, PharmD, BCPS.

8. The makers of eplerenone (Inspra) want to design a study to compare their medication to the current standard of spironolactone (Aldactone) in the treatment of heart failure. They decide to perform a parallel trial of the two agents in 2000 patients with NYHA classes II to IV heart failure over 2 years. The primary end point is mortality. Which of the following statistical tests would be most appropriate to use?

(A) ANOVA
(B) Fisher exact test
(C) Chi-square (χ^2)
(D) Mann-Whitney U test
(E) Student's *t* test

9. A retrospective study produces correlation/regression analysis between a high sodium intake ($>$ 2.4 g/day) and hypertension (HTN) reporting an $r = 0.45$. Which of the following is correct?

(A) 20% of HTN may be explained by high sodium intake.
(B) 20% of HTN is not explained by high sodium intake.
(C) 80% of HTN is explained by high sodium intake.
(D) 55% of HTN is not explained by high sodium intake.
(E) 45% of HTN may be explained by high sodium intake.

10. A study was performed to evaluate a possible correlation between the use of the herbal product Goldenseal and changes in pain relief (based on pain scale scores). Which type of correlation analysis should be used in this trial?

(A) Pearson
(B) Spearman
(C) Linear
(D) Cox

(For the next two questions) In the RE-LY trial, dabigatran (Pradaxa) was compared with warfarin (Coumadin) for the prevention of cerebrovascular accident (CVA) in atrial fibrillation (AF) patients. The primary outcome in this trial was CVA or systemic thromboembolism (TE). The results are presented as follows:

End point	Dabigatran ($n = 6076$)	Warfarin ($n = 6022$)	RR, 95% CI
CVA or TE	134 (2.2%)	159 (2.6%)	0.66 (0.53–0.82)
MI	89 (1.5%)	63 (1.0%)	1.38 (1.00–1.91)

11. What can be concluded about the outcome "CVA or TE"?

(A) Dabigatran (Pradaxa) has a clinically significant lower risk than warfarin (Coumadin), although it is not statistically significant because the CI does not include 1.
(B) Dabigatran (Pradaxa) has a clinically significant lower risk than warfarin (Coumadin), although it is not statistically significant because the CI does not include 0.
(C) Dabigatran (Pradaxa) has a clinically significant higher risk than warfarin (Coumadin), and it is statistically significant because the CI does not include 0.
(D) Dabigatran (Pradaxa) has a clinically significant lower risk than warfarin (Coumadin), and it is statistically significant because the CI does not include 1.

12. What can be concluded about the outcome "MI"?

(A) Dabigatran (Pradaxa) has a higher MI risk than warfarin (Coumadin), although it is not statistically significant because the CI includes 1.
(B) Dabigatran (Pradaxa) has a higher MI risk than warfarin (Coumadin), although it is not statistically significant because the CI does not include 0.
(C) Dabigatran (Pradaxa) has a higher MI risk than warfarin (Coumadin), and it is statistically significant because the CI includes 1.
(D) Dabigatran (Pradaxa) has a higher MI risk than warfarin (Coumadin), and it is statistically significant because the CI does not include 0.

13. A researcher was interested in examining the association between postmenopausal hormone replacement therapy (HRT) and development of heart disease. All women who were characterized as postmenopausal were approached regarding their interest in participating in the study by answering a questionnaire annually regarding their medication use and medical conditions. Of the 16,168 women who provided consent, the average length of follow-up was 12.5 years (range, 6 to 16 years). Which of the following best describes the study design?

(A) Case-control study
(B) Prospective cohort study
(C) Randomized controlled trial
(D) Meta-analysis

14. An investigator wishes to study a new drug for the treatment of hypertension in patients with diabetes. What is the best type of trial design the investigator should use for determining causality in this particular study?
    (A) A case-control study
    (B) A prospective cohort study
    (C) A prospective, randomized, placebo-controlled trial
    (D) A prospective, randomized, standard-of-care comparison trial
    (E) A meta-analysis

15. Which of the following would be appropriate for a crossover design study?
    (A) Effects of Drug A versus Drug B on hypertension in 100 patients
    (B) Effects of varenicline (Chantix) compared to placebo on smoking cessation
    (C) Effects of fluticasone/salmeterol (Advair) and budesonide/formoterol (Symbicort) on asthma exacerbations
    (D) Effects of hydralazine and hydrochlorothiazide (Microzide) on all-cause mortality

Answers and Explanations

1. **The answer is A** *[see II.A]*.
   Mean is the correct answer because it is affected by outliers. Median and mode are incorrect because they are not affected by outliers.

2. **The answer is A** *[see III.D]*.
   Parametric (aka continuous) data is correct. Standard deviation is only meaningful for parametric data. It is not meaningful for nominal data. Measures of variability are not meaningful for nominal data. Standard deviation is usually not meaningful for ordinal data. Interquartile range is the preferred measure of variability for ordinal data.

3. **The answer is C** *[see III.F]*.
   Answer C is correct because all values within a CI are statistically possible. Answer A is incorrect because range is descriptive only. Range is not inferential because one is unable to "infer" statistical significance for a data set based on range. Answer B is incorrect because SEM is always smaller than SD. Answer D is incorrect because CI is not only descriptive but also inferential since one is able to "infer" statistical significance for a data set based on CI.

4. **The answer is B** *[see IV.E]*.
   Answer B is correct. The difference was statistically significant because the *P* value was .04. Based on this *P* value, there is a 4% chance that a type 1 error occurred, which is less than the prespecified acceptable risk of 5% (preset α was 0.05 or 5%). However, the difference was not clinically meaningful because there was only a 1% difference in the primary end point (induction of remission) between the treatment groups. For these reasons, answers A, C, and D are incorrect.

5. **The answer is E** *[see V.A–B]*.
   Answer E is correct because a *t* test is the test of choice for evaluating statistical differences in parametric data (change in the number of cigarettes smoked daily) when only two groups are being evaluated and there are no detected confounders. Answer A is incorrect because one-way ANOVA is used for testing three or more groups. Answers B and C are incorrect because chi-square and Fisher exact test are used to test nominal data. Answer D is incorrect because Friedman test is used to test ordinal data.

6. **The answer is A** *[see V.C–D]*.
   Answer A is correct because one-way ANOVA is used to test parametric data (change in the number of cigarettes smoked daily) when there are three independent groups and no detected confounders are present. Answers B and C are incorrect because chi-square and Fisher exact test are used to test nominal data. Answer D is incorrect because Friedman test is used to test ordinal data. Answer E is incorrect because *t* test is used for evaluating statistical differences in parametric data when only two groups are being evaluated.

7. **The answer is D** *[see V.F]*.
   Answer D is correct because ANCOVA is used to test parametric data (change in BP) when two or more groups are being evaluated and two or more confounders (diet and exercise differences) are detected. Answer A is incorrect because one-way ANOVA is used when no detected confounders are present. Answers B and C are incorrect because chi-square and Fisher exact test are used to test nominal data. Answer E is incorrect because *t* test is used when no detected confounders are present.

8. **The answer is C** *[see VI.A–B]*.
Answer C is correct because chi-square is used to detect statistical differences for nominal data (mortality) when there are large numbers of patients in each treatment group. Answers A and E are incorrect because ANOVA and *t* test are used to test parametric data. Answer B is incorrect because Fisher exact test is used when there are small numbers of patients in each treatment group ($<$ 40 patients). Answer D is incorrect because Mann-Whitney *U* test is used to test ordinal data.

9. **The answer is A** *[see IX.B]*.
Answer A is correct because $r = 0.45$, *r*-squared (r^2) $= 0.2$ or 20%. Therefore, 20% of one variable (hypertension) may be explained by the other variable (high-sodium diet). This would mean that $1 - 0.2 = 0.8$ or 80% of hypertension would not be explained by a high-sodium diet. Therefore, answers B, C, D, and E are incorrect.

10. **The answer is B** *[see VIII.B]*.
Answer B is correct because pain scale scores are ordinal data, and Spearman is the sample correlation coefficient for ordinal data. Answer A is incorrect because Pearson is the sample correlation coefficient for linear (parametric) data. Answer C is incorrect because pain scale is ordinal data, not linear (parametric). Answer D is incorrect because Cox is a type of regression analysis, not a form of correlation analysis.

11. **The answer is D** *[see III.F.1.b, IV.E, and XV.B]*.
Answer D is correct because the outcome measure is relative risk (RR). For ratios like relative risk, it is the difference from 1 that determines statistical significance. Answer A is incorrect because there is a statistically significant difference in CVA or TE because the 95% CI does not include 1. Answers B and C are incorrect because, for ratios like relative risk, it is the difference from 1 that determines statistical significance, not difference from 0.

12. **The answer is A** *[see III.F.1.b, IV.E, and XV.B]*.
Answer A is correct because for ratios like relative risk, it is the difference from 1 that determines statistical significance. The 95% CI included 1, so although this may be clinically meaningful, it is not statistically significant. Answers B and D are incorrect because for ratios like relative risk, it is the difference from 1 that determines statistical significance, not difference from 0. Answer C is incorrect because all values within the 95% CI are statistically possible and the 95% CI for MI contains 1. Therefore, it is statistically possible that there is no difference between dabigatran (Pradaxa) and warfarin (Coumadin) for the outcome of MI.

13. **The answer is B** *[see XVI.C.4]*.
Answer B is correct because postmenopausal women were identified based on exposure (medications they were taking, i.e., whether or not they were taking HRT) as is done in cohort studies. Answer A is incorrect because, for case-control studies, subjects are identified based on disease (heart disease in this case) rather than exposure (HRT), which was not the setup for this study. Answer C is incorrect because patients were not randomized to an intervention. Answer D is incorrect because meta-analyses include multiple studies, which is not the case in this example.

14. **The answer is D** *[see XII.C.4 and XVI.D.3]*.
Answer D is correct because the most robust and ethical way of determining differences between hypertension treatments and determining causality is through a randomized trial with a standard of care control. Answer A is incorrect because a case-control study is very weak at determining causality. Answers B and E are incorrect because cohort studies and meta-analyses are weaker than randomized trials for establishing causality. Answer C is incorrect because it would be unethical to treat hypertensive, diabetic patients with a placebo rather than an established therapy that has been shown to improve cardiovascular outcomes.

15. **The answer is A** *[see XVI.D.2.a]*.
Answer A is correct. Answer B is incorrect because it would be unethical to ask those who had stopped smoking in the first part of the trial to restart smoking in order to obtain data for the second part of the study. Answer C is incorrect because crossovers are not good for treatment evaluation in unstable diseases. Asthma severity may vary depending on seasons. Answer D is incorrect because those who died in the first part of the crossover trial could not be evaluated during the second part of the trial.

Study Questions

Directions: Each of the questions, statements, or incomplete statements can be correctly answered or completed by **one** of the suggested answers or phrases. Choose the **best** answer.

1. A physician receives a call from the parent of a 2-year-old child who has ingested an unknown quantity of morphine controlled-release tablets and is now unconscious. The physician's initial recommendation is to

(A) Call emergency medical services (EMS) and have the child taken to the hospital emergency department.
(B) Administer 1 g/kg of activated charcoal with sorbitol.
(C) Administer syrup of ipecac 15 mL by mouth to induce vomiting.
(D) Suggest that the child receive emergency hemodialysis.
(E) Suggest that the child receive acid diuresis with ammonium chloride.

2. A grandfather arrives at your pharmacy asking to purchase a bottle of syrup of ipecac to keep in his home in the event of a poisoning when grandchildren are visiting. What should you tell him?

(A) Administer 15 mL of syrup of ipecac at the first sign of ingestion.
(B) Syrup of ipecac is no longer recommended by the American Association of Poison Control Centers and the American Academy of Pediatrics.
(C) Provide him with the toll-free number for the poison control center.
(D) Both B and C.

3. An unconscious patient is brought into the emergency department. The patient is given 50 mL of 50% dextrose in water, thiamine 100 mg IV, followed by naloxone 1 mg, at which point he awakens. This patient most likely has overdosed on which of the following substances?

(A) Methanol
(B) Amitriptyline
(C) Cocaine
(D) Haloperidol
(E) Heroin

4. Contraindications to the administration of syrup of ipecac include which of the following?

(A) An unconscious patient
(B) A patient who is experiencing a generalized tonic–clonic seizure
(C) A patient who has ingested a caustic substance
(D) All of the above
(E) None of the above

5. An unconscious patient is brought to the emergency department with a history of an unknown drug overdose. Which of the following actions should the physician perform?

(A) Administer 50 mL of 50% dextrose, thiamine 100 mg IV push, and naloxone 0.4 mg IV push.
(B) Protect the patient's airway and ensure that vital signs are stable.
(C) Order the following laboratory tests: complete blood count (CBC), electrolytes, and a toxicology screen.
(D) All of the above.

6. A patient who overdoses on acetaminophen is admitted to the hospital for antidotal therapy with *N*-acetylcysteine (NAC). The patient has the following medication orders: NAC 140 mg/kg loading dose followed by 70 mg/kg for a total of 17 doses, ranitidine 50 mg IV every 8 hrs, prochlorperazine 10 mg IM every 6 hrs as needed for nausea, thiamine 100 mg IV every day for three doses, and Darvocet-N 100 one to two tablets every 4 hrs as needed for headache. What is the best course of action?

(A) Call the physician to increase the dosage of ranitidine to 50 mg IV every 6 hrs.
(B) Call the physician to have the Darvocet-N 100 discontinued.
(C) Call the physician to initiate hemodialysis therapy.
(D) Have the patient prophylactically intubated to protect the airway.
(E) Administer ethanol 10% at a loading dose of 7.5 mL/kg over 1 hr, followed by a continuous infusion of 1.4 mL/kg/hr for 48 hrs.

7. Ethyl alcohol (EtOH) is administered to patients who have ingested either ethylene glycol or methanol because EtOH

(A) helps sedate patients.
(B) increases the metabolism of ethylene glycol and methanol.
(C) blocks the formation of the toxic metabolites of ethylene glycol and methanol.
(D) increases the renal clearance of ethylene glycol and methanol.
(E) is not an antidote for ethylene glycol or methanol overdoses.

8. A patient with renal failure is inadvertently given three doses of potassium chloride 40 mEq IV in 100 mL of 0.9% sodium chloride over a 3-hr period. This error is immediately discovered, and a STAT serum potassium level is 8.0 mEq/L. The patient is bradycardic with a markedly prolonged QRS complex. The patient should receive which of the following?

(A) Calcium chloride 10% 10 mL IV push
(B) Sodium bicarbonate 50 mEq IV push
(C) Insulin 10 U and 50% dextrose 50 mL IV push
(D) Sodium polystyrene sulfonate 30 g by mouth every 3 hr for four doses
(E) None of the above

9. Parenteral calcium is used as an antidote for which of the following situations?

(A) Verapamil overdoses
(B) Hyperkalemia
(C) Cocaine intoxication
(D) Verapamil overdoses and hyperkalemia

10. A 65-year-old woman with normal renal function is administered a 0.25 mg dose of digoxin IV push. A serum level obtained 1 hr after drug administration is 5 ng/mL. Your recommendation to the physician is which of the following?

(A) Administer two vials of digoxin immune antibodies STAT.
(B) Administer repetitive doses of activated charcoal.
(C) Call a nephrologist, and put the patient on hemodialysis.
(D) Repeat the serum digoxin level 6 to 8 hrs after the dose, and reassess the patient.

11. A 16-year-old woman is reported to have overdosed on 40 sustained-release theophylline tablets. She is transported to the emergency department, where gastric lavage was performed and she was given one dose of activated charcoal. An initial theophylline level is 42 μg/mL, but a follow-up level in the intensive care unit (ICU) is 95 μg/mL. What is the most appropriate course of therapy?

(A) Charcoal hemoperfusion and multiple-dose activated charcoal
(B) Syrup of ipecac administration
(C) Forced alkaline diuresis
(D) Nasogastric administration of sodium-polystyrene sulfonate

12. A 23-year-old man is admitted to the intensive care unit (ICU) after ingesting 20 acetaminophen tablets 500 mg with a six-pack of beer. He was initially awake and alert in the emergency department and was given one dose of activated charcoal. His initial acetaminophen level taken approximately 2 hrs after ingestion is 90 μg/mL. What would be the most appropriate course of action?

(A) Administer repeated doses of activated charcoal and sorbitol.
(B) Administer syrup of ipecac.
(C) Administer a loading dose of *N*-acetyl-L-cysteine (NAC), and repeat the acetaminophen level in 4 hrs.
(D) Discharge the patient to home.

13. An overdose victim presents to the emergency department with an elevated heart rate, decreased blood pressure, dilated pupils, and lethargy. Upon arrival to the intensive care unit (ICU), she has a generalized tonic–clonic seizure that is treated with IV diazepam and fosphenytoin. Which of the following is the most likely intoxicant?

(A) Ethyl alcohol
(B) Methanol
(C) Acetaminophen
(D) Oxycodone
(E) Amitriptyline

14. A 37-year-old man is admitted to the ICU with an overdose of approximately 50 tablets of Depakote 500 mg sustained-release tablets. He never lost consciousness. He denies fevers, syncope, headache, vision changes, weakness, shortness of breath, chest pain, nausea, vomiting, or diarrhea. His initial valproic acid level was 41 mg/dL (therapeutic range 50 to 100 μg/mL). His ammonia level was elevated and therapy with intravenous levocarnitine was begun. At this point, you should recommend the following:

(A) Discontinue levocarnitine.
(B) Transfer the patient to in-patient psychiatry because the patient is asymptomatic.
(C) Restart his home dose of valproic acid sustained-release tablets so that his level does not fall below the therapeutic range.
(D) Recheck a follow-up valproic acid level and continue to observe in the ICU.

Answers and Explanations

1. The correct answer is A *[see I]***.**
Patients with unstable vital signs should be taken to an emergency department for immediate treatment.

2. The correct answer is D *[see II.G.b]***.**
Induced vomiting is no longer an acceptable option of managing poisonings at home because it is a relatively ineffective method of removing toxins and results in a delay in administering antidotal therapy. It is important to counsel patients on poison prevention and to give parents and other friends and relatives the toll-free number for the poison control center. Parents should also know basic first aid and cardiopulmonary resuscitation (CPR).

3. The correct answer is E *[see III.Q]***.**
Naloxone reverses the effects of opioid receptor agonists, such as heroin, morphine, and propoxyphene.

4. The correct answer is D *[see II.G.a]***.**
Contraindications to ipecac include the three Cs: caustics, conscious, and convulsions; see also the answer to question 2. The use of syrup of ipecac is reserved for rare circumstances and only under the direction of the poison control center and/or a physician. These are new recommendations, and many parents, relatives, and friends may have this product in their medicine cabinets.

5. The correct answer is D *[see II]***.**
The management of unconscious overdose patients involves aggressive support of vital signs and the administration of empiric antidotal therapy, while obtaining various laboratory tests to determine the nature of the overdose.

6. The correct answer is B *[see III.a]***.**
Darvocet-N 100 is an acetaminophen-containing product that should not be given to a patient with documented acetaminophen toxicity. Be aware particularly of OTC products containing acetaminophen.

7. **The correct answer is C** *[see III.b]***.**
Ethanol saturates alcohol dehydrogenase and prevents the formation of the toxic metabolites of either ethylene glycol or methanol; however, this antidote is falling out of favor owing to its adverse metabolic and central nervous system effects. Fomepizole (Antizol), a specific inhibitor of alcohol dehydrogenase, is becoming the preferred antidote for methanol or ethylene glycol overdoses. Ethanol may be used in situations in which fomepizole is not available.

8. **The correct answer is A** *[see III.L.2]***.**
All of the selections are used to manage hyperkalemia, although, in an unstable patient, the cardiac effects of hyperkalemia must first be reversed with intravenous calcium.

9. **The correct answer is D** *[see III.F & G]***.**
Parenteral calcium is used to reverse the cardiac effects of calcium-channel blocker overuse and hyperkalemia.

10. **The correct answer is D** *[see III.K]***.**
The plasma–tissue distribution phase for digoxin is 6 to 8 hrs postadministration. Sampling digoxin levels sooner may give a falsely elevated level. Only symptomatic patients should receive digoxin immune antibodies. Hemodialysis is of no value in managing digoxin overdoses.

11. **The correct answer is A** *[see III.U]***.**
Large ingestions of sustained-release products may act as drug reservoirs, necessitating aggressive measures to remove the toxin.

12. **The correct answer is C** *[see III.A]***.**
Large acetaminophen ingestions ($>$ 140 mg/kg) may be fatal if unrecognized. The Rumack–Matthew nomogram requires a 4-hr level to accurately assess the potential for toxicity. If the 4-hr level is in the toxic range, the full course of NAC therapy should be administered.

13. **The correct answer is E** *[see III.D]***.**
Tricyclic antidepressant overdoses will produce seizures, hypotension, mydriasis, hypotension, and ventricular dysrhythmias. The cardiac and CNS effects of tricyclic antidepressant toxicity will respond to bicarbonate therapy. Opiates such as oxycodone will produce miosis.

14. **The correct answer is D** *[see II]***.**
The patient in this case ingested a sustained-release dosage form. Also from the history, it was estimated that the patient took 50 tablets that may produce a delayed release effect in and of itself. While the patient was asymptomatic, he may develop symptoms after a period as more drug are absorbed. In this case, a follow-up valproic acid level was 155 mg/dL, the patient was observed in the ICU, and carnitine therapy was continued. Carnitine has been shown to reverse the hyperaminemia induced by valproic acid and was continued while the patient was in the ICU. The next day, the valoproic acid level fell to 50 μg/dL, the patient remained asymptomatic, and he was transferred out of the ICU.

Study Questions

Directions: Each of the numbered items or incomplete statements in this section is followed by answers or by completions of the statement. Select the **one** lettered answer or completion that is **best** in each case.

1. Parenteral products with an osmotic pressure less than that of blood or 0.9% sodium chloride are referred to as

(A) isotonic solutions.
(B) hypertonic solutions.
(C) hypotonic solutions.
(D) iso-osmotic solutions.
(E) neutral solutions.

2. Aseptic technique should be used in the preparation of all of the following medications with the exception of

(A) neomycin irrigation solution.
(B) ganciclovir (Cytovene) intraocular injection.
(C) phytonadione (Aquamephyton) subcutaneous injection.
(D) ampicillin (Principen) IV admixture piggyback.
(E) bacitracin ointment.

3. Which needle has the smallest diameter?

(A) 25 gauge, 3 ¾ inches
(B) 24 gauge, 3 ½ inches
(C) 22 gauge, 3 ½ inches
(D) 20 gauge, 3 ⅜ inches
(E) 26 gauge, 3 ⅝ inches

4. Intra-articular injection refers to injection into the

(A) muscle mass.
(B) subcutaneous tissue.
(C) spinal fluid.
(D) superficial skin layer.
(E) joint space.

5. Advantages of the intravenous route include

(A) ease of removal of the dose.
(B) a depot effect.
(C) low incidence of phlebitis.
(D) rapid onset of action.
(E) a localized effect.

6. A central vein, either subclavian or internal jugular, may be considered a suitable route for IV administration in which of the following situations?

(A) When an irritating drug is given
(B) When hypertonic drugs are given
(C) For long-term therapy
(D) For administering dextrose 35% as parenteral nutrition
(E) All of the above

7. To prepare a total parenteral nutrition (TPN) that requires 10 mEq of calcium gluconate and 15 mM of potassium phosphate, the appropriate action to take would be which of the following?

(A) Add the calcium first, add the other additives, then add the phosphate last, thoroughly mixing the solution after addition.
(B) Add the calcium gluconate and potassium phosphate consecutively.
(C) Do not combine the agents together but give them as a separate infusion.
(D) None of the above.

8. Which needle gauge would be most likely used as a subcutaneous injection of epoetin?

(A) 25 gauge, ⅝ inch
(B) 16 gauge, 1 inch
(C) 18 gauge, 1 ½ inches
(D) 22 gauge, 1 ½ inches
(E) None of the above

9. Which of the following compounded sterile products should NOT be prepared in a horizontal laminar flow hood?

(A) Total parenteral nutrition (TPN)
(B) Dopamine
(C) Cisplatin (Platinol)
(D) Nitroglycerin
(E) Bretylium tosylate (Bretylol)

10. All of the following statements about D_5W are true EXCEPT

(A) its pH range is 3.5 to 6.5.
(B) it is hypertonic.
(C) it is a 5% solution of D-glucose.
(D) it should be used with caution in diabetic patients.
(E) it is often used in IV admixtures.

11. All of the following are potential hazards of parenteral therapy EXCEPT

(A) hypothermia.
(B) phlebitis.
(C) extravasation.
(D) allergic reactions.
(E) ileus.

12. Procedures for the safe handling of antineoplastic agents include all of the following EXCEPT

(A) use of Luer-Lok syringe fittings.
(B) wearing double-layered latex gloves.
(C) use of negative-pressure technique when medication is being withdrawn from vials.
(D) wearing closed-front, surgical-type gowns with cuffs.
(E) use of horizontal laminar flow hood.

13. In preparing an intraspinal dose of bupivacaine, the best pore size filter for cold sterilization would be

(A) 8-μm filter.
(B) 5-μm filter.
(C) 0.45-μm filter.
(D) 0.22-μm filter.
(E) None of the above.

14. Process simulation is a method of quality assurance that

(A) evaluates the adequacy of a practitioner's aseptic technique.
(B) requires the use of a microbial growth medium.
(C) is carried out in a manner identical to normal sterile admixture production under routine operating conditions.
(D) All of the above.

15. *USP* <797> was developed to
- **(A)** decrease microbial contamination of compounded sterile preparations.
- **(B)** ensure the proper use of aseptic technique during the manufacturing of sterile preparations.
- **(C)** prevent harm to patients, including death.
- **(D)** decrease unintended physical and chemical contaminates found in compounded sterile preparations.

16. When withdrawing drug solution from an ampoule, the one-way use of what kind of needle is required?
- **(A)** 5 micron filter needle
- **(B)** 25-gauge needle
- **(C)** 27-gauge needle
- **(D)** tuberculin needle

17. Proper use of sterile gloves includes which of the following:
- **(A)** Glove packaging should be discarded by touching only the sterile glove outerwrapper.
- **(B)** Sterile gloves should be donned after gowning, hand washing, and entering the ISO 5 direct compounding area.
- **(C)** Gloves can be placed on the hands by touching any sterile portion of the glove.
- **(D)** Gloves should be rinsed frequently with ethyl alcohol-based product, and changed when their integrity is compromised.

18. According to EPA regulations, the following form of pharmaceutical waste can be disposed of in a yellow container:
- **(A)** Nonregulated drugs
- **(B)** Hazardous toxic
- **(C)** Hazardous infectious
- **(D)** Trace chemotherapy

19. Low-risk compounded sterile products are prepared using the following:
- **(A)** Complex aseptic manipulations
- **(B)** Multiple pooled sterile commercial products
- **(C)** Sterile commercial drugs using commercial sterile devices
- **(D)** Nonsterile ingredients or with nonsterile devices

20. Proper preparation of the laminar airflow work bench
- **(A)** requires that all nonsterile supplies be removed from their outer packaging and wiped down with 70% isopropyl alcohol.
- **(B)** includes wiping down all surfaces by using side-to-side motions while working from the front of the work bench to the back.
- **(C)** does not include sterilizing the rubber stoppers of medication vials because they are sealed with a sterile safety cap.
- **(D)** allows the placement of larger supplies to be placed in the back of a horizontal airflow work bench.

Case Presentation

The pharmacist receives a prescription for hydromorphone (Dilaudid) injection to be compounded to a solution of 15 mg/mL. Dilaudid is commercially available in an ampoule, but the concentration is 10 mg per mL. The physician would like a more concentrated solution prepared so that 50 mL can be instilled into the titanium reservoir of a Medtronic infusion pump. The hydromorphone solution will be continuously infused, intrathecally, over approximately 30 days, for a patient with chronic back pain, uncontrolled with oral narcotics. The pharmacist checks his inventory and finds a bottle of hydromorphone powder, *USP*. He proceeds to weigh out enough powder for a 60 mL preparation. The weighing step is checked by a colleague pharmacist.

21. According to *USP* Chapter 797, this sterile preparation would be considered a
- **(A)** high-risk level CSP.
- **(B)** medium-risk level CSP.
- **(C)** low-risk level CSP.
- **(D)** None of these.

22. What would be an appropriate environment for the aseptic manipulations required for this preparation?
- **(A)** Pharmacy workbench or counter in ambient room air
- **(B)** Inside an anteroom, with ISO class 8 quality air
- **(C)** Inside a Barrier Isolator with ISO class 5 quality air
- **(D)** A horizontal laminar flow workbench, newly installed, with no certification, but manufacturer guaranteed to be ISO 5 class air quality.

23. The pharmacist begins to gather his supplies for this preparation. These should include:

(A) Millipore 0.45 μm HV Filter with sterile water for injection.
(B) Millipore 0.22 μm GS Filter with sodium chloride 0.9%.
(C) Bectin-Dickinson 16-gauge, 5 micron filter needle with sodium chloride 0.9%.
(D) Millipore AA 0.8 μm Filter with dextrose 5% in water.

24. After the solution was prepared, what would the appropriate quality assurance or double check by another pharmacist include?

(A) Inspection of the powder and the label to ensure hydromorphone was the prepared ingredient and that the label contained a beyond use date and the 15 mg per mL concentration.
(B) Sending a solution sample or aliquot to a microbiology lab to test for the presence of bacteria and pyrogens prior to dispensing.
(C) Check to ensure a correct sterilizing filter was used.
(D) Visual inspection to ensure the final aqueous solution had no visible participates.
(E) All of the above.

Answers and Explanations

1. The answer is C *[see IX.B.1.b]***.**
Hypotonic solutions have an osmotic pressure less than that of blood (or 0.9% saline), whereas hypertonic solutions have an osmotic pressure greater than that of blood, and isotonic or iso-osmotic solutions have an osmotic pressure equal to that of blood.

2. The answer is E *[see II.A.4]***.**
Irrigation solutions, ophthalmic preparations and parenteral products, and subcutaneous and IV medications should be prepared using aseptic technique. Because bacitracin ointment is applied to the skin and does not bypass the body's protective barriers, its preparation would not be held to the same requirements.

3. The answer is E *[see XI.A.1]***.**
The gauge size refers to the outer diameter of the needle. The lower the gauge size number, the larger the needle.

4. The answer is E *[see VIII.I]***.**
Intra-articular injection refers to an injection into the joint space. This administration route generally is used for certain types of corticosteroids to reduce inflammation associated with injury or rheumatoid arthritis.

5. The answer is D *[see VIII.C]***.**
The IV route of drug administration allows for rapid onset of action and, therefore, immediate therapeutic effect. There can be no recall of the administered dose, and phlebitis or inflammation of a vein can occur. In addition, a depot effect (i.e., accumulation and storage of the drug for distribution) cannot be achieved by administering a drug intravenously. Delivering a drug intravenously results in a systemic rather than a localized effect.

6. The answer is E *[see XII.A.2]***.**
Irritating drugs, hypertonic drugs, long-term therapy, and dextrose 35% are best given by central IV administration. Peripheral vein injection is used for postoperative hydration, administration of nonirritating drugs, or isotonic solutions and for short-term IV therapy.

7. The answer is A *[see IX.E.4]***.**
Physical incompatibilities occur when two or more products are combined and produce a change in the appearance of the solution, such as the formation of a precipitate. Calcium and phosphate solutions when directly combined or added consecutively to a solution will form a white precipitate. By altering the order of mixing, they can be safely added to TPN solutions.

8. The answer is A *[see XI.A.1]***.**
Because subcutaneous injection does not require penetration through several skin layers or muscle tissue, a short needle with a narrow diameter is used. A 16- or 18-gauge needle is most commonly used in the pharmacy for preparing parenteral solutions. A 22-gauge needle would be used for intramuscular injection.

9. The answer is C *[III B 2 a]***.**
Cisplatin is an antineoplastic agent and, consequently, should be prepared only in a vertical laminar flow hood because of the potential hazard of these toxic agents to the operator.

10. The answer is B *[see IX.B.1.a]***.**
D_5W (dextrose [D-glucose] 5% in water) is acidic, its pH ranges from 3.5 to 6.5, and it is isotonic. It is often used in IV admixtures and should be used with caution in diabetic patients.

11. The answer is E *[see XII.E.1]*.
Parenteral therapy is often a treatment for ileus. Hypothermia, phlebitis, extravasation, and allergic reactions can be hazards of parenteral therapy.

12. The answer is E *[see IX.D.2]*.
In order to prevent drug exposure, a vertical flow laminar hood (not horizontal) should be used when an antineoplastic agent is prepared. The other precautions mentioned in the question are important safety measures for handling parenteral antineoplastics. All pharmacy and nursing personnel who handle these toxic substances should receive special training.

13. The answer is D *[see VI.D.2.c.ii]*.
Because intraspinal and epidural doses of bupivacaine are frequently prepared from nonsterile powders, cold sterilization, accomplished by filtration, is a simple method of ensuring complete microbial removal. The filters listed 8 μm to 0.45 μm will remove only particulate matter. A 0.22-μm filter ensures the removal of microorganisms.

14. The answer is E *[see.V.F]*.
Process simulation is one part of an overall quality assurance program. It requires duplicating sterile product preparation using a growth medium in place of actual products. It serves to evaluate the aseptic technique of the individual performing all the necessary steps of sterile product preparation.

15. The answer is C *[see I]*.
Chapter <797> of the *USP* was developed to prevent harm to patients, including death. This is accomplished by following a rigorous set of guidelines, including the proper use of aseptic technique during the manufacturing of sterile preparations, and decreasing microbial and unintended physical and chemical contaminates found in compounded sterile preparations.

16. The answer is A *[see IV.J.2.a]*.
Although when done properly, ampoule with opening resulting in a clean break with no glass shards, a single pass through a 5 micron filter needle or straw is still required to remove any unseen particulate matter that may be created.

17. The answer is D *[see IV.D]*.
Proper use of sterile gloves includes rinsing frequently with a 62% w/w ethyl alcohol product and changing when integrity is compromised by coming in contact with nonsterile surfaces, or the glove is coughed or sneezed into.

18. The answer is D *[see IX.D.2.f.(3)]*.
A color-coded system was created by the EPA to help facilities ensure safe and proper disposal of waste. Hazardous toxic, hazardous ignitable, and hazardous infectious waste should be disposed in a black container. Trace chemotherapy waste should be disposed of in a yellow container. Drain disposal waste can be flushed down the sink or sewer. Nonregulated pharmaceutical waste should be placed in a white with blue top or cream with purple top.

19. The answer is C *[see II.A.6.a.(1)]*.
Low-risk CSPs are compounded from sterile commercial drugs using commercial sterile devices in an ISO class 5 located within an ISO 7 buffer area. Compounding procedures involve only transferring, measuring, and mixing manipulations using not more than three sterile products and not more than two entries into each sterile container.

20. The answer is A *[see IV.E]*.
All nonsterile supplies, such as vials and infusions bags, should be removed from their outer packaging and wiped down with 70% isopropyl alcohol and lint-free cleaning cloths prior to being placed on the sterile workbench.

21. The answer is A.
The hydromorphone preparation is a high-risk level CSP because it is made from nonsterile powder.

22. The answer is C.
USP Chapter 797 requires an ISO class 5 air quality environment for this preparation. A Barrier Isolator within a clean room creates an ISO class 5 environment. Ambient room air is unacceptable for any preparation. An anteroom is generally an area of relatively high personnel and supply traffic. Although air quality may be acceptable, it does not provide an acceptable critical site of aseptic manipulations. All new laminar flow work benches should be tested for air velocity and filter integrity prior to use.

23. The answer is B.
The hydromorphone requires sterilization prior to intrathecal administration. This is best achieved with a 0.22 μm filter. Sodium chloride 0.9% is the solution most similar to the CNS fluid and would be a better choice over sterile water of dextrose 5% injection.

24. The answer is E.
Each step in sterile compounding should have an associated quality assurance double check. Inspection of the initial ingredients, review of supplies, monitoring of aseptic technique, and examination of the final product creates multiple opportunities to intercept an error and make necessary corrections. High-risk level CSPs should be used within 24 hrs in the absence of sterility testing. Given that this product will be administered over 30 days, a sterility and pyrogen test would be appropriate.

Study Questions

Directions: Each of the numbered items or incomplete statements in this section is followed by answers or by completions of the statement. Select the **one** lettered answer or completion that is **best** in each case.

1. When a patient is fitted with an axillary crutch, how far below the underarm should the top of the crutch rest?

(A) 0.5 inch
(B) 1 inch
(C) 2 inches
(D) 3 inches
(E) 4 inches

2. What angle should the elbow form when a cane is the correct height?

(A) 10 degree
(B) 25 degree
(C) 45 degree
(D) 60 degree
(E) 90 degree

3. A product that delivers moisture to the air by heating water to produce steam is called a

(A) nebulizer.
(B) humidifier.
(C) ventilator.
(D) peak flow meter.
(E) vaporizer.

4. An absorbent product designed for patients with light incontinence problems is a

(A) brief.
(B) shield.
(C) undergarment.
(D) underpad.
(E) catheter.

5. When an oral temperature is taken, the thermometer should be placed into the mouth for

(A) 1 to 2 mins.
(B) 3 to 4 mins.
(C) 5 to 6 mins.
(D) 7 to 8 mins.
(E) > 9 mins.

6. The diameter of urinary catheters is measured by which of the following scales?

(A) Leur
(B) English
(C) French
(D) gauge
(E) metric

7. A cervical collar that immobilizes the neck is called a

(A) soft cervical collar.
(B) hard cervical collar.
(C) foam cervical collar.
(D) extrication collar.
(E) rigid cervical collar.

8. Incontinence that is caused by an obstruction of the bladder is called

(A) overflow incontinence.
(B) urge incontinence.
(C) stress incontinence.
(D) functional incontinence.
(E) transient incontinence.

9. A colostomy or ileostomy could be performed for all of the following conditions *except*

(A) lower bowel obstruction.
(B) malignancy of the colon or rectum.
(C) ulcerative colitis.
(D) duodenal ulcer.
(E) Crohn disease.

10. Pregnancy test kits are designed to detect which substance?

(A) luteinizing hormone (LH)
(B) progesterone
(C) human chorionic gonadotropin (hCG)
(D) estrogen
(E) follicle-stimulating hormone

Answers and Explanations

1. **The answer is C** *[see I.B.2.a]*.
When a patient is fitted for an axillary crutch, the top of the crutch should be 2 inches below the axilla (underarm).

2. **The answer is B** *[see I.A.1]*.
When a patient is properly fitted for a cane, the elbow should form a 25-degree angle. This allows for maximum weight transfer.

3. **The answer is E** *[see X.B]*.
A vaporizer produces moisture by heating water to produce steam. A humidifier also produces moisture; however, it works by mechanically creating small water particles. A nebulizer is used to deliver liquid to the mouth and throat. A ventilator is used to assist in breathing. A peak flow meter is used to detect airway constriction.

4. **The answer is B** *[see VII.B.1]*.
Shields are pads that are placed in the underwear and held with adhesive strips. They are used for patients with light incontinence problems.

5. **The answer is B** *[see XI.A.1]*.
Oral temperature is taken by inserting the bulb of the thermometer under the tongue and sealing the lips around the thermometer for 3 to 4 mins.

6. **The answer is C** *[see XII.B]*.
The French scale is used to measure the diameter of a urinary catheter. The Leur scale is used to measure syringe tip size. The gauge scale is used to measure needle diameter. The metric scale is a general system of measurement.

7. **The answer is D** *[see VIII.D.3]*.
An extrication collar (also known as a Philadelphia collar) is used to immobilize the neck. It is commonly used in emergency situations. Soft or foam cervical collars provide mild support and remind the patient to keep the neck straight. Hard or rigid cervical collars provide moderate support but allow some movement.

8. **The answer is A** *[see VII.A.3]*.
Overflow incontinence is caused by obstruction of the bladder. Urge incontinence is caused by uncontrolled bladder contractions. Stress incontinence is caused by increases in intra-abdominal pressure. Functional incontinence is related to physical or psychological problems. Transient incontinence is caused by medications, urinary tract infections, or mental impairments.

9. **The answer is D** *[see IX.A.1–2]*.
Lower bowel obstruction, malignancy of the colon or rectum, and diverticulitis may all require a colostomy. Ulcerative colitis and Crohn disease may require an ileostomy. The treatment of a duodenal ulcer would not include a colostomy or an ileostomy.

10. **The answer is C** *[see V.B.1.d]*.
Pregnancy tests detect hCG in the urine. This is secreted after the embryo has implanted in the uterus. Ovulation-prediction tests detect LH. Progesterone, estrogen, and follicle-stimulating hormone are all involved in controlling the menstrual cycle.

3. Hold the lower eye lid down to form a pouch between the lid and the eyeball.
4. **Always apply eye drops before applying eye ointment.** Dispense the recommended number of drops into the pouch for eye drops. Keep the eyelids closed and apply gentle pressure to the inner canthus for 1 to 2 mins. Wait 5 to 10 mins before instilling another eye medication.
5. Ointments should be applied to the lower conjunctival sac as a 1/2-inch ribbon. To minimize blurred vision, a decreased amount of ointment may be applied to the eye. Blurred vision will be less noticed by the patient if the ointment is administered at bedtime, if feasible.

Study Questions

Directions for questions 1-17: Each of the questions, statements, or incomplete statements in this section can be correctly answered or completed by **one** of the suggested answers or phrases. Choose the **best** answer.

1. Which of the following nonprescription products is approved by the U.S. Food and Drug Administration (FDA) for treatment of impacted cerumen?
   (A) olive oil
   (B) carbamide peroxide
   (C) isopropyl alcohol 95% in anhydrous glycerin
   (D) docusate sodium

2. Which of the following otic conditions can be treated with a nonprescription agent?
   (A) vertigo
   (B) tinnitus
   (C) external otitis
   (D) water-clogged ear

3. Which of the following conditions is appropriate for the use of isopropyl alcohol 95% in anhydrous glycerin?
   (A) treatment of impacted cerumen
   (B) treatment of water-clogged ears
   (C) prevention of external otitis
   (D) treatment of external otitis

4. All of the following are true regarding carbamide peroxide *except* which one?
   (A) Carbamide peroxide softens earwax by the foaming action produced when oxygen is released.
   (B) Carbamide peroxide is safe for pharmacist recommendation in patients age 6 years and older.
   (C) Appropriate dosing for carbamide peroxide is 5 to 10 drops in the ear two times daily.
   (D) Carbamide peroxide should be used for a maximum of 4 days unless otherwise directed.

5. All of the following are true regarding external otitis *except* which one?
   (A) Initial treatment for external otitis is an oral antibiotic and corticosteroid.
   (B) Symptoms of external otitis include otic itching, pressure and fullness in the ear, pain, and otic discharge.
   (C) Mechanical trauma to the ear with cotton-tipped applicators can contribute to increased susceptibility to external otitis.
   (D) External otitis is also referred to as swimmer's ear.

6. Which of the following is an appropriate counseling tip for administration of otic drops?
   (A) Pull the earlobe up and back to straighten the ear canal for children.
   (B) Pull the earlobe down and back to straighten the ear canal for adults.
   (C) Fill the otic syringe with hot water.
   (D) If cotton is used, it should not be left in the ear for longer than 1 hr.

7. All of the following are true regarding ophthalmic formulations *except* which one?
   (A) Vehicles enhance contact time of the ophthalmic product.
   (B) Antioxidants prevent product deterioration.
   (C) Wetting agents reduce surface tension of the lens.
   (D) Tonicity adjusters are used to maintain a pH between 6.0 and 8.0.

8. Which of the following is appropriate treatment of diagnosed corneal edema?
   (A) hyperosmotic agent
   (B) vasoconstrictor
   (C) antihistamine
   (D) ophthalmic demulcent

9. Which of the following is also known as "pink eye"?

(A) allergic conjunctivitis
(B) bacterial conjunctivitis
(C) viral conjunctivitis
(D) environmental conjunctivitis

10. All of the following are antioxidants used for the treatment and/or prevention of ophthalmic disorders *except*

(A) vitamin D.
(B) β-carotene.
(C) vitamin C.
(D) lutein.

11. Which of the following solutions may be used to clean and moisten the surface of the contact lens while the lens is still in the eye?

(A) cleaning solution
(B) wetting solution
(C) soaking solution
(D) rewetting solution

12. Which of the following is true regarding ophthalmic antihistamines?

(A) Pheniramine and tetrahydrozoline are the only two nonprescription ophthalmic antihistamines available.
(B) Ophthalmic antihistamines are available only in combination with naphazoline.
(C) Ophthalmic antihistamines may cause burning, stinging, dry eyes, or mydriasis.
(D) Ophthalmic antihistamines may produce rebound congestion if used in excess or for extended durations.

13. Which of the following is the only astringent used in nonprescription ophthalmic agents that is recommended by the U.S. Food and Drug Administration (FDA)?

(A) edetic acid
(B) benzalkonium chloride
(C) zinc sulfate
(D) povidone

14. The definition of a surfactant (an ingredient in toothpaste) can best be described by which of the following statements?

(A) It prevents drying of the preparation.
(B) It removes debris by its detergent action and causes foaming, which is usually desired by the patient.
(C) It physically removes plaque and debris.
(D) It determines the texture, dispersiveness, and appearance of the product.
(E) It adds flavor to the preparation, which makes it more appealing to the patient.

15. A 16-year-old girl stops by a pharmacy on her way home from school. She says to the pharmacist, "I have been using Crest Whitestrips daily to bleach my teeth in preparation for my spring formal. However, my teeth are becoming very sensitive." Each of the following statements is advice that the pharmacist might suggest *except* which one?

(A) There is a possibility that you may damage the gingival tissue and tooth pulp.
(B) Oxidizing agents may have the potential for mutating or enhancing the carcinogenic effects of other agents (e.g., tobacco).
(C) Bleaching teeth is best done under dental supervision.
(D) Tooth sensitivity is not related to the frequency of use for such products.
(E) The most common ingredient in products responsible for teeth whitening is hydrogen peroxide, which can cause sensitivity.

16. All of the following products may be recommended by a pharmacist for the treatment of canker sores *except*

(A) benzocaine.
(B) Zilactin-B.
(C) Bayer aspirin placed directly on the oral lesion.
(D) Anbesol.
(E) Orajel.

17. The U.S. Food and Drug Administration (FDA) has approved which ingredient for protection against painful sensitivity of the teeth caused by cold, heat, acids, sweets, or contact?

(A) dicalcium phosphate
(B) sodium lauryl sulfate
(C) 5% potassium nitrate
(D) zinc chloride
(E) calcium carbonate

Directions for questions 18–20: The questions and incomplete statements in this section can be correctly answered or completed by **one or more** of the suggested answers. Choose the answer, **A–E**.

A if **I only** is correct
B if **III only** is correct
C if **I** and **II** are correct
D if **II** and **III** are correct
E if **I**, **II**, and **III** are correct

18. Which of the following compounds is/are considered a suspending agent (an ingredient in dentifrices)?

I. dicalcium phosphate
II. karaya gum
III. methylcellulose

19. Cold sore treatment might include which of the following ingredients?
    - **I.** benzocaine
    - **II.** docosanol
    - **III.** camphor

20. Pharmacists can recommend over-the-counter (OTC) drug treatment for which of the following ear conditions?
    - **I.** Swimmer's ear
    - **II.** Accumulated earwax
    - **III.** Water-clogged ears

Answers and Explanations

1. **The answer is B** *[see I.B.1.d.(1)]*.
Carbamide peroxide is the only FDA-approved agent for cerumen removal. Olive oil, docusate sodium, and mineral oil are used to remove cerumen, but are not FDA approved. Isopropyl alcohol 95% in anhydrous glycerin is FDA approved for water-clogged ears, but not cerumen removal.

2. **The answer is D** *[see I.B.1.d; I.B.2–4]*.
Patients exhibiting symptoms of vertigo, aside from motion sickness, should be referred to a medical provider. There is no FDA-approved treatment for tinnitus. External otitis (swimmer's ear) should be treated with a prescription otic antibiotic and corticosteroid. Only impacted cerumen and water-clogged ears may be treated with nonprescription products.

3. **The answer is B** *[see I.B.5]*.
Isopropyl alcohol 95% in anhydrous glycerin is FDA approved only for treatment of water-clogged ears. Labels on products of isopropyl alcohol 95% in anhydrous glycerin should not claim to be used for treatment or prevention of external otitis (swimmer's ear) because this is a separate disorder from water-clogged ears. Treatment for impacted cerumen is carbamide peroxide.

4. **The answer is B** *[see I.B.1.d.(1)]*.
Carbamide peroxide softens earwax through its foaming action when oxygen is released. It is labeled for ages 12 and older. Therefore, for children, age 12 with suspected cerumen impaction should be seen by a medical provider. Patients should instill 5 to 10 drops of carbamide peroxide into the ear two times daily for up to 4 days.

5. **The answer is A** *[see I.B.4.]*.
External otitis is referred to as swimmer's ear. Although prolonged exposure to moisture is the typical cause of external otitis, mechanical trauma, such as the use of cotton-tipped applicators, fingers, or sharp objects in the ear, may cause the external ear canal to be more susceptible to damage and microorganism infiltration. Patients with external otitis may present with otic itching, a sensation of pressure or fullness in the ear, pain, or an otic discharge. Initial treatment is with an otic antibiotic and corticosteroid, not an oral antibiotic. Oral antibiotics are indicated when the infection is unresponsive to otic treatment, the individual is immunocompromised, or a middle ear infection coexists.

6. **The answer is D** *[see I.C]*.
The earlobe should be pulled up and back to straighten the canal for adults and down and back to straighten the canal in children. Only warm water should be used in the otic syringe, as cold or hot water may induce dizziness. If cotton is used in the ear to retain the medication, it must be large enough to remove easily and should not be left in the ear for longer than 1 hr.

7. **The answer is D** *[see III.B]*.
Buffers are used in ophthalmic preparations to maintain a pH between 6.0 and 8.0. Tonicity adjusters ensure the product is isotonic.

8. **The answer is A** *[see III.D.4]*.
Once diagnosed by a physician, corneal edema is treated with hyperosmotic agents such as Muro solution or ointment to draw the fluid away from the cornea.

9. **The answer is C** *[see III.D.2]*.
Viral conjunctivitis is most often attributable to the adenovirus and is more commonly known as "pink eye."

10. **The answer is A** *[see III.E]*.
The antioxidant vitamins examined for the prevention and/or treatment of ophthalmic disorders include vitamin A (retinol and β-carotene), vitamin C, and vitamin E. Lutein is an antioxidant pigment that functions to filter and protect the visual apparatus and its vascular supply. Lutein is therefore thought to be beneficial for improvement in vision in patients with dry age-related macular degeneration and prevention of cataracts. Vitamin D is not an antioxidant vitamin.

11. **The answer is D** *[see III.F.2]*.
Rewetting solutions are the only contact lens solutions that may be used while the lens is still in the eye.

12. The answer is C *[see III.C.4]***.**
Currently, there are three available ophthalmic antihistamines: ketotifen, pheniramine, and antazoline. Pheniramine and antazoline are only available in combination with the ophthalmic decongestant naphazoline. Ophthalmic antihistamines may cause burning, stinging, dry eyes, or mydriasis. Vasoconstrictors, not antihistamines, may produce rebound congestion when used in excess or for extended durations.

13. The answer is C *[see III.B]***.**
Edetic acid is an antioxidant and benzalkonium chloride (BAK) is a preservative used in ophthalmic formulations. Zinc sulfate is the only FDA-recommended astringent. Povidone is a vehicle used in ophthalmic formulations.

14. The answer is B *[see II.B.2.d.(1)]***.**
Sodium lauryl sulfate is used frequently as a surfactant in most dentifrices. Its detergent action aids in the removal of debris, and the foaming is usually desired by the patient. There is no evidence that surfactants possess anticaries activity or decrease periodontal disease. The FDA considers surfactants an inactive ingredient in dentifrices.

15. The answer is D *[see II.B.2.d.(4)]***.**
Teeth-whitening agents usually contain a peroxide-based ingredient, which can penetrate the surface area of the tooth to whiten. Cosmetic agents can alter the normal flora or cause tissue irritation, gingivitis, and teeth sensitivity. Antiseptics have been used as cosmetic whiteners (e.g., Gly-Oxide) along with hydrogen peroxide (e.g., Crest Whitestrips).

16. The answer is C *[see II.C.1.c.(2)]***.**
Local anesthetics can provide relief of canker sore pain. The most common local anesthetics found in OTC products include benzocaine and butacaine. Some examples are Anbesol, Zilactin-B, and Orajel. Aspirin should not be retained in the mouth before swallowing or placed in the area of the oral lesions because of the high risk for chemical burn with necrosis.

17. The answer is C *[see II.B.2.d.(5)]***.**
Desensitizing agents should not be abrasive or used on a chronic basis unless directed by a dentist. The products approved by the ADA include the ingredients: 5% potassium nitrate, 10% strontium chloride, and dibasic sodium citrate 2% in pluronic gel.

18. The answer is D (II, III) *[see II.B.2.d.(1).D]***.**
Suspending agents are products that add thickness to the dentifrices. Examples are tragacanth, karaya gum, and methylcellulose. Dicalcium phosphate is categorized as an abrasive product.

19. The answer is C (I, II) *[see II.C.2.a–b]***.**
Cold sore treatment involves keeping the lesion moist with emollient creams, petrolatum, or protectants. Local anesthetics (e.g., benzocaine, dyclonine, salicyl alcohol) may be used. In addition, docosanol 10% cream (Abreva) and tetracaine 2% (Viractin) are available without a prescription for the treatment of cold sores. Topical counterirritants (e.g., camphor) and caustics or escharotic agents (e.g., phenol, menthol, silver nitrate) are not recommended because they may further irritate the tissue. Cold sores are usually self-limiting and heal within 10 to 14 days without scarring.

20. The answer is D (II, III) *[see I.B]***.**
Swimmer's ear requires an otic antibiotic, which is by prescription only.

Study Questions

Directions: Each of the questions, statements, or incomplete statements can be correctly answered or completed by **one** of the suggested answers or phrases. Choose the **best** answer.

1. A woman who has not been in the sun for 4 months develops redness on her chest after lying in the sun for 20 mins. The next day, she applies a suntan lotion and develops the same degree of redness on her back in 2 hrs and 20 mins. What is the likely sun protection factor (SPF) of the lotion she is using?

(A) 14
(B) 10
(C) 12
(D) 9
(E) 7

2. Which of the following cleansing products would a pharmacist recommend for a patient with inflammatory acne?

(A) an abrasive facial sponge and soap used four times a day
(B) aluminum oxide particles used two times a day
(C) sulfur 5% soap used two times a day
(D) mild facial soap used two times a day

3. If a patient needs a second application of an over-the-counter (OTC) pyrethrin pediculicide shampoo, how many days after the first application should this be done?

(A) 4 to 5
(B) 6
(C) 7 to 10
(D) 14 to 21
(E) 15 to 17

4. All of the following treatments for personal articles infested with head lice would be effective *except*

(A) placing woolen hats in a plastic bag for 2 weeks.
(B) using an aerosol of pyrethrins with piperonyl butoxide sprayed in the air of all bathrooms.
(C) machine-washing clothes in hot water and drying them using the hot setting on the dryer.
(D) dry-cleaning woolen scarves.
(E) soaking hair brushes in hot water for 15 mins.

5. All of the following sunscreen agents or combinations of agents would likely help prevent a drug-induced photosensitivity reaction *except*

(A) titanium dioxide.
(B) octyl methoxycinnamate plus homosalate.
(C) oxybenzone and padimate O.
(D) zinc oxide.
(E) padimate O plus avobenzone.

6. All of the following would be appropriate recommendations for an adult patient in the acute stage (i.e., blistering, weeping) of poison ivy contact dermatitis *except*

(A) 60 mg per day of prednisone initially, then tapered over 15 days.
(B) Burow's solution; 1:20 wet dressing to area for 15 to 30 mins, four times per day.
(C) two soaks per day in Aveeno Bath Treatment.
(D) two applications of Ivy Block.

7. Pharmacists educating patients about acne should mention all of the following *except*

(A) eliminating all chocolate and fried foods from the diet.
(B) cleansing skin gently two to three times daily.
(C) using water-based noncomedogenic cosmetics.
(D) not squeezing acne lesions.
(E) keeping in mind that acne usually resolves by one's early 20s.

8. A 15-year-old male patient has been using benzoyl peroxide 5% cream faithfully every day for the past 2 months with no apparent side effects. All of the following can be said about this patient *except*

(A) he has been using this product for a long enough time to determine if the dose and dosage form are going to have any benefit.
(B) he should use this product no more frequently than every other day because of its irritating properties.
(C) this starting dose and dosage form are useful, especially if he has dry skin or it is wintertime.
(D) his scalp hair may look bleached if the product comes in contact with it.
(E) the product would sting if it got into his eyes.

9. All of the following descriptions match the therapeutic agent for poison ivy *except*

(A) calamine, phenolphthalein gives it the pink color.
(B) Ivy Block, useful in preventing poison ivy dermatitis.
(C) benzocaine, data regarding incidence of hypersensitivity are conflicting.
(D) hydrocortisone, useful for its antipruritic and anti-inflammatory effects.

10. All of the following statements related to sun protection are true *except* which one?

(A) The sun's intensity increases 20% when going from sea level to an altitude of 5000 ft.
(B) Water-resistant labeling on a sunscreen product indicates that it will retain its SPF after 40 mins of activity in water, sweating, or perspiring.
(C) Baby oil is not a sunscreen, but its application to the skin after tanning causes melanin to rise to the surface.
(D) Per the FDA, a product with an SPF of $>$ 50 must now be labeled SPF "50+".
(E) The SPF is really only a measure of ultraviolet B (UVB) protection.

11. All of the following statements about sunscreens are correct *except* which one?

(A) Malignant melanoma formation may be associated with intense, intermittent overexposure to the sun (sunburning).
(B) Any benefits that might be derived from using sunscreens with an SPF $>$ 30 are negligible.
(C) Sunscreens are best applied immediately before going out in the sun.
(D) Avobenzone provides sunscreen coverage for the UVA spectrum.
(E) Basal cell carcinoma is the most common of all skin cancers and accounts for about 80% of skin cancers.

12. All of the following statements are proper counseling point for a patient suffering with dry skin *except*?

(A) Avoid alcohol and caffeine, as these can exacerbate dry skin.
(B) Following a bath or shower, pat the skin down with a towel, leaving bits of moisture on the skin.
(C) Soak in a tub two to three times per week for at least 20 mins to allow for adequate water absorption into the skin.
(D) Avoid extremely hot baths and showers.
(E) Ensure adequate daily intake of water (about 8 oz glasses of water per day).

13. Dandruff is

(A) the result of decreased turnover of epidermal cells.
(B) typically not a serious medical concern.
(C) also known as cradle cap.
(D) rarely accompanied by pruritus.

14. All of the following are potential treatment options for psoriasis *except*

(A) salicylic acid.
(B) topical hydrocortisone.
(C) coal tar.
(D) ketoconazole.

15. Which of the following tinea infections is not appropriate for self-treatment and must be referred to a physician?

(A) Tinea nigra
(B) Tinea corporis
(C) Tinea cruris
(D) Tinea pedis

Answers and Explanations

1. The answer is E *[see VI.E.1]*.
The SPF is the minimal erythema dose (MED) of protected skin divided by the MED of unprotected skin. Thus, 2 hrs and 20 mins (140 mins) divided by 20 mins equals an SPF of 7.

2. The answer is D *[see IV.E.2]*.
For patients with inflammatory acne, the best product is a mild facial soap used two times a day. The soap should be gently rubbed into the skin with only the fingertips. Cleansing products that irritate already inflamed skin should be avoided.

3. The answer is C *[see IX.G.4.b.(5).(f)]*.
Reapplication of pyrethrins with piperonyl butoxide should be within 7 to 10 days of the first application. Any lice nits that were not killed on the first application would have time to hatch and then be killed with the second application.

4. The answer is B *[see IX.G.4.a; IX.G.6.c]*.
Pyrethrins with piperonyl butoxide in an aerosol form can be sprayed directly on inanimate objects (e.g., chairs, headrests) to kill head lice, but the combination should not be sprayed in the air like an aerosol deodorizer. Moreover, vacuuming the furniture would

probably be as effective as spraying it. The other selections are appropriate for personal articles infested with head lice.

5. **The answer is B** *[see VI.E.2; VI.D.3.c]*.
Octyl methoxycinnamate and homosalate protect against only UVB exposure. Because photosensitivity reactions are often associated with UVA radiation exposure, people also need sunscreen protection for this portion of the UV radiation band. The other agents listed cover at least part of both UVA and UVB spectra.

6. **The answer is D** *[see I.D.3–4; I.E.2]*.
Ivy Block is used as a barrier protectant for the prevention of poison ivy dermatitis, *not* for the treatment of an acute eruption. The other options are appropriate to recommend to someone suffering from the acute stage of poison ivy dermatitis.

7. **The answer is A** *[see IV.D.3]*.
Evidence does not show that acne definitively worsens from any particular type of food, including chocolate or fried foods. The other choices are pieces of information that the pharmacist should convey to a patient with acne.

8. **The answer is B** *[see IV.E.4.a]*.
Although the irritating properties of benzoyl peroxide might dictate applying it only every other day on initiating treatment, this patient has tolerated the agent on a daily basis for 2 months. Thus, there would be no need to decrease the application frequency. All of the other choices do apply to this patient's use of benzoyl peroxide.

9. **The answer is A** *[see I.D.4.a]*.
Ferric oxide provides the pink color of calamine. All of the other descriptions match their associated agents.

10. **The answer is C** *[see VI.C.2.; VI.E.1.a.(2); VI.E.1.b.; VI.E.1.b.(1)]*.
Baby oil is not a sunscreen, and it has no effect on melanin. SPF does measure UVB protection, and an SPF higher than 50 must be labeled SPF "50+". Water-resistant sunscreen products must retain their SPF value after 40 mins of water activity. The intensity of the sun does increase by 4% with each 1,000-ft rise in elevation.

11. **The answer is C** *[see VI.D.2; VI.E.1; VI.E.2.b; VI.E.2.b.(5)]*.
Optimally, sunscreens should be applied 1 to 2 hrs before exposure to the sun. This allows time for the product to bind to the stratum corneum, which provides better protection. The other responses are correct.

12. **The answer is C** *[see V.D.1.a–c]*.
Patients who suffer with dry skin should be counseled on bathing or showering for brief periods (3 to 5 mins) with lukewarm water.

13. **The answer is B** *[see II.A.2; II.C.1.c; II.C.1.f; II.D.1.i]*.
Dandruff is not typically a serious medical condition, but embarrassment to the patient is a real concern and must be considered when offering the patient treatment options.

14. **The answer is D** *[see II.E.2.a.(2)–(3)]*.
Ketoconazole is not an appropriate treatment option for psoriasis (the only scaly dermatosis for which ketoconazole is not indicated).

15. **The answer is A** *[see III.D.2.a.(1)]*.
Only three types of tinea infections respond to self-treatment with nonprescription therapies: tinea corporis, tinea cruris, and tinea pedis. All other tinea infections should be referred to a physician for evaluation and treatment.

Study Questions

Directions: Each of the questions, statements, or incomplete statements can be correctly answered or completed by **one** of the suggested answers or phrases. Choose the **best** answer.

1. All of the following statements about dietary supplements are true *except* which one?

(A) Manufacturers are not required to demonstrate product safety and efficacy before marketing supplements.
(B) Adherence to good manufacturing practices is not mandatory for manufacturers of dietary supplements.
(C) The U.S. Food and Drug Administration (FDA) files action against supplements determined unsafe.
(D) The Federal Trade Commission (FTC) takes action against manufacturers who present misleading product advertising.

2. All of the following statements about chitosan are true *except* which one?

(A) It is a common ingredient found in fat-trapper supplements.
(B) It is derived from the Indian cluster bean.
(C) Its safety is questionable for individuals with shellfish allergies.
(D) It is purported to inhibit dietary fat absorption.

3. Jane is 36 years old and wants to lose weight. Her current body mass index (BMI) is 32 kg/m^2, her waist circumference is 40 inches, and her weight is 202 lbs. She has lost a minimal amount of weight in the past using fad diets and nonprescription weight loss products but has been unable to maintain the weight loss. All of the following are true, *except*

(A) Based on her BMI, Jane is considered obese.
(B) Her waist circumference of 40 inches increases her risk for cardiovascular disease.
(C) A safe rate of weight loss for Jane would be 1 to 2 lb/week.
(D) Initiation of exercise will provide more weight loss than dietary intake changes.
(E) Her weight is a risk factor for the development of type 2 diabetes.

4. Since the sudden death of his father 2 weeks ago, Bob has been unable to sleep at night. He has difficulty going to sleep and awakens early in the morning, unable to return to sleep. Which of the following would be the correct classification of Bob's current insomnia?

(A) transient, primary insomnia
(B) short-term, primary insomnia
(C) transient, secondary insomnia
(D) short-term, secondary insomnia

5. William works the swing shift at the local manufacturing plant. Based on a recommendation from a friend at work, William would like to try melatonin to help him get to sleep faster. Which of the following is true regarding William's use of melatonin?

(A) An appropriate starting dose of melatonin is 5 mg/night.
(B) William may experience continued drowsiness the following morning owing to melatonin's long half-life.
(C) Recent trials have noted the effectiveness of melatonin in individuals participating in shift work.
(D) Tobacco use will increase endogenous melatonin production.

6. Which of the following complementary alternative medicines (CAM) is most strongly associated with hepatotoxicity, including hepatitis, cirrhosis, and liver failure?

(A) melatonin
(B) kava
(C) chitosan
(D) valerian root
(E) dandelion

7. Sylvia is 33 years old and wishes to purchase a sleep aid for her recent bout of insomnia (duration is 2 days). She has linked it to an overwhelming amount of stress she has been under lately at work, trying to meet deadlines, and her recent lack of sleep is not helping. She has no current medical conditions and takes a multivitamin daily. All of the following are true regarding Sylvia's taking diphenhydramine and doxylamine *except* which one?

(A) Sylvia may benefit from diphenhydramine 50 mg used nightly.
(B) Sylvia may use diphenhydramine for insomnia for up to 10 consecutive nights.
(C) Sylvia may benefit from doxylamine 50 mg used nightly as needed.
(D) Sylvia may experience anticholinergic side effects with the use of doxylamine.

8. Jill, a 22-year-old college student, has been encouraged by her health care provider to stop smoking. She tells her doctor that she wants to quit, but she does not want to gain weight right now or to sacrifice her grades as a result of an inability to concentrate during the day. According to the five As and the transtheoretical model of change, what is the next step Jill's health care provider should take?

(A) Jill is in the precontemplation stage of change. Her provider should reassess her willingness to quit at the next visit.
(B) Jill is in the contemplation stage of change. Her provider should reassess her willingness to quit at the next visit.
(C) Jill is in the preparation stage of change. Her provider should reassess her willingness to quit at the next visit.
(D) Jill is in the preparation stage of change. Her provider should offer her counseling and/or pharmacologic therapy for smoking cessation.

9. Zack is 55 years old and wishes to start taking nicotine lozenges to quit smoking. Which of the following is important in the recommendation and selection of nicotine lozenges?

(A) number of cigarettes smoked daily
(B) timing of his first urge for a cigarette
(C) concomitant disease states and therapies
(D) both the number of cigarettes smoked daily and concomitant disease states and therapies
(E) both the timing of his first urge for a cigarette and concomitant disease states and therapies

10. All of the following are important counseling tips for the use of nicotine replacement therapies *except* which one?

(A) Do not eat or drink within 15 mins of chewing nicotine gum.
(B) The initial start of nicotine replacement therapy may be 30 mins after the last cigarette.
(C) Skin irritation associated with the use of a patch may be minimized by rotating the patch site.
(D) Patches should be removed after 8 hrs of use if the person experiences insomnia.

11. Wendy, a 45-year-old female, is seeking advice about the use of Alli® for weight loss. Her current weight is 228 lbs and her height is 5′6″. At her last provider visit, her provider suggested she set a weight loss goal of 2 lbs per week through diet and exercise. Wendy has type 2 diabetes and hypertension, both of which are well controlled. Which of the following would be appropriate information to provide Wendy?

(A) Orlistat may assist in modest amounts of weight loss, but noticeable results may not be evident for several months.
(B) Orlistat is contraindicated in individuals with diabetes mellitus.
(C) Orlistat is taken as 1 capsule three times daily 1 hr after a fat-containing meal.
(D) Orlistat may reduce the absorption of fat-soluble vitamins, thus a multivitamin should be taken when nonprescription orlistat is initiated.

Answers and Explanations

1. The answer is B *[see I.C]*.
Manufacturers of dietary supplements (DS) are not required to demonstrate product safety and efficacy before marketing. Previously, manufacturers of DS were not required to adhere to good manufacturing practices. However, in 2007, FDA ruled that DS must be manufactured in a manner that ensures quality and the DS must be properly packaged and labeled.

2. The answer is B *[see I.C.5.e]*.
Derived from the exoskeleton of shellfish, chitosan is purported to block dietary fat absorption and thus is a common ingredient found in fat-trapper supplements. Because it is derived from the exoskeleton of shellfish, the safety of chitosan in individuals with shellfish allergies remains in question.

3. The answer is D *[see I.A.1–2; I.B.1.b–c; I.B.2]*.
A BMI $>$ 30 kg/m^2 is considered obese. Women with a waist circumference $>$ 35 inches are at increased risk of developing cardiovascular disease, as well as type 2 diabetes, sleep apnea, and osteoarthritis. If Jane's BMI had been $>$ 35 kg/m^2, her waist circumference measurement would not be valid for determining an increased cardiovascular risk. Diet and exercise are the best approach to weight loss; however, exercise only adds a modest amount of weight loss. Decreased dietary consumption will provide the most benefit in her efforts to lose weight. A reasonable weight loss is 1 to 2 lb/week.

4. The answer is D *[see II.B.3–4]*.
Transient insomnia is insomnia lasting $<$ 1 week, and short-term insomnia is insomnia lasting from 1 to 3 weeks. Primary insomnia is a pathological condition in which the patient experiences continued insomnia in the absence of a related medical or psychiatric condition. Secondary insomnia can be attributed to a variety of situations, especially situational stress, such as the death of a loved one.

5. The answer is C *[see II.B.5.b.(3)]*.
Melatonin effectiveness for sleep onset has been observed in recent trials in individuals participating in shift work. However, melatonin is not FDA approved for this purpose. An initial starting dose of melatonin is 0.1 to 0.3 mg in the evening for patients desiring improved sleep onset. Doses $>$ 1 mg daily have not been able to demonstrate the quality sleep restoration seen in 0.3-mg doses. Melatonin has minimal, if any, residual effects the following morning, owing to its short half-life of 30 to 50 mins. Tobacco, alcohol, and certain medications can decrease endogenous melatonin production.

6. The answer is B *[see II.B.5.b.(5)]*.
Kava, typically used for anxiety disorders, has been associated with hepatoxicity, including hepatitis, cirrhosis, and liver failure. An FDA advisory committee has recommended against the use of kava because of the reports of hepatotoxicity.

7. The answer is C *[see II.B.5.b.(1)–(2)]***.**
Diphenhydramine may be dosed as 25 to 50 mg nightly for a sleep aid used for up to 7 to 10 consecutive nights. The recommended dosage for doxylamine is 25 mg nightly. Both diphenhydramine and doxylamine are ethanolamine antihistamines. Therefore, anticholinergic effects may be experienced with the use of either agent.

8. The answer is B *[see III.E.6]***.**
Jill is in the contemplation stage, as she is considering a change in the future, but she does not feel that this is the right time to begin a smoking cessation program. Therefore, Jill's provider should reassess her willingness to quit at her next visit, when, it is hoped that Jill will be ready to quit.

9. The answer is E *[see III.F.3.b]***.**
Dosing is based on the timing of the first urge for a cigarette, either within or after 30 mins of waking up. Concomitant disease states should be considered as well. If the patient has hypertension, he will need to be monitored more closely while using nicotine replacement therapy. If he uses certain prescription medications for asthma or depression, his medication may need to be adjusted when he stops smoking.

10. The answer is D *[see III.F.3.a–c]***.**
Nicotine patches should be worn for 24 hrs. If the patient develops insomnia or vivid dreams from the patch, it may be removed before bed, thus allowing only 16 hrs of exposure to the nicotine. Use of the patch for only 8 hrs is not an acceptable recommendation. Patch application sites should be rotated to avoid skin irritation and patients should be counseled not to eat or drink within 15 mins of chewing the gum.

11. The answer is A *[see I.B.2]***.**
Orlistat may alter metabolic control, necessitating a change in diabetes medication dosing regimen; however, orlistat is not contraindicated in patients with diabetes. Orlistat is dosed as 1 capsule three times daily with a fat-containing meal, but for optimal effects, it should be dosed during or within 1 hr of the meal not after the meal. It is advisable to recommend a multivitamin to individuals who will be using doses of orlistat greater than 180 mg/day or who will be using orlistat for longer than 2 to 3 months. However, at initiation of nonprescription strength orlistat (60 mg thrice daily), a multivitamin has not been observed as necessary; however, it would be advisable if the individual does continue the medication past 2 to 3 months to recommend a MVI.

Study Questions

Directions: Each of the questions, statements, or incomplete statements can be correctly answered or completed by **one** of the suggested answers or phrases. Choose the **best** answer.

1. Which statement concerning the use of over-the-counter (OTC) analgesic agents is true?

(A) Aspirin is indicated for mild to moderate analgesia, inflammatory diseases, antipyresis, and prophylaxis for patients with ischemic heart disease.
(B) Ibuprofen is indicated for mild to moderate analgesia, reduction of fever, and prophylaxis for patients with ischemic heart disease but not for inflammatory disorders.
(C) Acetaminophen is indicated for mild to moderate analgesia but not for reduction of fever and osteoarthritis.
(D) Naproxen sodium is indicated for mild to moderate analgesia, antipyresis, and prophylaxis for patients with ischemic heart disease.

2. Which statement concerning drug interactions with over-the-counter (OTC) analgesic agents is true?

(A) Aspirin potentiates the effects of antihypertensives, cardiac glycosides, and anticoagulants.
(B) Ibuprofen potentiates the effect of zidovudine, hypoglycemics, and aminoglycosides.
(C) Acetaminophen potentiates the effect of zidovudine.
(D) For naproxen sodium, the OTC dosage recommendations are similar to the prescription dosage.

3. All of the following statements concerning contraindications with chronic use of over-the-counter (OTC) analgesic agents are correct *except* which one?

(A) Aspirin, ibuprofen, and naproxen sodium are contraindicated in patients with bleeding disorders, peptic ulcer, and the third trimester of pregnancy.
(B) Aspirin, acetaminophen, and ibuprofen are implicated in Reye syndrome.
(C) Acetaminophen is contraindicated in patients with active alcoholism, hepatic disease, or viral hepatitis.

4. Which statement concerning dosage recommendations for over-the-counter (OTC) analgesic agents is true?

(A) Aspirin for analgesia or antipyresis in adults is 325 to 650 mg every 4 hrs or 650 to 1000 mg every 6 hrs, with a maximum daily dose of 4000 mg for no longer than 10 days for pain or 3 days for fever without consulting a physician; the antirheumatic dosage for adults is 3600 to 4500 mg daily in divided doses; and patients with ischemic heart disease should take 325 mg daily or every other day.
(B) Ibuprofen for analgesia or antipyresis in adults is 300 to 600 mg every 6 to 8 hrs, with a maximum daily dose of 1800 mg for no longer than 10 days for pain or 3 days for fever without consulting a physician; the anti-inflammatory dosage for adults is 1800 to 3600 mg daily in divided doses.
(C) Acetaminophen for analgesia or antipyresis in adults is 325 mg every 8 to 2 hrs, with a maximum daily dose of 2000 mg for no longer than 10 days for pain and 3 days for fever without consulting a physician; patients with ischemic heart disease take 325 mg daily or every other day.

5. Which of the following is an inhaler ingredient deemed safe and effective for nasal congestion?

(A) oxymetazoline
(B) phenylephrine
(C) levmetamfetamine
(D) pseudoephedrine

6. A 27-year-old presents with sneezing, rhinorrhea, and nasal itching, which started 2 days ago. She feels miserable with her symptoms, which worsen when she cleans the house. Her current medications include calcium carbonate and docusate sodium. Which of the following would be the *best* recommendation for immediate symptom alleviation?

(A) chlorpheniramine
(B) pseudoephedrine
(C) topical nasal strips
(D) intranasal cromolyn

7. A 48-year-old presents with a chief complaint of a dry, hacking cough, which started yesterday. He denies fever, chills, sore throat, or congestion. His only medical condition is hypertension, which is controlled with hydrochlorothiazide (HCTZ). What would be the *best* recommendation for alleviation of his cough?

(A) dextromethorphan
(B) phenylephrine
(C) fexofenadine
(D) guaifenesin

8. Which of the following is an appropriate candidate for self-treatment with codeine for cough?

(A) 4-year-old with nonproductive cough
(B) 6-year-old with nonproductive cough
(C) 15-year-old with productive cough
(D) 22-year-old with productive cough
(E) 92-year-old with nonproductive cough

For questions 9–10: A 42-year-old male complains of a scratchy throat, nasal congestion, and a cough that started 2 days ago. When he coughs, he brings up yellow-white phlegm. He has hypertension and dyslipidemia. Current medications include simvastatin, lisinopril, hydrochlorothiazide, carvedilol, hydralazine, isosorbide dinitrate, and amlodipine.

9. Which of the following would be the *best* recommendation for this person's cough?

(A) codeine
(B) dextromethorphan
(C) diphenhydramine
(D) guaifenesin

10. Which of the following would be the *most* appropriate recommendation for his nasal congestion?

(A) Oral pseudoephedrine
(B) Oral phenylephrine
(C) Topical oxymetazoline
(D) Topical levmetamfetamine

11. A 22-year-old female presents with sneezing, watery and itchy eyes, and a runny nose. She has no significant medical history, but she is in the midst of final exams and must remain alert. What would be the *best* recommendation for her symptoms?

(A) Fexofenadine
(B) Diphenhydramine
(C) Brompheniramine
(D) Levmetamfetamine

Answers and Explanations

1. The answer is A *[see I.B]*.
Aspirin is the only analgesic agent with an approved labeling for analgesia, antipyresis, inflammation, and prophylaxis for ischemic heart disease.

2. The answer is C *[see I.C]*.
Acetaminophen may competitively inhibit the metabolism of zidovudine, resulting in potentiation of zidovudine or acetaminophen toxicity. As for the other choices, OTC dosage levels are generally one-half the prescription dosage; aspirin is not commonly recognized to interact with antihypertensives or cardiac glycosides; nor is acetaminophen expected to interact with aminoglycosides.

3. The answer is B *[see I.B.4.b]*.
Aspirin is the only analgesic agent associated with the development of Reye syndrome.

4. The answer is A *[see I.B.3; I.C.3; I.D.3]*.
The aspirin dosage OTC recommendations are correct; the levels for acetaminophen are too low, and for ibuprofen, too high. In addition, acetaminophen does not carry an ischemic heart disease prophylaxis recommendation.

5. The answer is C *[see II.F.1.b.(1)]*.
Levmetamfetamine is an inhaler ingredient that has been deemed by the FDA as safe and effective as a nasal decongestant. It is currently found in Vicks Vapor Inhaler. Oxymetazoline and phenylephrine are topical nasal decongestants found in pumps and drops but not in inhalers.

6. The answer is A *[see II.F.4; III.E.5]*.
Rhinorrhea, sneezing, and nasal itching are symptoms of allergic rhinitis. Pseudoephedrine and topical nasal strips are indicated for nasal congestion, which she does not have. Both chlorpheniramine and intranasal cromolyn sodium are recommended treatments for the relief of sneezing and rhinorrhea. However, this patient needs immediate relief, and cromolyn sodium will take 1 to 2 weeks for noticeable symptom improvement.

7. The answer is A *[see II.F.6]*.
The complaint is a dry, hacking cough, warranting the use of an antitussive rather than an expectorant (e.g., guaifenesin). Dextromethorphan is the only choice of antitussives provided.

8. **The answer is B** *[see II.F.6.b]***.**
Codeine is appropriate for ages 6 and up for a nonproductive cough. Although a 92-year-old with a nonproductive cough fits this criteria, caution should be taken due to adverse effects associated with codeine.

9. **The answer is D** *[see II.F.5]***.**
The patient is experiencing a productive cough, as noted by the yellow-white phlegm. An expectorant is the best agent for relief of a productive cough. The only available expectorant is guaifenesin, which works to loosen sputum and to thin bronchial secretions by irritating the gastric mucosa and stimulates secretions of the respiratory tract.

10. **The answer is D** *[see II.F.1.c]***.**
Pseudoephedrine, phenylephrine, and oxymetazoline should be used cautiously in the patient with hypertension, particularly a patient on this many antihypertensive agents, due to stimulation of adrenergic receptors. Levmetamfetamine lacks a vasopressor effect and therefore is the least likely agent to affect his blood pressure.

11. **The answer is A** *[see III.E.2]***.**
Levmetamfetamine, a nasal decongestant, would offer no benefit for the symptoms described. Although diphenhydramine and brompheniramine are first generation antihistamines, both would cause significant sedation when the patient needs to remain alert. Additionally, brompheniramine is not available as a single-ingredient product. Fexofenadine would alleviate the described symptoms without causing increased sedation.

Study Questions

Directions: Each of the questions, statements, or incomplete statements in this section can be correctly answered or completed by **one** of the suggested answers or phrases. Choose the **best** answer.

1. Which laxative should *not* be used to treat acute constipation because of its slow onset of action?

(A) glycerin
(B) bisacodyl suppository
(C) psyllium
(D) milk of magnesia

2. All of the following statements about emollient stool softener laxatives are true *except* which one?

(A) They are not first-line treatment for the typical individual with acute constipation.
(B) They are appropriate for individuals who should not strain by passing a hard stool.
(C) They are known as surfactants and include docusate calcium and docusate sodium.
(D) They are highly associated with the development of acute phosphate nephropathy.

3. Which of the following statements adequately describes bulk-forming laxatives?

(A) They can cause diarrhea if not taken with at least 8 oz of water.
(B) They are derived from polysaccharides and resemble fiber in mechanism of action.
(C) They have a relatively fast onset of action of 4 to 8 hrs and duration of 12 to 24 hrs.
(D) They produce a more complete evacuation of the bowels than stimulant products.

4. Which local anesthetic should be used to treat symptoms of pain, itching, burning, and discomfort in patients with an established lidocaine allergy?

(A) tetracaine
(B) dibucaine
(C) pramoxine
(D) benzocaine

5. Which of the following is the most common sign/symptom of hemorrhoids?

(A) bleeding
(B) pain
(C) seepage
(D) pruritus

6. Which of the following agents is designated as a safe and effective analgesic, anesthetic, and antipruritic by the FDA?

(A) witch hazel
(B) juniper tar
(C) hydrocortisone
(D) phenylephrine

7. All of the following symptoms associated with gastroesophageal reflux may be treated with nonprescription agents *except*

(A) burning sensation located in the lower chest.
(B) pain that is worse after meals.
(C) pain or difficulty when swallowing.
(D) pain that is worse in a recumbent position.

8. Which of the following is an appropriate nonpharmacological recommendation for patients with gastroesophageal reflux?

(A) Eat larger but fewer meals.
(B) Avoid meals high in protein.
(C) Eat evening meals at least 3 hrs before bed.
(D) Prop the head up with two pillows at night.

9. Which of the following would be the most appropriate to recommend for self-care to an individual wanting fast but extended relief from heartburn?

(A) Proton pump inhibitor
(B) H_2RA
(C) Aluminum (+) Magnesium antacid
(D) H_2RA (+) antacid

10. All of the following are acceptable uses of magnesium hydroxide *except*

(A) heartburn.
(B) dyspepsia.
(C) hemorrhoids.
(D) constipation.

Answers and Explanations

1. **The answer is C** *[see I.B.2]*.
Glycerin and the bisacodyl suppository all produce stools in 30 mins to a few hours, whereas psyllium, a bulk-forming laxative, produces stool in 24 to 72 hrs in the same manner as a normal bolus of food or fiber.

2. **The answer is D** *[see I.B.2.d]*.
These agents, known as surfactants (docusate calcium and docusate sodium), have a long onset of action (24 to 48 hrs); thus they should never be used for acute constipation but should be used mainly for patients who should not strain to pass hard stools (e.g., pregnant patients, postsurgical patients, postmyocardial infarction). Oral sodium phosphate (OSP), a saline laxative, has been associated with acute phosphate nephropathy, but not emollient laxatives.

3. **The answer is B** *[see I.B.2.a; I.B.2.c]*.
Stimulant products result in a quicker, more complete, and often more violent evacuation of the bowel than do the bulk-forming agents. Bulk-forming agents are developed from complex sugars, similar to fiber, that provide bulk to increase gastrointestinal motility and water absorption into the bowel. However, patients must drink plenty of water to facilitate the absorption of water into the bowel, or they may become more constipated.

4. **The answer is C** *[see III.F.2.a.(2)]*.
Because of its chemically distinct structure, pramoxine exhibits less cross-sensitivity compared to the other anesthetics and should be used in patients with a lidocaine allergy.

5. **The answer is A** *[see III.D.1]*.
The most common sign/symptom of hemorrhoids is painless bleeding occurring during a bowel movement.

6. **The answer is B** *[see III.F.2.f]*.
Juniper tar, menthol, and camphor are the only three agents deemed safe and effective as analgesics, anesthetics, and antipruritics by the FDA.

7. **The answer is C** *[see IV.A.5]*.
Pain on swallowing often suggests severe esophageal mucosal damage, which would require prescription medications for healing. Difficulty on swallowing may indicate an esophageal stricture, cancer, or motor disorder. All of these conditions require diagnosis and treatment by a health care provider.

8. **The answer is C** *[see IV.B.1.a–g]*.
Patients should be instructed to eat evening meals at least 3 hrs before going to bed. This allows sufficient time for gastric emptying, so that the volume of refluxed material will be smaller and less irritating to the esophagus.

9. **The answer is D** *[see IV.B.2.e]*.
Proton pump inhibitors have an extended duration of action but a long onset of action, compared to antacids, which have a quick onset of action but a short duration of action. The combination of a H_2RA and an antacid (e.g., Pepcid Complete) allows for a quick onset of action (antacid) with an extended duration of action (H_2RA).

10. **The answer is C** *[see I.B.2.e; IV.B.2.a]*.
Magnesium hydroxide (e.g., Milk of Magnesia) may be used for the symptomatic relief of heartburn, dyspepsia, and constipation. Magnesium hydroxide is most noted for its potential to cause diarrhea. Indirectly, it may provide relief from hemorrhoids if they are due to constipation but will not have a direct effect on alleviation of hemorrhoids.

Study Questions

Directions for questions 1–8: Each of the questions, statements, or incomplete statements in this section can be correctly answered or completed by **one** of the suggested answers or phrases. Choose the **best** answer.

1. The most common cause of vaginal yeast infections is

(A) *Candida albicans.*
(B) *Candida glabrata.*
(C) *Trichomonas.*
(D) anaerobic bacteria.

2. A female complains of vaginal burning and itching with a distinct "fishy" odor. Which of the following would be the most appropriate recommendation?

(A) Purchase the Vagisil pH monitor.
(B) Referral to a medical provider.
(C) Treatment with a 1-day VVC product.
(D) Treatment with a 7-day VVC product.

3. Which of the following would be appropriate to counsel on for a woman who is purchasing a female condom?
   (A) The FC2 is superior to the male condom for pregnancy prevention.
   (B) The FC2 can protect against all sexually transmitted infections.
   (C) The FC2 should be used concomitantly with a male condom.
   (D) The FC2 can be inserted several hours prior to intercourse.

4. When assisting a female with the purchase of a vaginal pH monitor, which of the following should be discussed?
   (A) The pH monitor is not recommended in postmenopausal women.
   (B) An elevated pH indicates the presence of a yeast infection.
   (C) The pH of a clean-catch morning urine sample should be used.
   (D) The pH monitor can detect the presence of sexually transmitted infections.

5. Which of the following would be an appropriate counseling point for a female purchasing intravaginal miconazole?
   (A) Avoid treatment during menstruation.
   (B) All male partners should be treated.
   (C) Avoid concomitant use of external creams.
   (D) Side effects can include burning or irritation.

6. All of the following statements regarding contraceptives are correct *except* which one?
   (A) Using the basal temperature method, intercourse should be avoided for a full 6 days after the noted temperature transition.
   (B) If a condom should break or leak, one could recommend immediate insertion of a vaginal spermicide foam.
   (C) Vaginal spermicides may kill many of the causative agents of sexually transmitted diseases (STDs), but they should not be relied on alone for STD prevention.
   (D) Latex condoms can be labeled for the prevention of HIV transmission.
   (E) Nonoxynol-9 is a safe and effective vaginal spermicide.

7. Which of the following agents can be used alone for protection against sexually transmitted infections?
   (A) Contraceptive foam
   (B) Contraceptive sponge
   (C) Female condom
   (D) Diaphragm

8. A 17-year-old female reports breakage of a condom last night during intercourse. She has not been using oral contraception because she smokes. Which of the following would be appropriate to counsel for this patient on Plan-B One-Step?
   (A) She needs a prescription to purchase Plan-B One-Step.
   (B) Take one tablet now and the second tablet 12 hrs later.
   (C) Take Plan B One-Step within 72 hrs of intercourse.
   (D) She is not a candidate for EC because of her tobacco use.
   (E) She can use this continuously for back-up contraception.

Directions for questions 9–10: Each statement in this section is most closely related to **one** of the following drug types. The drug types may be used more than once or not at all. Choose the **best** answer, **A–D**.

A Diuretics
B Salicylates
C Nonsteroidal anti-inflammatory drugs (NSAIDs)
D Narcotic analgesics

9. The primary nonprescription pharmacological treatment for pain associated with dysmenorrhea

10. Recommended by the FDA for elimination of water before and during menstruation

Answers and Explanations

1. **The answer is A** *[see II.A.1.b]*.
   Candida albicans remains the most common cause. Infections caused by *C. glabrata* are increasing. *Trichomonas* and anaerobic bacteria cause other types of vaginal infections.

2. **The answer is B** *[see II.A.3.f]*.
   The symptoms of vaginal burning and itching are consistent with VVC; however, the distinct "fishy" odor is more indicative of bacterial vaginosis, which requires prescription treatment. Although a pH monitor may show that the vaginal pH is elevated with a bacterial infection, the woman would still have to seek medical care.

3. **The answer is D** *[see III.B.4.a]*.
   The FC should not be used concomitantly with the male condom because of the increased risk of breakage. Its pregnancy rates are higher than the male condom; and although it does protect against some sexually transmitted infections, it does not protect against all of them. The FCs can be inserted up to 8 hrs prior to intercourse.

4. **The answer is A** *[see II.A.2]*.
   The vaginal pH should not change with a yeast infection but may with other vaginal infections. The sample is taken by pressing a wand against the vaginal wall, not collecting a urine sample. The monitor is not recommended for women who lack estrogen (such as postmenopausal women) or for the detection of sexually transmitted diseases.

5. **The answer is D** *[see II.A.4.e]*.
   Intravaginal treatment for VVC can be used during menstruation and can be used in combination with external creams. It is not necessary for male partners to be treated. Side effects can include burning or irritation.

6. **The answer is A** *[see III.B.1.b]*.
   Intercourse should be avoided for a full 3 days after the noted temperature transition. All of the other statements are correct.

7. **The answer is C** *[see III.B]*.
   The diaphragm and spermicidal agents such as the contraceptive foam or sponge can be used alone to protect against pregnancy but cannot be used alone for prevention of sexually transmitted diseases.

8. **The answer is C** *[see III.B.7]*.
   Plan B One-Step is most efficacious when taken within 24 hrs of intercourse but can be used up to 72 hrs after with efficacy data. It is FDA approved as a nonprescription item for individuals ages 17 and up and is a single dose tablet, as opposed to Next Choice, which is a two-step process described in answer choice B. Smoking is not a contraindication to the use of this agent.

9. **The answer is C** *[see I.B.1.d.(2)]*.
   NSAIDs are approved by the FDA for the treatment of primary dysmenorrhea.

10. **The answer is A** *[see I.B.2.c.(1).(a)]*.
    For premenstrual and menstrual relief of water retention, bloating, and tension, the FDA has approved OTC diuretics.

Study Questions

Directions for questions: Each of the questions, statements, or incomplete statements can be correctly answered or completed by **one** of the suggested answers or phrases. Choose the **best** answer.

1. Which of the following herbs is known to cause cancer?

(A) Chaparral
(B) Comfrey
(C) Ma huang
(D) Licorice
(E) St. John's wort

2. Which of the following is a correct statement?

(A) Dietary supplements must be proven safe and effective before marketing in the United States.
(B) The following statement is optional for labeling of herbal products: "This product has not been evaluated by the FDA. It is not intended to diagnose, treat, cure, or prevent."
(C) Herbs must be standardized to be considered dietary supplements.
(D) Dietary supplement manufacturers may claim that their products affect the structure and function of the human body.
(E) Congress determines what is considered a supplement and what is considered a drug.

3. Tom would like to try echinacea to prevent cold and flu during the winter months. Which of the following statements is true about echinacea?

(A) It is contraindicated in patients allergic to parsley.
(B) It should be taken continuously only for 3 months.
(C) It is contraindicated in patients with lupus and leukosis.
(D) Prolonged use of echinacea will up regulate the immune system.
(E) Side effects include headache, rash, and dizziness.

4. Mary has a family history of heart disease and wonders if garlic would be beneficial to her. Which of the following statements is correct about garlic?

(A) Enteric-coated tablets release their contents in the stomach.
(B) Side effects include heartburn, flatulence, and sweating.
(C) The safety of garlic in pregnancy is unknown.
(D) Garlic does not interact with warfarin.

5. An 80-year-old man takes warfarin for his mechanical heart valve. He would also like to take the following herbs: Asian ginseng, feverfew, garlic, and dong quai. Which of these herbs may decrease the effectiveness of warfarin?

(A) Asian ginseng
(B) Feverfew
(C) Fish oil
(D) Garlic
(E) Dong quai

6. A 30-year-old female is 10 weeks pregnant with her second child. During her first pregnancy, she became depressed and was started on Prozac 20 mg every day. She is already beginning to notice early symptoms of depression during her second pregnancy. She would like to try St. John's wort for her depression. Which of the following statements is correct regarding St. John's wort?

(A) The safety of St. John's wort in pregnancy is unknown.
(B) St. John's wort is not helpful in treating mild depression.
(C) St. John's wort may interact with serotonin reuptake inhibitors.
(D) St. John's wort may interact with dairy products like milk and eggs.
(E) St. John's wort decreases the effects of clopidogrel (Plavix).

7. A 65-year-old is interested in taking ginkgo. Which of the following statements is correct regarding ginkgo?
   (A) There are no contraindications with ginkgo.
   (B) There is a drug–herb interaction between ginkgo and aspirin.
   (C) Toxic effects include hypertension and cardiac arrest.
   (D) There is a drug–herb interaction between ginkgo and phenelzine.
   (E) Ginkgo is contraindicated in patients with gallstone pain.

8. A 20-year-old athletic man would like to take Asian ginseng to increase his physical stamina. His girlfriend suggested that he ask a pharmacist about the safety of Asian ginseng. Which of the following statements is not correct?
   (A) Asian ginseng may interact with phenelzine, warfarin, and digoxin.
   (B) Asian ginseng should be used with caution in patients with a history of breast cancer.
   (C) Asian ginseng may interact with stimulants, including caffeine (Cafcit).
   (D) Asian ginseng should be avoided in patients with hypertension.
   (E) Asian ginseng may cause bradycardia due to increasing the QT interval.

Answers and Explanations

1. **The answer is B** *[see I.B.f]*.
   Comfrey may be carcinogenic. Chaparral may be hepatotoxic. High doses of licorice for long periods may cause pseudoaldosteronism. Ma huang may cause myocardial infarction, strokes, or seizures. St. John's wort has many drug interactions.

2. **The answer is D** *[see I.A.3.a–f]*.
   The Dietary Supplement Health and Education Act of 1994 states that dietary supplements are not considered drugs or food. Because dietary supplements are not regulated as drugs, their safety and efficacy are not mandated by the FDA. Dietary supplements are intended to supplement the diet, do not have to be standardized, may make claims regarding only the effects on structure or function of the body. The following is the correct required labeling statement: "This product has not been evaluated by the FDA. It is not intended to diagnose, treat, cure, or prevent."

3. **The answer is C** *[see II.E.1–6]*.
   Echinacea is contraindicated in infectious and autoimmune diseases such as tuberculosis, leukosis, collagenosis, multiple sclerosis, AIDS, HIV, and lupus. Caution should be used in patients who are allergic to members of the ragweed family. Therapy should not exceed 8 weeks. Theoretically, prolonged use of echinacea may depress the immune system, possibly through overstimulation. Side effects include nausea, vomiting, allergic reactions, anaphylaxis, and interference with male fertility.

4. **The answer is B** *[see II.I.1–8]*.
   Garlic should be avoided in pregnancy because it is an emmenagogue and abortifacient. It may interact with anticoagulants, increasing the risk of bleeding. Side effects include gastrointestinal discomfort (heartburn, flatulence), sweating, light-headedness, allergic reactions, and menorrhagia. Enteric-coated tablets or capsules allow more absorption because they pass through the stomach and release their contents in the alkaline medium of the small intestine.

5. **The answer is A** *[see II.L.5.b]*.
   Asian ginseng may decrease the INR of warfarin. Feverfew, fish oil, garlic, and dong quai may increase the INR of warfarin.

6. **The answer is C** *[see II.O.2–8]*.
   St. John's wort is indicated by Commission E for depression and anxiety. St. John's wort should be avoided in pregnancy because it is an emmenagogue and abortifacient. St. John's wort interacts with many medications, including serotonin reuptake inhibitors. It may interact with clopidogrel by increasing its antiplatelet effects. Food interactions may be similar to those of the MAOIs (tyramine-containing foods: cheese, beer, wine, herring, and yeast).

7. **The answer is B** *[see II.K.1–6]***.**
Contraindications and precautions for ginkgo include diabetes, epilepsy, bleeding disorders, and infertility. Ginkgo may potentiate the bleeding properties of antiplatelets. Side effects include gastric disturbances, headache, dizziness, and vertigo. Toxic ingestion may produce tonic–clonic seizures and loss of consciousness.

8. **The answer is E** *[see II.L.6.e]***.**
Asian ginseng is capable of causing tachyarrhythmias due to QT interval prolongation. Asian ginseng's contraindications include patients with hypertension. Asian ginseng may interact with phenelzine, producing hallucinations and psychosis; may decrease the INR of warfarin; and may interfere with immunosuppressants. Siberian ginseng's contraindications/precautions include hypertension. It may interact with anticoagulants and antihypertensives and may inhibit cytochrome P450 isoenzymes.

Study Questions

Directions: Each of the numbered items or incomplete statements in this section is followed by answers or by completions of the statement. Select the one lettered answer or completion that is **best** in each case.

1. Define therapeutic drug monitoring. What is meant by the term TDM?

(A) The use of drug serum concentration measurements for drugs in which there is (1) a correlation between serum concentration and response and (2) a narrow range of effective and safe concentrations, to assess patient status as an adjunct to clinical observation

(B) The use of drug serum concentration measurements to determine population values for a drug's half-life value

(C) The use of drug serum concentration measurements to assess the accuracy of the drug concentration assay

(D) Observing the effects of drugs in human

(E) Using drug serum concentration measurements to differentiate effective from ineffective drugs

2. The therapeutic range for digoxin is often stated as 0.8 to 2.0 ng/mL. What does this mean?

(A) Fifty percent of people taking digoxin show a safe and effective response when the serum drug concentration is between 0.8 and 2.0 ng/mL.

(B) Most people achieve the desired response to digoxin with minimum adverse effects when the serum digoxin concentration is maintained between 0.8 and 2.0 ng/mL. Fewer patients are managed effectively at < 0.8 ng/mL, but some may respond quite appropriately at lower levels. The frequency of adverse effects increases as the level increases above the upper limit of the therapeutic range, but a few patients are managed effectively without adversity above the range.

(C) Twenty-five percent of people show an effective response to digoxin at < 0.8 ng/mL, and 75% show an effective response at 2.0 ng/mL.

(D) Twice daily administration of digoxin, but not three times daily, requires that serum drug concentrations stay within 0.8 to 2.0 ng/mL.

(E) Digoxin serum drug concentrations outside of the 0.8 to 2.0 ng/mL range are ineffective and/or unsafe.

3. Assume that for digoxin, the therapeutic range is cited as $C_{avg,ss}$ = 0.8 to 2.0 ng/mL. If the patient is assumed to have an estimated digoxin $t_{½}$ of 48 hrs, how long would you wait to take a serum digoxin concentration measurement, and when during τ would you schedule it?

(A) 28 days, then 3 to 4 hrs after the dose is administered
(B) 14 days, then 6 to 8 hrs after the dose is administered
(C) 7 days, then 10 to 14 hrs after the dose is administered
(D) 3 days, then 1 to 2 hrs after the dose is administered
(E) 1 day, then 18 to 22 hrs after the dose is administered

4. Differentiate linear from nonlinear drug clearance. What is the effect on TDM?

(A) Linear drug clearance is first order, the Cl and $t_{½}$ are independent of drug dosage, and proportional changes in dose result in the same proportional changes in C_{ss}. Nonlinear drug clearance is zero order, Cl and $t_{½}$ change as dose changes (or as the amount of drug in the body changes), and proportional changes in dose yield disproportionate changes in C_{ss}.
(B) Linear drug clearance presents fewer serum concentration peaks and troughs during the dosage interval than does nonlinear drug clearance.
(C) Linear drug clearance is zero order, the Cl and $t_{½}$ are dependent on drug dosage, and proportional changes in dose do not result in the same proportional changes in C_{ss}. Nonlinear drug clearance is first order, and equations are not available to predict drug serum concentration from the dose rate.
(D) Drugs with linear clearance have shorter $t_{½}$ values than drugs with nonlinear clearance.
(E) Drugs with linear clearance are administered less often than drugs with nonlinear clearance.

5. What is the positive predictive value of a diagnostic test?

(A) The fraction of patients with a positive outcome who have a positive test result.
(B) Being more than 50% correct in predicting success or failure upon using a drug regimen.
(C) The fraction of patients who achieve a successful response in using a drug.
(D) The fraction of patients with a positive test result who turn out to have a positive outcome.
(E) The probability that knowledge of a drug serum concentration results in a successful response to treatment.

6. A 70-year-old, 80-kg male with serum creatinine of 3 mg/dL is scheduled to start tobramycin therapy. What regimen is recommended to achieve $C_{max,ss}$ within 5 to 10 mcg/mL (use the midpoint of 7.5 mcg/mL for the calculation) and $C_{min,ss} < 2$ mcg/mL. Try an every 24-hr regimen to start and, if unsuccessful in achieving the target concentration goals, alter τ and recalculate. Assume in normals the following values: $t_{½}$ = 2.5 hrs, V = 0.25 L/kg, F = 0.98, S = 1, f = 1, Cl_{cr} = 120 mL/min

(A) A loading dose of 1.8 to 2.0 mg/kg followed by 1.0 mg/kg every day
(B) A loading dose of 1.8 to 2.0 mg/kg followed by 1.5 mg/kg every day
(C) 2.0 mg/kg every day
(D) 1.0 mg/kg every day
(E) 0.5 mg/kg every day

Answers and Explanations

1. **The answer is A** *[see I.B.1]*.

2. **The answer is B** *[see II.B]*.

3. **The answer is C** *[see II.D.3]*.
   If the patient's estimated $t_{½}$ is 48 hrs, 90% of steady state is expected to be achieved between 3 and 4 $t_{½}$ intervals or 6 to 8 days in this case. For clinical purposes, we choose 90% attainment of steady state as the minimum time to estimate drug accumulation. A level drawn at 7 days seems reasonable. Once a τ_{ss} has been selected, the time for scheduling a level should correspond with the reference time for the therapeutic range. In this case, $C_{avg,ss}$ was cited as the reference time, so a measurement scheduled for sometime near the midpoint of τ_{ss} (around 12 hrs) is reasonable.

4. **The answer is A** *[see IV.A–C]*.
   This presents challenges in TDM because for linear drugs, the clinician can expect a change in C_{ss} proportional to a change in dose, but for nonlinear drugs, this is not true.

5. **The answer is D** *[see VII.B]*.
   The positive predictive value of a diagnostic test is an index of how effective the test is in classifying patients correctly. For example, using a C_{ss} measure for a given drug, knowing that the positive predictive value is 0.8, given a group of patients with a C_{ss} above the test cutoff value, 80% of the patients will be accurately classified as having a positive outcome. If the test is being used to classify toxic versus nontoxic patients, 80% of the patients with C_{ss} above the test cutoff will experience drug-induced toxicity. If, instead, the test is being used to classify effective versus subeffective response in patients, 80% of the patients with C_{ss} above the test cutoff will experience effective response.

6. **The answer is B** *[see IV.D.3]*.
   Using the equation for estimating Cl_{cr} in this patient from IV.B.1:

$$Cl_{cr} = (140 - 70 \text{ yrs})(80 \text{ kg})/(3 \text{ mg/dL})(72)$$
$$= 26 \text{ mL/min}$$

   Then, using the equation for estimating $t_{½}$ in this patient from IV.B.2:

$$\frac{(2.5 \text{ hrs})}{(t_{½})_{ri}} = 1 - 0.98 + 0.98\ (26/120)$$
$$= 0.23(t_{½})_{ri} = 10.9 \text{ hrs}$$

   Then, using equation [IV.D.3.c], first determine a loading dose (D_L) to achieve the desired $C_{max,ss}$ of 7.5 mcg/mL:

$$D_L = (C_{max,ss})(V)/(S)(f)$$

$$D_L = (7.5 \text{ mcg/mL})(0.25 \text{ L/kg})/(1)(1) = 1.9 \text{ mg/kg}$$

   Then, determine fraction of drug lost during τ, assuming a τ_{ri} of 24 hrs, and using the $(t_{½})_{ri}$ of 10.9 hrs estimated earlier using the equation in IV.D.3.c:

$$\text{fraction lost} = 1 - 10^{-0.3(24/10.9)} = 0.78$$

$$\text{fraction left} = 10^{-0.3(24/10.9)} = 0.22$$

   Lastly, calculate D per τ_{ri}:

$$\text{D per } \tau_{ri} = (D_L)(\text{fraction lost per } \tau_{ri})$$
$$= (1.9 \text{ mg/kg})(0.78) = 1.5 \text{ mg/kg}$$

   This dose of 1.5 mg/kg every 24 hrs is based on achieving an estimated $C_{max,ss}$ = 7.5 mcg/mL, as noted earlier. To check the estimated $C_{min,ss}$ use equation (3) in [4.A.3]:

$$C_{min,ss} = (C_{max,ss})\ [10^{-0.3(\tau/t_{½})}]$$
$$= (7.5)\ [10^{-0.3(24/10.9)}] = 1.6 \text{ mcg/mL}$$

   Thus, a D_L of 1.9 mg/kg followed by 1.5 mg/kg every 24 hrs is expected to attain the desired $C_{max,ss}$ and $C_{min,ss}$ levels in this patient. Of course, many estimates were made along the way (Cl_{cr}, $t_{½}$, V), so if the patient's $C_{max,ss}$ and $C_{min,ss}$ vary from what has been expected from the calculations, it is likely because of the estimates being at variance with the actual value(s) in the patient.

Study Questions

Directions for questions 1–14: Each of the questions, statements, or incomplete statements in this section can be correctly answered or completed by **one** of the suggested answers or phrases. Choose the **best** answer.

For questions 1–4: AH is a 1.2-kg female born prematurely at 30 weeks of gestational age. Her mother had an infection with a fever at the time of delivery. AH was admitted to the neonatal intensive care unit for presumed sepsis and placed on empiric antibiotic therapy with ampicillin (50 mg/kg IV every 12 hrs) and gentamicin (2.5 mg/kg IV every 8 hrs).

1. Which of the following variables will *most* likely be used to calculate doses for AH's antibiotics?

(A) Height
(B) Hepatic function
(C) Weight
(D) Age
(E) Serum creatinine

2. After the administration of four doses of gentamicin, a serum concentration obtained 5 mins before the next dose was 2.5 mcg/mL. Which of the following answers best describes the pharmacokinetic differences observed in premature neonates (compared to older children and adults) that might explain this value?

(A) Larger volume of distribution, longer half-life
(B) Larger volume of distribution, shorter half-life
(C) Smaller volume of distribution, longer half-life
(D) Smaller volume of distribution, shorter half-life
(E) Similar volume of distribution, shorter half-life

3. Ampicillin may exhibit pharmacokinetic differences in AH because of its protein binding characteristics. Which of the following answers best describes the effect of AH's age on ampicillin protein binding?

(A) Increased protein binding, resulting in a greater free fraction
(B) Increased protein binding, resulting in a reduced free fraction
(C) Decreased protein binding, resulting in a greater free fraction
(D) Decreased protein binding, resulting in a reduced free fraction
(E) Decreased protein binding, resulting in no significant change in free fraction

4. As the pharmacist providing services for the neonatal intensive care unit, you evaluate medication orders and make recommendations to the medical team. Which of the following would be the *most* appropriate recommendation for AH's care?

(A) Change to oral antibiotics for better absorption.
(B) Double-check the calculations to avoid decimal errors.
(C) Dilute the gentamicin with a larger volume of IV fluids to make it easier to measure.
(D) Use a pediatric-specific therapeutic range for monitoring gentamicin.
(E) Change to sulfamethoxazole and trimethoprim (Bactrim) for single-agent antibacterial coverage.

5. Although the total body water content of an adult accounts for approximately 60% of body weight, the total body water content of a healthy newborn is

(A) 40%.
(B) 50%.
(C) 70%.
(D) 80%.
(E) 90%.

6. Administration of a sulfonamide antibiotic may displace bilirubin from binding sites on which of the following substances, leading to passage of bilirubin into the brain and the development of kernicterus?

(A) α_1-acid glycoprotein
(B) albumin
(C) β-adrenergic receptors
(D) uridine 5′-diphosphate glucuronosyltransferase
(E) sulfotransferase

7. Caffeine administered to neonates for the treatment of apnea of prematurity undergoes metabolism through which of the following cytochrome P450 enzymes, also the last major drug-metabolizing enzyme to develop after birth?

(A) CYP1A2
(B) CYP2C19
(C) CYP2D6
(D) CYP3A4
(E) CYP3A7

8. Both glomerular filtration and tubular secretion rates are reduced in infants compared to adults. Which list of drugs is the *most* likely to have prolonged clearance during infancy because of immature renal function alone?

(A) Amikacin, caffeine, and retinoic acid
(B) Acetaminophen, atomoxetine, and retinoic acid
(C) Acetaminophen, benzyl alcohol, and vancomycin
(D) Amikacin, gentamicin, and vancomycin
(E) Atomoxetine, lopinavir, and vancomycin

9. As a pharmacy manager in a children's hospital, you are responsible for implementing new technologies that have the potential to reduce medication errors in children. Which of the following has the *most* potential to reduce the largest number of errors?

(A) Bar-code scanning
(B) CPOE with dose-checking software
(C) Inventory management systems
(D) Smart pump technology
(E) Standard IV concentrations

10. You are counseling the grandmother of a 3-year-old boy who has a prescription for amoxicillin/clavulanate (Augmentin) to treat uncomplicated otitis media. Which of the following issues would be *least* likely to affect medication adherence (compliance)?

(A) Lack of education about the medication
(B) Cost
(C) Dosing interval (frequency)
(D) Taste
(E) Autonomy

Answers and Explanations

1. **The answer is C** *[see I.D.1]*.
Most pediatric doses are based on body weight. This single variable incorporates growth and maturation while allowing a simple calculation for dose. Height is often difficult to measure accurately in children, and the calculation of body surface area is typically reserved for those drugs with narrow therapeutic indices, such as chemotherapy.

2. **The answer is A** *[see I.B.3.a; I.B.5]*.
Aminoglycosides such as gentamicin exhibit a larger volume of distribution in neonates because of their larger body water content. Neonates also typically have a longer elimination half-life as the result of having reduced renal function during the first 6 months of life.

3. **The answer is C** *[see I.B.3.b; Table 27-2]*.
Neonates have both a reduced quantity of plasma proteins as well as a reduction in the affinity of albumin to bind to other substances. As a result, the free fraction of many drugs, including ampicillin, is increased.

4. **The answer is B** *[see I.D; I.E]*.
All pediatric orders should be carefully checked for calculation errors. Errors are more common in the pediatric population as the result of weight-based dosing and the need for mathematical calculations. The use of the oral route would not be advisable in this patient because of the potential reduced drug absorption. Likewise, the dilution of the dose with more IV fluid or the use of a sulfa drug would not be appropriate for this patient's age. Finally, the therapeutic range for gentamicin is the same in pediatric patients as in adults.

5. **The answer is D** *[see I.B.3.a]*.
A healthy newborn will have total body water content approximately 80% of his or her body weight. The higher total body water content is the result of larger extracellular body water content. This value will decrease over the first year of life to reach adult values by 1 year of age.

6. **The answer is B** *[see I.B.3.b; I.B.4.b]*.
Like bilirubin, sulfonamides and other acidic drugs bind to albumin in human serum. In contrast, basic substances bind to α_1-acid glycoprotein. Uridine 5′-diphosphate glucuronosyltransferase and sulfotransferase are metabolic enzymes involved in conjugation.

7. **The answer is A** *[see I.B.4.a]*.
Caffeine is metabolized via CYP1A2 to demethylated xanthines: paraxanthine, theobromine, and theophylline. CYP1A2 is the last of the major drug-metabolizing enzymes to develop during infancy, reaching peak enzymatic activity by 4 to 6 months of life. The pharmacokinetic profile of caffeine during infancy has been extensively studied, with initial publications dating to the 1970s.

8. **The answer is D** *[see I.B.4–5]*.
The aminoglycosides (amikacin, gentamicin, and tobramycin) and vancomycin are examples of drugs that undergo renal elimination and as a result have prolonged clearance in infants. Acetaminophen, atomoxetine, caffeine, lopinavir, and retinoic acid are metabolized. Their clearance is more heavily influenced by hepatic enzymatic activity than by glomerular filtration or tubular secretion rates.

9. **The answer is B** *[see I. D]*.
Mistakes made during ordering account for the largest percentage of pediatric medication errors. The need to calculate the appropriate weight-based dose places the prescriber at risk for mathematical errors, including decimal errors resulting in 10-fold variations in dose. Dose-checking software, a common feature of the CPOE systems of many hospitals and many retail pharmacies, has been shown in several studies to significantly reduce prescriber errors. The other methods, although all associated with reductions in medication error rates, have produced less dramatic results.

10. **The answer is E** *[see I.G]*.
Although the other options are all important aspects of counseling to enhance medication adherence in children, autonomy (the ability to provide self-care or give medications independently) would not be a consideration for a 3-year-old child. Autonomy becomes a much more critical issue in determining adherence in adolescence.

Study Questions

Directions for questions 1–14: Each of the questions, statements, or incomplete statements in this section can be correctly answered or completed by **one** of the suggested answers or phrases. Choose the **best** answer.

1. Which of the following medications due to its lack of active metabolites and dependency on phase II hepatic reactions is least likely to cause a fall in a geriatric patient?

(A) amitriptyline (Elavil®)
(B) haloperidol (Haldol®)
(C) benztropine (Cogentin®)
(D) diazepam (Valium®)
(E) oxazepam (Serax®)

2. Which of the following drugs would be expected to cause anticholinergic adverse effects in the elderly?

(A) diazepam (Valium®)
(B) ciprofloxacin (Cipro®)
(C) tolterodine (Detrol®)
(D) propranolol (Inderal®)
(E) cimetidine (Tagamet®)

3. Which of the following antihypertensive agents should be avoided in elderly patients?

(A) amlodipine (Norvasc®) 5 mg every day
(B) atenolol (Tenormin®) 25 mg every day
(C) benazepril (Lotensin®) 10 mg every day
(D) hydrochlorothiazide (HydroDIURIL®) 25 mg every day
(E) methyldopa (Aldomet®) 250 mg three times a day

4. Which of the following benzodiazepines is expected to cause the *least* amount of adverse effects in the elderly?

(A) chlordiazepoxide (Librium®)
(B) diazepam (Valium®)
(C) flurazepam (Dalmane®)
(D) lorazepam (Ativan®)
(E) temazepam (Restoril®)

5. Which of the following factors is associated with an increased risk of noncompliance in the elderly?

(A) Polypharmacy
(B) Hypertension
(C) Living with a spouse in an isolated environment
(D) Expensive medications
(E) Good relationship with physician

Directions for questions 6-7: The questions and incomplete statements in this section can be correctly answered or completed by **one or more** of the suggested answers. Choose the answer, **A–E**.

A if **I only** is correct
B if **III only** is correct
C if **I and II** are correct
D if **II and III** are correct
E if **I, II, and III** are correct

6. Which of the following pharmacokinetic parameters is most likely to affect the manner in which a drug will affect a geriatric patient?

I. Drug absorption
II. Phase I reactions within the liver
III. Drug distribution

7. Which of the following statements regarding renal excretion in the geriatric patient is correct?

I. All renally eliminated drugs should be monitored for the need for dose reductions in order to reduce potential toxicity.
II. Cockcroft–Gault formula provides a good estimation of creatinine clearance in most patient populations.
III. Serum creatinine is a very sensitive indicator of renal function in the elderly.

8. Patient AM is a 60-year-old obese Caucasian male who is about to be started on several renally eliminated drugs for various diseases he has been diagnosed with. Patient is 5′9″, weighs 220 lb, and has a serum creatinine of 2.0 mg/dL. What is Mr. AM's calculated creatinine clearance?

(A) 56 mL/min
(B) 128 mL/min
(C) 47 mL/min
(D) 109 mL/min
(E) 100 mL/min

Answers and Explanations

1. The answer is E *[see I.D.4.b–c and I.B.4.b]***.**
Medications that can cause orthostatic hypotension, drowsiness, dizziness, blurred vision, or confusion have the potential to cause falls in geriatric patients. Psychoactive agents such as haloperidol along with long-acting benzodiazepines such as diazepam are associated with an increased risk of falls in the elderly. Additionally, agents that have high anticholinergic effects can cause blurred vision while also being capable of inducing delirium (amitriptyline [Elavil®]; benztropine [Cogentin®]). However, oxazepam is a short-acting benzodiazepine dependent on phase II reactions for metabolism, which are not affected by advancing age, and would be a suitable alternative in the elderly patient.

2. The answer is C *[see I.D.5.a; Table 28-3]***.**
Tricyclic antidepressants, antispasmodics, antiemetics, and Parkinson's agents represent the largest group of drugs possessing anticholinergic activity, which have the potential for inducing significant negative effects in the elderly. Blurred vision, urinary retention, constipation, dry mouth, tachycardia, and memory impairment are a few of the significant side effects associated with their use in the elderly. Tolterodine, an antispasmodic, works by antagonizing acetylcholine receptors, which aids patients with an overactive bladder. However, this anticholinergic effect can pose substantial problems in elderly patients due to the side effects associated with its use.

3. The answer is E *[see I; Table 28-2]***.**
The use of methyldopa should be avoided in elderly patients owing to risk of CNS adverse effects and hypotension. Hydrochlorothiazide should be avoided in elderly patient when doses are expected to exceed 25 mg per day.

4. The answer is D *[see I.B.4.a–b and I.D.4.c; Table 28-2]***.**
Chlordiazepoxide, diazepam, and flurazepam should be avoided in elderly patients owing to active metabolites and long-elimination half-lives. Lorazepam represents the safest alternative because of a relatively short half-life, absence of active metabolites, and it is dependent on phase II hepatic metabolism, which is minimally affected with aging while being devoid of phase I hepatic metabolism.

5. The answer is A *[see I.A.1.e]***.**
Lower socioeconomic status, living alone, polypharmacy, complicated drug regimens, poor relationships with health care providers, and multiple disease states are all risk factors for noncompliance in the geriatric population.

6. **The answer is D; II and III are correct** *[see I.B.1–4]*.
Phase I reactions (oxidation, reduction, and hydrolysis) can be reduced in the elderly, and several therapeutic classes such as benzodiazepines and select analgesics represent situations in which changes in hepatic metabolism may be important due to a prolongation of plasma half-lives with a resultant drug accumulation. Drug absorption has been shown to be altered in the elderly; however, the level of alterations has not yet been shown to affect the extent of absorption being reduced. Phase II reactions in the liver are represented by glucuronidation, acetylation, and sulfation and have not yet been shown to require therapeutic adjustments while dosing such agents.

7. **The answer is C; I and II are correct** *[see I.B.3.a–d]*.
The disposition of drugs administered to patients, which are eliminated renally, is the best documented age-related change, which occurs in the elderly. The need to monitor such agents and adjust their doses based on elimination characteristics will help reduce added accumulation and the tendency for toxicity in those with declining renal function. The elderly are predisposed to such effects as renal function is reduced with advancing age. The Cockcroft–Gault formula is a useful tool for estimating most patients' creatinine clearance, when given a serum creatinine; however, it must be recognized that it provides merely an estimate and might not reflect exact renal function is all patient populations. The serum creatinine is used as an indirect measurement for renal function primarily due to its relationship to creatinine clearance and glomerular filtration rate. However, in the elderly due to reduced levels of muscle and consequent reductions in the degree of creatinine produced, normal levels of serum creatinine do not translate into normal levels of renal function.

8. **The answer is A** *[see I.B.3.d]*.

$$\text{Creatinine Clearance (mL/min)} = \frac{(140 - \text{age}) \times (\text{weight kg})}{72 \times \text{serum creatinine (mg/dL)}}$$

$$\text{Creatinine Clearance (mL/min)} = \frac{(140 - 60) \times (100\ \text{kg})}{72 \times \text{serum creatinine (2.0 mg/dL)}}$$

$$\text{Creatinine Clearance (mL/min)} = \frac{(80) \times (100\ \text{kg})}{72 \times (2.0\ \text{mg/dL})}$$

$$\text{Creatinine Clearance (mL/min)} = \frac{8000}{144}$$

$$\text{Creatinine Clearance (mL/min)} = 55.6\ \text{mL/min} = 56$$

Study Questions

Directions for questions 1–8: Each of the questions, statements, or incomplete statements in these sections can be correctly answered or completed by **one** of the suggested answers or phrases. Choose the **best** answer.

1. A 23-year-old woman was diagnosed with significant PMS in her teens, now presents with persistent irritation with her significant other resulting in frequent arguments. Possible therapies for her include all of the following *except*

(A) sertraline 100 mg days 14 to 28.
(B) paroxetine 30 mg daily.
(C) venlafaxine XR 75 mg daily.
(D) clonazepam 1 mg twice daily.
(E) citalopram 20 mg daily.

2. The best therapy for an obese woman with PCOS to improve menstrual regularity will be

(A) spironolactone.
(B) metformin.
(C) weight loss.
(D) pioglitazone.

3. Which of the following therapies enhances osteoblast activity?

(A) Calcium and vitamin D
(B) Calcitonin
(C) Denosumab
(D) Teriparatide
(E) Risedronate

4. Which of the following medications is safe to use in the third trimester of pregnancy?
   (A) Acetaminophen
   (B) Nonsteroidal anti-inflammatory drugs
   (C) Warfarin
   (D) OxyContin
   (E) Aspirin

5. Placental transfer of a drug is affected by all of the following characteristics *except*
   (A) molecular weight.
   (B) fetal gender.
   (C) gestational age.
   (D) lipid solubility of the drug.
   (E) plasma protein binding.

6. When selecting a benzodiazepine product for a woman who has chronic panic disorder, all of the following drug properties are desirable for breastfeeding her 8-month-old infant who was born at term *except*
   (A) hepatic metabolism to inactive metabolites.
   (B) a short half-life.
   (C) a rapid onset of action.
   (D) high lipid solubility.

7. Drug safety in pregnancy of a specific agent can be assessed best by
   (A) the FDA classification system, especially category C drugs.
   (B) case reports.
   (C) physician knowledge.
   (D) databases such as REPROTOX.

8. The primary difference between PMS and PMDD is
   (A) PMS has an earlier onset of symptoms.
   (B) PMS is more debilitating.
   (C) PMDD can be treated with antidepressants.
   (D) PMDD is more common.

Directions for questions 9–12: The questions and incomplete statements in this section can be correctly answered or completed by **one or more** of the suggested answers. Choose the answer, **A–E**.
   (A) if **I only** is correct
   (B) if **III only** is correct
   (C) if **I and II** are correct
   (D) if **II and III** are correct
   (E) if **I**, **II**, **and III** are correct

9. The definition of polycystic ovarian syndrome includes
   I. hyperandrogenism
   II. diabetes
   III. obesity

10. Therapy for stress urinary incontinence can include
   I. oxybutynin
   II. tamsulosin
   III. imipramine

11. Behavioral therapy and bladder retraining is most helpful in which types of incontinence?
   I. stress incontinence
   II. urge incontinence
   III. overflow incontinence

12. According to the principles of drug excretion into the breast milk, which combination of the following properties would result in the *highest* drug concentration in breast milk?
   I. low molecular weight, moderately lipophilic
   II. low plasma protein bound, weakly basic
   III. highly plasma protein bound, weakly acidic

13. Following principles of teratogenicity, drug exposure during which of the following times could cause fetal abnormalities?
   I. first 2 weeks of gestation
   II. weeks 3 to 8 of gestation
   III. the fetal period

Answers and Explanations

1. **The answer is D** *[see I.D.6 and Table 29-1]*.
Clonazepam can be used in premenstrual dysphoric syndrome but should be limited to women who have anxiety as the most prevalent symptom. That is not the case for this woman. All of the remaining agents are appropriate for PMDD. Luteal phase dosing has been studied and may not be as effective as daily therapy.

2. **The answer is C** *[see II.E.1.3-5]*.
Weight loss of 5% to 10% can restore cycle regularity in more than 50% of women. Weight loss and an appropriate diet will also decrease insulin and androgen levels. Spironolactone is helpful for hirsutism but not cycle regularity. Metformin and thiazolidinediones have both been used to improve ovulation and thus cycle regularity. Metformin can also reduce the risk of diabetes development; however, weight loss in the long run will provide the most benefit to the patient.

3. **The answer is D** *[see VII.D.2-8]*.
Teriparatide increases bone mass by stimulating osteoblast activity. Estrogens also stimulate osteoblast activity, but other therapies work by inhibiting osteoclast activity. Denosumab involves the RANK ligand, which then inhibits osteoclast activity.

4. **The answer is A** *[see III.B.3.e.(1)–(2);III.B.4.a–d]*.
Acetaminophen is a safe and effective analgesic that can be used in therapeutic doses during pregnancy. NSAIDs may interfere with the onset or progress of labor when used in the third trimester. NSAIDs and warfarin, when used near delivery, may cause bleeding problems in the newborn infant. In addition, warfarin use in the third trimester may be associated with fetal CNS abnormalities. OxyContin use in the third trimester may induce neonatal withdrawal following delivery.

5. **The answer is B** *[see III.B.2]*.
Fetal gender does not affect placental transfer of a drug. The molecular weight and the lipid solubility of a drug greatly influence its ability to cross the placental membranes. Plasma protein binding affects the amount of free drug available to cross the placenta. Gestational age influences the volume of distribution of the drug as well as the thickness of the placental membranes.

6. **The answer is D** *[see IV.B.5; IV.F.1.a]*.
When any drug is used by a nursing mother, it is desirable to have the least amount of active drug available in the maternal circulation to diffuse into the breast milk. A rapidly acting (for maternal onset of action), rapidly eliminated (i.e., short half-life) drug with inactive metabolites is optimal. If the drug is highly lipid soluble, it is more likely to pass into breast milk.

7. **The answer is D** *[see III.B.3.f]*.
The FDA classification system does not assess risk well in category C drugs. Category A and to some extent category B drugs have been shown to be safest in pregnancy. Case reports of pregnancy exposures tend to bias data toward adverse outcomes. The best source of information is from available databases, such as REPROTOX or Teris, or with published books such as Brigg's *Drugs in Pregnancy and Lactation*.

8. **The answer is C** *[see I.A]*.
PMDD is more debilitating than PMS, usually due to major depression that can accompany the other symptoms. Several antidepressants are available for treatment of PMDD. The onset of symptoms varies with both conditions. PMS is much more common than PMDD.

9. **The answer is A (I)** *[see II.A,B]*.
The definition of polycystic ovarian syndrome includes hyperandrogenism and hyperinsulinemia. Insulin resistance is common and diabetes can result, but these conditions are not part of the diagnosis. Only half of the women with PCOS are obese.

10. **The answer is B (III)** *[see V.E.1.d.(4)]*.
Imipramine is helpful to paralyze the bladder, leading to decreased contractility. Oxybutynin is an anticholinergic agent indicated for urge incontinence. The use of this agent can be helpful in mixed incontinence. Tamsulosin is helpful in some cases of overflow incontinence and this agent can certainly worsen stress incontinence.

11. **The answer is E (I, II, III)** *[see V.E.1.a; V.F.1.a; V.G.1.a]*.
Bladder retraining and behavioral therapy is helpful for all types of incontinence. The type of bladder retraining depends on the type of incontinence although the concepts are similar between stress and urge incontinence. Overflow incontinence bladder also involves voiding at regular intervals, but they are typically not as frequent as those involved with the other types of incontinence.

12. **The answer is C (I, II)** *[see IV.B.1–5]*.
High-molecular-weight substances are less likely to pass into breast milk because of their size. Drugs that are highly plasma protein bound may reach the breast milk only in small amounts, because a large portion of the drug is bound to the maternal plasma proteins and, therefore, only a small amount is free to diffuse into breast milk. A low molecular weight, moderately lipophilic drug passes easily into breast milk. A drug that has a low degree of plasma protein binding has a significant amount of drug free to diffuse into breast milk. A weakly basic drug may ionize after reaching the breast milk and therefore remain trapped in the milk.

13. **The answer is D (II, III)** *[see III.A.1–3]*.
During first 2 weeks after fertilization, the embryo is impervious to teratogens. Any exposure during this time will have either no effect or the embryo will be destroyed. During the remaining weeks of the pregnancy, teratogens may exert effects on the fetus. Teratogenic effects are not always structural in nature; they can be functional or behavioral. Therefore, exposures during the fetal period can also be problematic.

Study Questions

Directions for questions 1–16: Each of the questions, statements, or incomplete statements in this section can be correctly answered or completed by **one** of the suggested answers or phrases. Choose the **best** answer.

1. Hematological testing of a patient with AIDS is most likely to show which of the following abnormalities?

(A) basophilia
(B) eosinophilia
(C) lymphopenia
(D) reticulocytosis
(E) agranulocytosis

2. Hematological studies are most likely to show a low reticulocyte count in a patient who has which of the following abnormalities?

(A) aplastic anemia secondary to cancer chemotherapy
(B) acute hemolytic anemia secondary to quinidine treatment
(C) severe bleeding secondary to an automobile accident
(D) iron-deficiency anemia 1 week after treatment with ferrous sulfate
(E) megaloblastic anemia owing to folate deficiency 1 week after treatment with folic acid

3. All of the following findings on a routine urinalysis would be considered normal *except* which one?
   (A) pH: 6.5
   (B) glucose: negative
   (C) ketones: negative
   (D) white blood cells (WBCs): 3 per high-power field (HPF), no casts
   (E) red blood cells (RBCs): 5 per HPF

4. A 12-year-old boy is treated for otitis media with cefaclor (Ceclor). On the seventh day of therapy, he spikes a fever and develops an urticarial rash on his trunk. Which of the following laboratory tests could best confirm the physician's suspicion of a hypersensitivity (allergic) reaction?
   (A) complete blood count (CBC) and differential
   (B) serum hemoglobin (Hb) and reticulocyte count
   (C) liver function test profile
   (D) lactate dehydrogenase (LDH) isoenzyme profile
   (E) red blood cell (RBC) count and serum bilirubin

5. An increased hematocrit (Hct) is a likely finding in all of the following individuals *except* which one?
   (A) a man who has just returned from a 3-week skiing trip in the Colorado Rockies
   (B) a woman who has polycythemia vera
   (C) a hospitalized patient who mistakenly received 5 L of intravenous (IV) dextrose 5% in water (D_5W) over the last 24 hrs
   (D) a man who has been rescued from the Arizona desert after spending 4 days without water
   (E) a woman who has chronic obstructive pulmonary disease

6. A 29-year-old white man is seen in the emergency room. His white blood cell (WBC) count is 14,200 with 80% polys. All of the following conditions could normally produce these laboratory findings *except* which one?
   (A) a localized bacterial infection on the tip of the index finger
   (B) acute bacterial pneumonia caused by *Streptococcus pneumoniae*
   (C) a heart attack
   (D) a gunshot wound to the abdomen with a loss of 2 pints of blood
   (E) an attack of gout

7. A 52-year-old male construction worker who drinks "fairly heavily" when he gets off work is seen in the emergency room with, among other abnormal laboratory results, an increased creatine kinase (CK) level. All of the following circumstances could explain this increase *except* which one?
   (A) He fell against the bumper of his car in a drunken stupor and bruised his right side.
   (B) He is showing evidence of some liver damage owing to the heavy alcohol intake.
   (C) He has experienced a heart attack.
   (D) He received an intramuscular (IM) injection a few hours before the blood sample was drawn.
   (E) He pulled a muscle that day when lifting a heavy concrete slab.

8. A 45-year-old man with jaundice has spillage of bilirubin into his urine. All of the following statements could apply to this patient *except* which one?
   (A) His total bilirubin is increased.
   (B) His direct bilirubin is increased.
   (C) He may have viral hepatitis.
   (D) He may have hemolytic anemia.
   (E) He may have cholestatic hepatitis.

For questions 9–11: A 70-year-old black man weighing 154 lbs complains of chronic fatigue. Several laboratory tests were performed with the following results:

blood urea nitrogen (BUN) 15 mg/dL
aspartate aminotransferase (AST) within normal limits
white blood cell (WBC) count 7500/mm^3
red blood cell (RBC) count 4 million/mm^3
hematocrit (Hct) 29%
hemoglobin (Hb) 9 g/dL

9. This patient's mean cell hemoglobin concentration (MCHC) is
   (A) 27.5.
   (B) 28.9.
   (C) 31.0.
   (D) 33.5.
   (E) 35.4.

10. His mean cell volume (MCV) is
    (A) 61.3.
    (B) 72.5.
    (C) 77.5.
    (D) 90.2.
    (E) 93.5.

11. From the data provided and from the calculations in questions 9 and 10, this patient is best described as

(A) normal except for a slightly increased blood urea nitrogen (BUN).
(B) having normochromic, microcytic anemia.
(C) having sickle-cell anemia.
(D) having hypochromic, normocytic anemia.
(E) having folic acid deficiency.

12. All of the following statements about sodium (Na) are true *except* which one?

(A) The normal range for sodium is 135 to 147 mEq/L.
(B) Sodium is the major cation of the extracellular fluid, and the laboratory test is used mainly to detect disturbances in water balance.
(C) Hyponatremia usually results from the total body depletion of sodium or through a dilutional effect.
(D) Control of the sodium concentration is mainly through regulation of arterial pH.

13. A 53-year-old woman with diabetes mellitus is seen in the emergency room. Her blood glucose is 673 mg/dL and ketones are present in her blood. A diagnosis of diabetic ketoacidosis (DKA) is made. Other important laboratory values are potassium of 4.8 mEq/L, 4+ glucose in urine, and an arterial pH of 7.1. All of the following statements apply to this patient *except* which one?

(A) Her potassium value is normal; therefore, no potassium supplementation is likely to be necessary.
(B) Her potassium value should be corrected owing to her acidosis; a corrected potassium would be 3.0 mEq/L.
(C) Potassium supplementation should be instituted because her total body potassium is depleted.
(D) Factors affecting potassium in this patient include glycosuria and arterial pH.

14. A 50-year-old man presents with bicarbonate of 18 mEq/L. All of the following could be a cause of his low bicarbonate level *except*

(A) metabolic acidosis.
(B) salicylate toxicity.
(C) diuretic therapy.
(D) diarrhea.

15. All of the following statements about calcium (Ca) and phosphorus (PO_4) are true *except* which one?

(A) An alcoholic with a serum albumin of 2.0 g/dL and a serum total calcium of 8.0 mg/dL has a corrected total calcium of 9.6 mg/dL.
(B) Calcium and PO_4 levels should be interpreted together because many of the same factors influence both minerals.
(C) Metastatic cancer often induces a decrease in serum calcium levels.
(D) A patient with renal failure may present with hypocalcemia and hyperphosphatemia.

16. All of the following are important functions of magnesium (Mg) *except*

(A) nerve conduction.
(B) phospholipid synthesis.
(C) muscle contractility.
(D) carbohydrate, fat, and electrolyte metabolism.

Directions for questions 17–19: The questions and incomplete statements in this section can be correctly answered or completed by **one or more** of the suggested answers. Choose the answer, **A–E**.

A if **I only** is correct
B if **III only** is correct
C if **I and II** are correct
D if **II and III** are correct
E if **I**, **II**, **and III** are correct

17. Factors likely to cause an increase in the blood urea nitrogen (BUN) level include

I. intramuscular (IM) injection of diazepam (Valium).
II. severe liver disease.
III. chronic kidney disease.

18. A patient who undergoes serum enzyme testing is found to have an increased aspartate aminotransferase (AST) level. Possible underlying causes of this abnormality include

I. methyldopa-induced hepatitis.
II. congestive heart failure (CHF).
III. pneumonia.

19. Serum enzyme tests that may aid in the diagnosis of myocardial infarction include

I. alkaline phosphatase.
II. creatine kinase (CK).
III. lactate dehydrogenase (LDH).

Answers and Explanations

1. **The answer is C** *[see II.B.2.d.(2)]*.
Valuable diagnostic information can be obtained through quantitative and qualitative testing of the cells of the blood. A finding of lymphopenia (i.e., decreased number of lymphocytes) suggests an attack on the immune system or some underlying immunodeficiency. AIDS attacks the T_H4 population of lymphocytes and thus may result in lymphopenia.

2. **The answer is A** *[see II.A.5]*.
The reticulocyte count measures the amount of circulating immature RBCs, which provides information about bone marrow function. A low reticulocyte count is a likely finding in a patient with aplastic anemia—a disorder characterized by a deficiency of all cellular elements of the blood owing to a lack of hematopoietic stem cells in bone marrow. A variety of drugs (e.g., those used in anticancer therapy) and other agents produce marrow aplasia. A high reticulocyte count would likely be found in a patient with hemolytic anemia or acute blood loss or in a patient who has been treated for an iron, vitamin B_{12}, or folate deficiency.

3. **The answer is E** *[see V.B; V.E–G]*.
Microscopic examination of the urine sediment normally shows $<$ 1 RBC and from 0 to 4 WBCs per HPF. Other normal findings on urinalysis include an acid pH (i.e., around 6) and an absence of glucose and ketones.

4. **The answer is A** *[see II.B.2.c]*.
An allergic drug reaction will usually produce an increase in the eosinophil count (eosinophilia). This could be determined by ordering a WBC differential.

5. **The answer is C** *[see II.A.2]*.
Overhydration with an excess infusion of D_5W produces a low Hct. The other situations described in the question result in increases of the Hct.

6. **The answer is A** *[see II.B.2.a]*.
The patient has leukocytosis with an increased neutrophil count (neutrophilia). A localized infection does not normally result in an increase in the total leukocyte count or neutrophil count. The other situations given in the question can produce a neutrophilic leukocytosis.

7. **The answer is B** *[see III.A]*.
Because CK is not present in the liver, alcoholic liver damage would not result in an increase in the level of this enzyme. CK is present primarily in cardiac and skeletal muscle. The other situations described in the question could all result in the release of increased amounts of CK into the bloodstream.

8. **The answer is D** *[see IV.B]*.
The patient with jaundice (deposition of bilirubin in the skin) usually has an increase in the total bilirubin serum level. Spillage of bilirubin into the urine requires an increased level of direct bilirubin, which is likely with viral hepatitis or cholestatic hepatitis. In hemolytic anemia, direct bilirubin is not usually increased, and therefore, there would be no spillage of bilirubin into the urine.

9. **The answer is C** *[see II.A.4.c]*.

10. **The answer is B** *[see II.A.4.a]*.

11. **The answer is B** *[see II.A.4; VI.B.2]*.
The MCHC is calculated as follows:

$$\text{MCHC} = \frac{\text{Hb} \times 100}{\text{Hct}} = \frac{9 \times 100}{29} = 31.0$$

The mean cell volume (MCV) is calculated as follows:

$$\text{MCV} = \frac{\text{Hct (\%)} \times 10}{\text{RBC (millions)}} = \frac{29 \times 10}{4} = 72.5$$

The patient described in the question is anemic because his Hb is 9 (normal: 14 to 18). The anemia is normochromic because the patient's MCHC of 31 is normal (normal range: 31 to 37), but the anemia is microcytic because the patient's MCV is 72.5 (normal: 80 to 100). The patient's BUN, 15 mg/dL, is within the normal range of 10 to 20 mg/dL.

12. **The answer is D** *[see VII.A.1; VII.A.5–7]*.
Sodium, the major extracellular cation, is measured mainly to assist in the determination of fluid status and water balance. Regulation of sodium is mainly through the kidneys via ADH and aldosterone.

13. **The answer is A** *[see VII.B.2; VII.B.4; VII.B.6]*.
A "normal" potassium level in the setting of metabolic acidosis, especially in a patient with DKA, should be treated appropriately. If the serum potassium level is corrected for the patient's acidosis, the corrected level is 3.0 mEq/L. This corresponds to depletion in total body potassium stores. Once the acidosis and hyperglycemia begin to correct with appropriate treatment, potassium levels will decrease precipitously unless supplementation is begun. It is important to recognize that a laboratory value in the "normal" range may not actually be normal, especially when potassium is involved.

14. **The answer is C** *[see VII.D.3–4]*.
Low HCO^{-3} is usually found in patients with acidosis or renal failure and after hyperventilation or severe diarrhea. In general, disturbances in acid–base balance cause alteration in the serum HCO^{-3} or CO_2 content. Diuretic therapy can cause an alkalosis and an increase in HCO^{-3}.

15. The answer is C *[see VIII.A.2–4; VII.B.2]*.
Malignancy or other metastatic diseases are most often associated with hypercalcemia, not hypocalcemia. Ionized calcium is the free active form, and this level is increased in the setting of a low albumin. Therefore, the total calcium level must be adjusted to account for increased ionized calcium in this setting. Both minerals are influenced by many of the same factors and thus are often interpreted together. Renal function is one such factor whereby a decrease in renal function (i.e., renal failure) can result in a low level of calcium and a high level of PO_4.

16. The answer is B *[see VIII.C.1]*.
Magnesium is the second most abundant intracellular and extracellular cation. It is an activator of numerous enzyme systems that control carbohydrate, fat, and electrolyte metabolism; protein synthesis; nerve conduction; muscular contractility; and membrane transport and integrity. PO_4, on the other hand, is important for ATP and phospholipid synthesis.

17. The answer is B (III) *[see VI.B.2]*.
Chronic kidney disease can cause an increase in the BUN level; a heavy protein diet and bleeding into the GI tract are other factors that can produce this finding. Severe liver disease can prevent the formation of urea and, therefore, is likely to cause a decrease in the BUN level. Although an IM injection of diazepam (Valium) may cause an increase in the serum CK or AST level, it would have no effect on the BUN.

18. The answer is C (I, II) *[see III.D]*.
A lung infection, such as pneumonia, normally would not cause an increase in the release of AST, an enzyme primarily found in the liver and heart. In acute hepatitis, a marked increase of AST is a likely finding. AST levels also can be increased with passive congestion of the liver, as occurs in CHF.

19. The answer is D (II, III) *[see III.A–C]*.
Usually, the CK, ALT, AST, and LDH enzyme levels are increased after a myocardial infarction. Alkaline phosphatase is not present in cardiac tissue and, therefore, would not be useful in the diagnosis of a myocardial infarction.

Study Questions

Directions for questions 1–16: Each of the questions, statements, or incomplete statements in this section can be correctly answered or completed by **one** of the suggested answers or phrases. Choose the **best** answer.

1. Exertion-induced angina, which is relieved by rest, nitroglycerin, or both, is referred to as

(A) Prinzmetal angina.
(B) unstable angina.
(C) stable angina.
(D) variant angina.
(E) preinfarction angina.

2. Myocardial oxygen demand is increased by all of the following factors *except*

(A) exercise.
(B) smoking.
(C) cold temperatures.
(D) isoproterenol.
(E) metoprolol.

3. Which of the following agents used in Prinzmetal angina has spasmolytic actions, which increase coronary blood supply?
   (A) nitroglycerin
   (B) diltiazem
   (C) timolol
   (D) isosorbide mononitrate
   (E) propranolol

4. The development of ischemic pain occurs when the demand for oxygen exceeds the supply. Determinants of oxygen demand include all of the following choices *except* which one?
   (A) contractile state of the heart
   (B) myocardial ejection time
   (C) left ventricular volume
   (D) right atrial pressure
   (E) systolic pressure

5. Myopathy is an adverse effect of all the following agents *except*
   (A) lovastatin.
   (B) simvastatin.
   (C) pravastatin.
   (D) gemfibrozil.
   (E) colestipol.

Directions for question 6 : The question can be correctly answered by one or more of the suggested answers. Choose the answer, **A–E**.

(A) if **I only** is correct
(B) if **III only** is correct
(C) if **I and II** are correct
(D) if **II and III** are correct
(E) if **I, II, and III** are correct

6. Which of the following is considered a component of acute coronary syndrome (ACS)?
   I. unstable angina
   II. non–ST-segment elevated myocardial infarction (NSTEMI)
   III. ST-segment elevated myocardial infarction (STEMI)

Directions for questions 7–11: Each of the following descriptions is most closely related to one of the following drugs. The descriptions may be used more than once or not at all. Choose the **best** answer, **A–E**.

(A) Inhibition of intestinal absorption of cholesterol
(B) Lowering of low-density lipoproteins (LDLs), triglycerides, and increased high-density lipoprotein (HDL) along with potential anti-inflammatory effects
(C) Recommendations for this agent have been substantially expanded beyond an alternative for aspirin-intolerant patients due to recent trials demonstrating its benefit in select ACS patients.
(D) Recommended for ACS patients who cannot tolerate aspirin
(E) Recommended over unfractionated heparin (UFH) as an anticoagulant in patients with unstable angina (UA) or NSTEMI

7. tirofiban (Aggrastat®)

8. enoxaparin (Lovenox®)

9. simvastatin (Various)

10. clopidogrel (Plavix®)

11. ezetimibe (Zetia®)

Answers and Explanations

1. **The answer is C** *[see II.C.1.a–f]*.
   Classic, or stable, angina refers to the syndrome in which physical activity or emotional excess causes chest discomfort, which may spread to the arms, legs, neck, and so forth. This type of angina is relieved promptly (within 1 to 10 mins) with rest, nitroglycerin, or both.

2. **The answer is E** *[see II.H.3.a; Table 31-1]*.
   Owing to the β-adrenergic blocking effects of metoprolol (e.g., decreased heart rate, decreased blood pressure, decreased inotropic effect), there is a net decrease in myocardial oxygen demand. This is the direct opposite of the effects seen with the β-agonist isoproterenol. Exercise, cigarette smoking, and exposure to cold temperatures have all been shown to increase myocardial oxygen demand.

3. **The answer is B** *[see II.4.d and II.H.4.c]*.
   Calcium-channel blocking agents such as diltiazem have been shown to be capable of reversing spasm and, therefore, increasing coronary blood flow in Prinzmetal angina. The calcium-channel blockers have proven benefit in the treatment of Prinzmetal angina, a syndrome believed due more to a spastic event than to a fixed coronary occlusion. β-adrenergic blockers such as timolol and propranolol (Inderal®) are not indicated in the treatment of Prinzmetal angina, and nitrates such as nitroglycerin and isosorbide mononitrate are not the primary agents indicated and in many cases do not have any effect.

4. **The answer is D** *[see I.F.2.B.(1)–(4)]*.
As with most muscles in the body, the contractile force of the heart dictates the amount of oxygen that the heart needs to perform efficiently. Consequently, as contractility decreases, the oxygen needs of the heart increase. As contractility continues to decrease, the volume of fluid in the left ventricle increases owing to poor muscle performance and increasing tension within the ventricle, resulting in additional oxygen requirements. As the amount of tension within the ventricle increases per cardiac cycle, there is again an added requirement for oxygen by the heart muscle.

5. **The answer is E** *[see II.G.2.d.(3); II.G.3.c.(2)]*.
Myopathy is an adverse effect of all the HMG-CoA reductase inhibitors (lovastatin, simvastatin, pravastatin, atorvastatin, fluvastatin, and rosuvastatin), and the combination of the fibric acid derivatives (gemfibrozil, fenofibrate, and clofibrate) has been shown to increase the creatine kinase levels and predispose patients to myopathies and rhabdomyolysis.

6. **The answer is E (I, II, III)** *[see I.E.2]*.
During recent years, there has been an attempt to link the various clinical symptoms of IHD into key categories, based on the presentation and symptoms at the time of evaluation. ACS refers to those situations that reflect an acute ischemic event and includes UA, NSTEMI, and STEMI. Clinical guidelines have incorporated treatment modalities based on these three presentations. UA and NSTEMI have similar recommended therapies, and STEMI has different treatment guidelines. Stable angina is not considered one of the ACS but represents the starting point for the progression of atherosclerosis, resulting in IHD.

7. **The answer is C** *[see III.G.3.a.(5)]*.
Tirofiban is an antiplatelet that is referred to as a glycoprotein IIb/III, a receptor antagonist. This class of drugs works to prevent platelet aggregation by inhibiting the interaction between the primary binding site of platelets and has been shown to be effective in the prevention of thrombosis.

8. **The answer is E** *[see III.G.3.a.(7) and III.H.4.a.(3).(d).(iii); Table 31-5]*.
Enoxaparin is an example of a low-molecular-weight heparin (LMWH). As a group, the major advantage of these drugs over the more traditional heparin is that they exhibit a more predictable anticoagulant response. Owing to their lower molecular weight and decreased binding to plasma proteins, they have better bioavailability than heparin. In addition, their decrease in plasma protein binding and binding to the endothelium results in half-lives that are two to four times longer than that of heparin. Current clinical practice guidelines recommend enoxaparin over heparin in patients with UA or NSTEMI, unless CABG is planned within 24 hrs.

9. **The answer is B** *[see II.G.2.c.(7)]*.
Simvastatin is one of the currently available HMG-CoA reductase inhibitors that have been shown to significantly reduce LDL levels and nonfatal MI or CHD (30% to 40% reduction). Recent studies have demonstrated that inflammation may be an important mechanism involved in ACS and that statins might exert an important anti-inflammatory effect within coronary arteries (independent of their cholesterol-lowering effects).

10. **The answer is D** *[see II.H.5.c]*.
The most recently introduced guidelines for the treatment of ACS has incorporated recent trials, which have shown the value of clopidogrel in various patient populations with ACS. Besides being used in those who are unable to take or tolerate aspirin, it is included as "add-on" therapy for patients receiving aspirin who suffer from ACS.

11. **The answer is A** *[see II.G.5.a]*.
Ezetimibe reduces cholesterol levels via a different mechanism of action than previous agents. By selectively blocking the intestinal absorption of cholesterol, it is able to stop one of the major pathways responsible for increasing available cholesterol within the body. Ezetimibe has demonstrated the ability to reduce total cholesterol, LDL, apolipoprotein B, and triglyceride levels while increasing HDL levels in patients with hypercholesterolemia. Simvastatin has recently been incorporated into a combination product with ezetimibe (Vytorin), which uses the individual class properties of the HMG-CoA reductase inhibitors (simvastatin) to reduce cholesterol production with the absorption-inhibiting properties of ezetimibe to target cholesterol with two different mechanisms, which might also aid in improving patient compliance with taking the medication.

e. **Additional use.** Adenosine has been used as an adjunctive agent in patients undergoing various types of pharmacological stress testing (e.g., thallium). In this situation, adenosine is given as a continuous infusion over a period of 4 to 6 mins and is able to provide a form of exercise tolerance test in patients not able to exert themselves owing to age, fatigue, and various other physical handicaps.

3. **Magnesium sulfate (Various)**
   a. **Indications.** Previous national guidelines have recommended magnesium for the treatment of drug-induced long QT syndrome. In the most recent ACLS guidelines, published in 2010, magnesium received a class IIb rating with a "class B" level of evidence, for its use *strictly* in patients presenting with TdP associated with a long QT interval. Additionally, magnesium has been used in the treatment of arrhythmias (ventricular tachycardia/fibrillation, due to hypomagnesemia).
   b. **Mechanism of action.** Acts on the myocardium by slowing the rate of impulse formation at the SA node and therefore slows down conduction. Magnesium is also necessary in the exchange of calcium, sodium, and potassium in and out of cells, which in the case of TdP might lower the amplitude of the early after depolarizations.
   c. **Administration and dosage.** For the treatment of TdP, 1 to 6 g over several minutes, occasionally followed by approximately 3 to 20 mg/min by IV infusion for 5 to 48 hrs, depending on response and serum magnesium concentrations.
      (1) Alternatively, for TdP associated with cardiac (pulseless) arrest, 1 to 2 g in 10 mL 5% dextrose injection over 5 to 20 mins.
      (2) Alternatively, for TdP in a patient with pulses, give a loading dose of 1 to 2 g (8 to 16 mEq) in 50 to 100 mL 5% dextrose injection over 5 to 60 mins.
      (3) **Intraosseous** TdP associated with cardiac (pulseless) arrest, 1 to 2 g in 10 mL 5% dextrose injection over 5 to 20 mins.
   d. **Precautions and monitoring effects**
      (1) Routine monitoring of magnesium levels, in order to prevent hypermagnesemia, while also monitoring calcium levels and phosphorus levels, which can be reduced when administering IV magnesium.

4. **Digoxin (Lanoxin®)**
   a. **Indications.** Recent guidelines recommend that digoxin is effective in stable, narrow-complex regular tachycardias if rhythm remains uncontrolled or unconverted by adenosine or vagal maneuvers or if SVT is recurrent. Additionally, digoxin has been shown effective to control the ventricular rate in patients with atrial fibrillation or atrial flutter.
   b. **Mechanism of action.** As a cardiac glycoside, digoxin has positive inotropic effects; however, for rhythm control digoxin relies on its "parasympathomimetic properties," which slow conduction through the AV node and decrease impulses going through to the ventricles.
   c. **Administration and dosage.** Digoxin can be given as 8 to 12 mcg/kg with half of that being given over 5 mins, and the remaining 50% given in two doses at 4 and 8 hrs later.
   d. **Precautions and monitoring effects**
      (1) The onset of action is slow and depending on the circumstances might not be acceptable for acute arrhythmias.
      (2) Long-term use of digoxin will expose the patient to numerous monitoring requirements, including renal function, drug–drug interactions, and fluid and electrolyte monitoring, in order to minimize likelihood of adverse drug reactions.

5. **Dronedarone (Multaq®)**
   a. The newest antiarrhythmic, which was a major focal point for recently updated guidelines for the treatment of atrial fibrillation, and which has not yet been formally added into the current Vaughan Williams classification.
   b. Within the updated guidelines, dronedarone (Multaq®) received a class IIa rating with a "class B" level of evidence, to decrease the need for hospitalization for cardiovascular events in patients with paroxysmal atrial fibrillation or after conversion of persistent atrial fibrillation. Additionally, it was felt that dronedarone could be initiated during outpatient therapy. However, within the same guidelines, dronedarone was also given a class III for use in class IV HF or patients who have had an episode of decompensated HF in the past 4 weeks, especially with depressed left ventricular function (ejection fraction $< 35\%$).

Study Questions

Directions: Each of the questions, statements, or incomplete statements can be correctly answered or completed by **one** of the suggested answers or phrases. Choose the **best** answer.

1. Strong anticholinergic effects limit the antiarrhythmic use of

(A) quinidine (Various).
(B) procainamide (Various).
(C) mexiletine (Various).
(D) flecainide (Tambocor®).
(E) disopyramide (Norpace®).

2. A pronounced slowing of phase 0 of the myocardial action potential results in a prolongation of either atrial depolarization, causing a prolonged P wave on the electrocardiogram (EKG/ECG), or ventricular depolarization, causing a prolonged QRS complex characterized by which class of antiarrhythmics?

(A) Class I
(B) Class II
(C) Class III
(D) Class IV
(E) Class V

3. Which of the following class III antiarrhythmics has been reported as "carrying a risk for" causing torsades de pointes?

(A) lidocaine (Xylocaine®)
(B) amiodarone (Cordarone®)
(C) quinidine (Various)
(D) flecainide (Tambocor®)
(E) diltiazem (Cardizem®)

4. A patient receiving a class I antiarrhythmic agent complains of GI symptoms, including nausea, vomiting, and occasional diarrhea after taking a dose. The patient is most likely receiving

(A) lidocaine (Xylocaine®).
(B) procainamide (Various).
(C) quinidine (Various).
(D) flecainide (Tambocor®).
(E) propranolol (Inderal®).

5. Class III antiarrhythmics have which of the following effects to the cardiac cell's action potential?

(A) Slow the rate of rise for phase 0 of depolarization.
(B) Delay the fast-channel conductance of sodium ions.
(C) Prolong phases 2 and 3 of repolarization.
(D) Inhibit the slow-channel conductance of calcium ions.
(E) Prolong the refractory period of the action potential.

6. Which of the following drugs is a class IV antiarrhythmic that is primarily indicated for the treatment of supraventricular tachyarrhythmias?

(A) ibutilide (Corvert®)
(B) mexiletine (Various)
(C) diltiazem (Cardizem®)
(D) procainamide (Various)
(E) propranolol (Inderal®)

7. Relatively new antiarrhythmic agent, which has not yet been formally added into the Vaughan Williams classification table but received a class IIa rating with a class B level of evidence to decrease the need for hospitalization in patients with paroxysmal atrial fibrillation or after conversion of persistent atrial fibrillation. Which of the following agents is best described by the above statements?

(A) aliskiren (Tekturna®)
(B) inamrinone (Various)
(C) dronedarone (Multaq®)
(D) amiodarone (Cordarone®)
(E) dofetilide (Tikosyn®)

8. Which of the following drugs is a class III antiarrhythmic agent that is effective in the acute management of atrial fibrillation or atrial flutter of recent onset?

(A) propranolol (Inderal®)
(B) ibutilide (Corvert®)
(C) metoprolol (Lopressor®)
(D) disopyramide (Norpace®)
(E) diltiazem (Cardizem®)

9. All of the following problems represent concerns when patients are started on amiodarone *except*
   (A) extremely long $t_{½}$.
   (B) need for multiple daily doses.
   (C) development of hyperthyroidism or hypothyroidism.
   (D) development of liver toxicity.
   (E) interactions with numerous other drugs.

10. Based on the criteria used for recent national guidelines used within the cardiology arena, which of the following recommendations would most likely result in the use of a selected antiarrhythmic therapy for a patient with atrial fibrillation?
   (A) Class I; level C
   (B) Class I; level A
   (C) Class IIa; level B
   (D) Class III; level A
   (E) Class IIb; level A

Answers and Explanations

1. **The answer is E** *[see II.A.4.c.(4)]*.
Disopyramide has anticholinergic actions about one-tenth the potency of atropine. Effects include dry mouth, constipation, urinary retention, and blurred vision. Therefore, it cannot be used in patients with glaucoma or with conditions causing urinary retention. Moreover, disopyramide has a negative inotropic effect and must, therefore, be used with great caution, if at all, in patients with preexisting ventricular failure.

2. **The answer is A** *[see I.B.2 and II.A]*.
The class I antiarrhythmics (fast-channel blockers) slow impulse conduction by depressing the flow of sodium ions into cells during phase 0 of the action potential.

3. **The answer is B** *[see I.C.3.d; Table 32-1]*.
Torsades de pointes is a form of ventricular tachyarrhythmia characterized by electrocardiographic changes, which include a markedly prolonged QT interval. This potentially fatal reaction has now been reported for both antiarrhythmics and nonantiarrhythmics. Antiarrhythmics, which have been reported to cause torsades de pointes, include amiodarone, disopyramide, dofetilide, flecainide, ibutilide, procainamide, quinidine, and sotalol. Of the agents listed, only amiodarone is a class III antiarrhythmic.

4. **The answer is C** *[see II.A.4.a]*.
The patient's complaints are typical of many patients receiving quinidine as an antiarrhythmic. GI side effects are the major ones associated with quinidine administration, with diarrhea being reported in up to 30% of patients receiving the drug. These GI side effects are different from those associated with high serum concentrations of quinidine, where tinnitus, hearing loss, and blurred vision are added to the GI symptoms in a syndrome referred to as cinchonism.

5. **The answer is E** *[see II.C.2]*.
Class III antiarrhythmic agents work primarily on the potassium channels of the action potential and prolong the refractory period and action potential. Class Ia agents slow the rate of rise for phase 0 depolarization, as well as slowing fast-channel conduction of sodium and phases 2 and 3 of repolarization. Class IV agents (verapamil, diltiazem) inhibit the slow-channel conductance of calcium ions.

6. **The answer is C** *[see II.D.2]*.
Of the agents listed, diltiazem is a calcium-channel blocker and represents the class IV antiarrhythmics. Diltiazem has been used for its direct-acting effects on impulse conduction throughout the heart. Diltiazem is used to treat and prevent supraventricular arrhythmias. Ibutilide is a class III agent, procainamide is a class Ia drug, mexiletine is a class Ib agent, and propranolol, a β-adrenergic blocker, is class II. Mexiletine, quinidine, and propranolol are all also effective for supraventricular arrhythmias, and ibutilide is indicated for the treatment of atrial fibrillation/flutter of recent onset.

7. **The answer is C** *[see II.E.5.a–d]*.
Dronedarone (Multaq®) is the newest of the currently available antiarrhythmic agents and has yet to be included within the Vaughan Williams antiarrhythmic classification table. It also was the primary subject for a recently focused guidelines update for the treatment of patients with atrial tachyarrhythmias. Aliskiren (Tekturna®) is a relatively new agent referred to as a direct renin antagonist, which is available for the treatment of hypertension. Inamrinone (Various) is referred to as a phosphodiesterase inhibitor, which has been used for its positive inotropic actions in the treatment of heart failure. Amiodarone (Cordarone®) and dofetilide (Tikosyn®) are both considered class III Vaughan Williams antiarrhythmic agents.

8. The answer is B *[see II.C.1.d]*.
Dofetilide, ibutilide, amiodarone, and sotalol are class III antiarrhythmic agents. Class III agents prolong the refractory period and myocardial action potential and are used to treat ventricular arrhythmias. However, dofetilide and ibutilide are approved as class III agents indicated for the conversion from atrial fibrillation and flutter of recent onset to normal sinus rhythm. Propranolol, along with other β-blockers, is a class II antiarrhythmic; metoprolol is not routinely used in the treatment of arrhythmias; and disopyramide and diltiazem are class Ia and class IV antiarrhythmics, respectively.

9. The answer is B *[see II.C.3.a; II.C.4.a; II.C.5.a]*.
Amiodarone is a class III antiarrhythmic agent and acts by prolonging repolarization of cardiac cells. Amiodarone can be given either orally or parenterally and is often dosed as a once-a-day or twice-a-day maintenance dosage. Due to an extremely long elimination half-life, therapeutic response may be delayed for weeks. Therefore, an initial loading phase is often advisable. This requires hospitalization with close monitoring for desired effects, untoward reactions, and adjustments in dosage. Amiodarone has numerous drug–drug interactions with both other antiarrhythmic agents, as well as other nonarrhythmic agents. During therapy with amiodarone, patients may develop hypothyroidism or hyperthyroidism, pulmonary disorders (black box warning), hepatic dysfunction (black box warning), and various other unwanted effects.

10. The answer is B *[see I.H.1–2]*.
Recent national guidelines within the cardiology societies have used a scoring system, which includes two elements: one provides a recommendation based on benefit to risk where a class I recommendation has the greatest benefit compared to risk, as compared to class III where the risk may be equal to or worse than the risk; and a second element evaluates the degree of populations studied, where level A has been studied in numerous populations with well-controlled clinical trials, as compared to level C with very limited populations studied and reliance on opinion and case reports. A class I level A recommendation would be the best one would find, to help justify the use of a specific treatment or intervention, based on the cardiology guidelines criteria.

Study Questions

Directions for questions 1–6: Each of the questions, statements, or incomplete statements in this section can be correctly answered or completed by **one** of the suggested answers or phrases. Choose the **best** answer.

1. Which of the following agents represents an angiotensin II receptor antagonist (ARB)?

(A) trandolapril (Mavik®)
(B) carvedilol (Coreg®)
(C) irbesartan (Avapro®)
(D) moexipril (Univasc®)
(E) nimodipine (Various)

2. Reflex tachycardia, headache, and postural hypotension are adverse effects that limit the use of which of the following antihypertensive agents?

(A) prazosin (Minipress®)
(B) captopril (Capoten®)
(C) methyldopa (Various)
(D) guanabenz (Various)
(E) hydralazine (Various)

3. A 65-year-old man presents with stage I hypertension. He has diabetes mellitus and chronic kidney disease and is intolerant to lisinopril. Which of the following agents would be an appropriate selection for initial treatment in this patient based on the guidelines from the "Seventh Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure" (JNC-7)?

(A) chlorothiazide (Various)
(B) propranolol (Inderal®)
(C) nitroprusside (Nitropress®)
(D) candesartan (Atacand®)
(E) clonidine (Catapres®)

4. A patient with stage I hypertension who has bronchospastic airway disease and who is noncompliant would be best treated with which of the following β-blocking agents?

(A) timolol (Various)
(B) penbutolol (Levatol®)
(C) esmolol (Brevibloc®)
(D) acebutolol (Sectral®)
(E) propranolol (Inderal®)

5. Long-standing hypertension leads to tissue damage in all of the following organs *except* the

(A) heart.
(B) lungs.
(C) kidneys.
(D) brain.
(E) eyes.

6. According to the "Seventh Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure" (JNC-7), which of the following agents is suitable as initial therapy for treating stage I hypertension (assuming no compelling indications for another type of drug)?

(A) chlorothiazide (Various)
(B) labetalol (Trandate®)
(C) atenolol (Tenormin®)
(D) propranolol (Inderal®)
(E) bisoprolol (Zebeta®)

Directions for questions 7–9: The questions and incomplete statements in this section can be correctly answered or completed by **one or more** of the suggested answers. Choose the answer, **A–E**.

A if **I only** is correct
B if **III only** is correct
C if **I and II** are correct
D if **II and III** are correct
E if **I, II, and III** are correct

7. A patient treated with a spironolactone (Aldactone®) should be monitored regularly for altered plasma levels of

I. potassium.
II. serum creatinine.
III. blood urea nitrogen (BUN).

8. Before antihypertensive therapy begins, secondary causes of hypertension should be ruled out. Laboratory findings that suggest an underlying cause of hypertension include

I. a decreased serum potassium level.
II. an increased urinary catecholamine level.
III. an increased blood cortisol level.

9. In an otherwise healthy adult with stage I hypertension, appropriate initial antihypertensive therapy would be

I. chlorthalidone (Various)
II. metoprolol (Lopressor®)
III. bisoprolol (Zebeta®)

Directions for questions 10–14: Each list of adverse effects in this section is most closely associated with **one** of the following antihypertensive agents. The agents may be used more than once or not at all. Choose the **best** answer, **A–E**.

(A) clonidine (Catapres®)
(B) olmesartan (Benicar®)
(C) nitroprusside (Nitropress®)
(D) prazosin (Minipress®)
(E) propranolol (Inderal®)

10. Thiocyanate intoxication, hypotension, and convulsions

11. Bradycardia, bronchospasm, and cardiac decompensation

12. Angioedema, cough, and hyperkalemia

13. Rebound hypertension, dry mouth, and drowsiness

14. First-dose syncope, postural hypotension, and palpitations

Directions for questions 15–19: Each description listed in this section is most closely associated with **one** of the following β-adrenergic blocking agents. The agents may be used more than once or not at all. Choose the **best** answer, **A–E**.

(A) esmolol (Brevibloc®)
(B) labetalol (Trandate®)
(C) bisoprolol (Zebeta®)
(D) nadolol (Corgard®)
(E) pindolol (Visken®)

15. A β-blocker with intrinsic sympathomimetic activity

16. A β-blocker that also blocks α-adrenergic receptors

17. A β-blocker with an ultrashort duration of action

18. A β-blocker with a long duration of action and nonselective blocking activity

19. A β-blocker with relative cardioselective blocking activity

Answers and Explanations

1. **The answer is C** *[see III.B.5.a]*.
Irbesartan is one of the relatively new classes of drugs used in the treatment of hypertension referred to as an angiotensin II receptor antagonist, which blocks the production of angiotensin II and consequently its effects as a powerful vasoconstrictor and stimulant for aldosterone release. Trandolapril and moexipril are ACE inhibitors; carvedilol is a β-adrenergic blocking agent; and nimodipine is a calcium-channel blocker used in the treatment of subarachnoid hemorrhage.

2. **The answer is E** *[see III.B.7.a]*.
Hydralazine is a vasodilator that works by directly relaxing arterioles, thereby reducing peripheral vascular resistance. Its effectiveness as an antihypertensive agent is compromised; however, by the compensatory reactions it triggers (e.g., reflex tachycardia) and by its other adverse effects (e.g., headache, postural hypotension, nausea, palpitations). Fortunately, the unwanted effects of hydralazine are minimized when it is used in combination with a diuretic agent and a β-blocker. Hydralazine is most effective as a supplemental antihypertensive drug in combination with first-line therapy.

3. **The answer is D** *[see III.B.5.e.(3)]*.
Candesartan, an angiotensin II receptor blocker, which acts by blocking the binding of angiotensin II to the angiotensin II receptors. By blocking the receptor site, this class of drugs inhibits the vasoconstrictor effects of angiotensin II and prevents the release of aldosterone owing to angiotensin II from the adrenal glands. JNC-7 guidelines call for the use of diuretics in the initial treatment of hypertension, unless the patient has compelling indications that have been shown to benefit from the use of specific classes of drugs. This patient has diabetes and chronic kidney disease and is unable to tolerate the ACE inhibitor lisinopril; therefore, an ARB would be an acceptable alternative for this patient rather than a β-blocker (propranolol) or diuretic (chlorothiazide). Nitroprusside is normally used in the treatment of hypertensive emergencies as an intravenous infusion, and clonidine is not considered initial treatment for hypertension.

4. **The answer is D** *[see III.B.3.a.(7).(a)–(n)]*.
The β-adrenergic blocking agents continue to demonstrate effectiveness in the treatment of hypertension. A major feature of some of these agents is their relative selectivity for β_1-receptors (in the heart) rather than for β_2-receptors (in the lung), which provides advantages in the treatment of certain patients (e.g., those with bronchospastic airway or COPD). Of the β-blockers listed, acebutolol is less likely than the rest to block β_2-receptors because of its relative cardioselective-blocking activity. Acebutolol also has a long duration of action, which could be helpful in the noncompliant patient by requiring fewer doses per day. Penbutolol has weak intrinsic sympathomimetic activity like pindolol but lacks relative cardioselectivity, despite its long duration of action. Esmolol by nature of its continuous intravenous infusion would not lend itself to chronic ambulatory therapy. Timolol is a long-acting β-blocker and lacks the relative cardioselective properties that acebutolol possesses.

5. **The answer is B** *[see I.F; Table 33-3]*.
Left untreated, hypertension can be lethal because of its progressively destructive effects on major organs, such as the heart, kidneys, and brain. The eyes also suffer damage; the lungs, however, do not. End-organ damage caused by hypertension includes left ventricular hypertrophy, heart failure, angina pectoris, myocardial infarction, renal insufficiency caused by atherosclerotic lesions, nephrosclerosis, cerebral aneurysm and hemorrhage, retinal hemorrhage, and papilledema.

6. **The answer is A** *[see III.B.2.a]*.
Thiazide diuretics are considered the first-line treatment choice for hypertension and should be used alone or in combination with other antihypertensives, if necessary. β-Blockers such as labetalol, atenolol, bisoprolol, and propranolol are no longer considered initial agents for treating hypertension unless there is a compelling reason for their use. β-Blockers have shown positive clinical outcomes in patients with heart failure, post-MI, high coronary disease risk, and diabetes (compelling indications) and would be acceptable options for patients presenting with prehypertension or hypertension with a compelling indication.

7. **The answer is E (I, II, III)** *[see III.B.2.c.(4)]*.
Spironolactone is a direct-acting aldosterone-receptor blocker and decreases its effects on sodium and water retention. However, a benefit of spironolactone is its potassium-sparing effect, through the exchange of sodium for potassium in the kidney. Patients with reduced renal function and acute renal failure (evidenced by elevations in serum creatinine) lose their ability to excrete potassium, and this needs to be monitored when patients are started on spironolactone. BUN and creatinine are good indirect indicators of renal function.

8. **The answer is E (I, II, III)** *[see II.A.2]*.
Low serum potassium levels in a hypertensive patient suggest primary aldosteronism. Elevated urinary catecholamines suggest a pheochromocytoma; other signs and symptoms of this tumor include weight loss, episodic flushing, and sweating. Elevated serum cortisol levels suggest Cushing syndrome; the patient is also likely to have a round (moon) face and truncal obesity. Secondary hypertension requires treatment of the underlying cause; supplementary antihypertensive drug therapy may also be needed.

9. **The answer is A (I)** *[see III.B.2.a]*.
Thiazide diuretics such as chlorthalidone are now considered, based on the JNC-7, first-line therapy for hypertension, barring any compelling indications, such as heart failure, diabetes, chronic kidney disease, or post-MI, when other antihypertensive agents would be indicated. β-Adrenergic blockers, such as metoprolol and bisoprolol, are no longer indicated as initial antihypertensive agents for treating hypertension.

10. **The answer is C** *[see III.B.7.c.(2)]*.

11. **The answer is E** *[see III.B.3.a.(4)]*.

12. **The answer is B** *[see III.B.5.c.(2)]*.

13. **The answer is A** *[see III.B.3.c.(2).(c)]*.

14. **The answer is D** *[see III.B.3.b.(3).(a)]*.
The goal of treatment in hypertension is to lower blood pressure toward normal with minimal side effects. All antihypertensive drugs can cause adverse effects. The primary purpose of the JNC-7 guidelines is to acknowledge the long-term benefits of diuretics in the treatment of hypertension.

15. **The answer is E** *[see III.B.3.a.(7).(f)]*.

16. **The answer is B** *[see III.B.3.a.(7).(g)]*.

17. **The answer is A** *[see III.B.3.a.(7).(i)]*.

18. **The answer is D** *[see III.B.3.a.(7).(c)]*.

19. **The answer is C** *[see III.B.3.a.(7).(l)]*.
The β-adrenergic blocking agents are valuable for managing hypertension and are used as initial antihypertensives. The β-blockers are sympathetic antagonists. They act by blocking various receptors of the sympathetic nervous system. They differ in their selectivity for these sympathetic receptors. For example, β_1-blockers have relative cardioselective activity—that is, they block β_1-receptors (in the heart) rather than β_2-receptors (in bronchial smooth muscle) and, therefore, are highly useful antihypertensive agents. Intrinsic sympathomimetic activity also appears to reduce the problem of bronchoconstriction; moreover, drugs with this property can also maintain a satisfactory heart rate.

(2) **Moderate doses** of 5 to 10 mcg/kg/min increase cardiac output (positive inotropic effect) in HF patients.

(3) **High doses**

(a) As doses are raised above 10 mcg/kg/min, α-adrenergic stimulation occurs peripherally, resulting in increased total peripheral resistance and pulmonary pressures.

(b) When the infusion exceeds 8 to 9 mcg/kg/min, the patient should be monitored for tachycardia. If the infusion is slowed or interrupted, the adverse effect should disappear because dopamine has a very short half-life in plasma.

b. Dobutamine (Various) continuous intravenous infusions

(1) Patients who are unresponsive to, or adversely affected by, dopamine may benefit from dobutamine in doses of 5 to 20 mcg/kg/min.

(2) Although dobutamine resembles dopamine chemically, its actions differ somewhat. For example, dobutamine does not directly affect renal receptors and, therefore, does not act as a renal vasodilator. It increases urinary output only through increased cardiac output.

(3) Serious arrhythmias are a potential occurrence, although less likely to occur than with dopamine. Slowing or interrupting the infusion usually reverses this effect, as it does for dopamine.

(4) Dobutamine and dopamine have been used together to treat cardiogenic shock, but similar use in HF has yet to be accepted.

c. Inamrinone (Various) continuous intravenous infusion is referred to as nonglycoside, nonsympathomimetic, inotropic agents.

(1) A bipyridine derivative, inamrinone has both a positive inotropic effect and a vasodilating effect.

(2) By inhibiting phosphodiesterase located specifically in the cardiac cells, it increases the amount of cyclic adenosine monophosphate (cAMP).

(3) Inamrinone has been used in patients with HF that have been refractory to treatment with other inotropic agents.

(4) Effective regimens have used loading intravenous infusions of 0.75 mg/kg over 2 to 3 mins followed by maintenance infusions of 5 to 10 mg/kg/min.

(5) **Precautions and monitoring effects**

(a) Inamrinone is unstable in dextrose solutions and should be added to saline solutions instead. Because of fluid balance concerns, this can be a potential problem in patients with HF.

(b) Because of the peripheral dilating properties, patients should be monitored for hypotension.

(c) Thrombocytopenia has occurred and is dose dependent and asymptomatic.

(d) Ventricular rates may increase in patients with atrial flutter or fibrillation.

d. Milrinone (Various) continuous intravenous infusion is similar to inamrinone. It possesses both inotropic and vasodilatory properties.

(1) This agent has been used as short-term management to treat patients with HF.

(2) Most milrinone patients in clinical trials have also been receiving digoxin and diuretics.

(3) Effective dosing regimens have used a loading dose of 50 mcg/kg administered slowly over 10 mins intravenously, followed by maintenance doses of 0.375 mcg/kg/min by continuous infusion, based on the clinical status of the patient.

(4) **Precautions and monitoring effects**

(a) Renal impairment significantly prolongs the elimination rate of milrinone, and infusions need to be reduced accordingly.

(b) Monitoring is necessary for the potential arrhythmias occurring in HF, which may be increased by drugs such as milrinone and other inotropic agents.

(c) Blood pressure and heart rate should be monitored when administering milrinone, owing to its vasodilatory effects and its potential to induce arrhythmias.

(d) Additional side effects include mild-to-moderate headache, tremor, and thrombocytopenia.

L. Patient education

1. Patients should be made aware of the importance of taking their medications exactly as prescribed and should be advised to watch for signs of toxicity.

2. Patients should be educated on the need for lifestyle modifications that will have a positive effect on reducing HF development and reducing HF symptoms, including daily weight monitoring,

Study Questions

Directions for questions 1–8: Each of the questions, statements, or incomplete statements in this section can be correctly answered or completed by **one** of the suggested answers or phrases. Choose the **best** answer.

1. Which of the following combinations of drugs, when used together, particularly in black patients, has been shown to effectively reduce both preload and afterload?
   - **(A)** Nitroglycerin (Nitrostat®) and isosorbide dinitrate (Isordil Titradose®)
   - **(B)** Hydralazine (Various) and isosorbide dinitrate (Isordil Titradose®)
   - **(C)** Diltiazem (Cardizem®) and verapamil (Calan®)
   - **(D)** Prazosin (Minipress®) and angiotensin II (Various)
   - **(E)** Hydralazine (Various) and methyldopa (Aldomet®)

2. When spironolactone (Aldactone®) is used in a patient with heart failure (HF), it works through what primary mechanism?
   - **(A)** Positive inotropic effect
   - **(B)** Positive chronotropic effect
   - **(C)** Aldosterone antagonism
   - **(D)** Negative inotropic effect
   - **(E)** Angiotensin II blockade

For questions 3–4: A 60-year-old hypertensive woman is currently being treated with nitroglycerin, carvedilol (Coreg®), furosemide (Various), nifedipine (Procardia®), ramipril (Altace®), aspirin (Various), and digoxin (Lanoxin®). She is admitted with a diagnosis of stage C HF.

3. Which agent is most likely to be discontinued in this patient?
   - **(A)** Nifedipine (Procardia®)
   - **(B)** Carvedilol (Coreg®)
   - **(C)** Aspirin (Various)
   - **(D)** Digoxin (Lanoxin®)
   - **(E)** Furosemide (Lasix®)

4. Which of the following *does not* represent the goals of therapy for this patient?
   - **(A)** Treat underlying causes such as hypertension, cigarette smoking, lipid disorders
   - **(B)** Discourage the use of alcohol intake, illicit drug use, and dietary salt intake
   - **(C)** Consideration for drastic measures (i.e., heart transplant, etc.)
   - **(D)** Initiate therapy with diuretics for fluid retention
   - **(E)** Potential addition of angiotensin-converting enzyme inhibitor (ACEIs) and β-adrenergic blockers

5. Because of proven beneficial effects on cardiac remodeling, a particular group of agents is now indicated as first-line therapy in a wide array of HF patients. Which of the following is a representative of this group of drugs?
   - **(A)** Hydrochlorothiazide (Microzide®)
   - **(B)** Ramipril (Altace®)
   - **(C)** Losartan (Cozaar®)
   - **(D)** Carvedilol (Atacand®)
   - **(E)** Furosemide (Lasix®)

6. Which of the following statements is *not* correct as it relates to the current status of HF in the United States?
   - **(A)** HF is the one cardiovascular disorder that is increasing in incidence and prevalence.
   - **(B)** Medication costs for treating HF in the United States approaches $38 billion.
   - **(C)** Patients with advanced disease have a 30% to 40% risk of death annually.
   - **(D)** Approximately 5 million people in the United States currently suffer from HF.
   - **(E)** Approximately 500,000 people each year are diagnosed with HF in the United States.

7. If treating a patient with HF, which of the following dosages of dopamine would be used to elicit its positive inotropic effects?

(A) 2 mcg/kg/min
(B) 5 to 10 mcg/kg/min
(C) 10 to 20 mcg/kg/min
(D) 40 mcg/kg/min
(E) 40 mg/kg/min

8. The use of ACEIs in HF centers around what pharmacologic effect?

(A) Direct reduction in renin levels with a resultant decrease in angiotensin II and aldosterone levels
(B) Indirect reduction in angiotensin II and aldosterone levels owing to inhibition of angiotensin-converting enzyme
(C) Direct reduction in aldosterone secretion and angiotensin I production by inhibiting angiotensin-converting enzyme
(D) Increase in afterload owing to an indirect decrease in angiotensin II as well as a decrease in preload owing to an indirect reduction in aldosterone secretion
(E) Inhibition of the angiotensin II receptor, which results in reduced angiotensin II levels and reduced secretion of aldosterone

Directions for questions 9–10: The questions and incomplete statements in this section can be correctly answered or completed by **one or more** of the suggested answers. Choose the answer, **A–E**.

A if **I only** is correct
B if **III only** is correct
C if **I and II** are correct
D if **II and III** are correct
E if **I**, **II**, **and III** are correct

9. Correct statements about dobutamine include which of the following?

I. Doses of 5 to 20 mcg/kg/min have been associated with a positive inotropic effect in treating the patient with HF.
II. Patients receiving dobutamine should be monitored for increases in peripheral vascular resistance.
III. Dobutamine is considered a nonglycoside, nonsympathomimetic, positive inotropic agent.

10. Which statements accurately describe HF classification stage A?

I. Patients have a high risk for HF without structural heart disease or symptoms.
II. Patients need to receive ACEIs or angiotensin II receptor blockers (ARBs).
III. Patients should be treated for any underlying causes that would be responsible for causing HF.

11. A recently released drug for use in patients with HF has unfortunately achieved recommendations stated to be class III with a level C level of evidence supporting its use for a special patient population. Which of the following statements adequately summarizes the outcomes associated with such recommendations based on the cardiology group models utilized?

I. Risk of harm is greater than the potential benefit.
II. Clinical trials have been limited to small populations.
III. Literature demonstrating the evidence is derived from opinion and case reports.

Answers and Explanations

1. The answer is B *[see IV.C.2.c]***.**
The venous dilating properties of isosorbide dinitrate (preload) in conjunction with the arteriolar dilating effects of hydralazine (afterload) make this combination effective in reducing both preload and afterload. The most recent national guidelines suggest that the combination of the vasodilators hydralazine and isosorbide dinitrate received a level I, class A recommendation for HF therapy, particularly in black patients with NYHA III or IV HF.

2. The answer is C *[see IV.G.7.c]***.**
Spironolactone was the first aldosterone antagonist available for clinical use in the United States. In the completed RALES trial, spironolactone, given in 12.5- to 25-mg daily doses to HF patients with class IV symptoms who were taking ACEIs, reduced the risk of death and hospitalization. It is a weak diuretic but also works as a direct antagonist to the actions of aldosterone, which has demonstrated benefit in HF patients with moderate to severe symptoms.

3. **The answer is A** *[see IV.J.1 and IV.L.4]*.
Due to the potential to produce negative inotropic effects, calcium-channel blockers, such as nifedipine, have been identified as one of three groups of drugs to avoid in most HF patients. Besides calcium-channel blockers, antiarrhythmics, and NSAIDs should be avoided in most HF patients owing to their ability to induce HF symptoms.

4. **The answer is D** *[see Table 34-3]*.
The updated classification system was introduced with the newly established guidelines to demonstrate the progressive nature of HF and to provide a continuum of goals and treatment options as it progresses. Stage C represents the first stage in which the patient presents with structural heart disease, as well as current or prior symptoms of HF. Initial goals for earlier stages remain important goals for stage C, but the "restriction in dietary salt" is added to all of the previous goals. The use of diuretics for treatment of fluid retention as well as potential introduction of ACEIs and/or β-adrenergic blockers are also included within stage C. Stage D is the last of the four stages; and it is in this stage when more drastic measures such as "end-of-life planning," "cardiac transplantation," etc., are included within the recent guidelines.

5. **The answer is B** *[see Table 34-3 and IV.D.8]*.
ACEIs such as ramipril have shown an ability to have a positive effect on cardiac remodeling, which is believed to be the underlying change that results in the increased stresses and pathologic events that eventually cause the symptoms associated with HF. Recent studies have shown the positive benefits for each of the ACEIs used in HF patients, and today they represent a very critical component in the therapy for HF patients.

6. **The answer is B** *[see I.B–D]*.
The actual costs involved in the treatment of HF, including medical care, home health care, medication costs, and hospitalization costs, reported in 2005 were approximately $27.9 billion. Medication costs alone are a bit less but are still reported to be more than $2.9 billion annually.

7. **The answer is B** *[see IV.K.5.a.(1)–(3)]*.
Dopamine has shown great versatility in its effects. At doses of 2 to 5 mcg/kg/min, it increases renal blood flow through its dopaminergic effects through dopaminergic receptors. At doses of 5 to 10 mcg/kg/min, it increases cardiac output through its β-adrenergic stimulating effect. At doses of 10 to 20 mcg/kg/min, it increases peripheral vascular resistance through its α-adrenergic stimulating effects. There is no specific cutoff for any of these effects, so close titration is required to provide for individual response.

8. **The answer is B** *[see IV.D.4–5; Figure 34-2]*.
By directly inhibiting the angiotensin-converting enzyme, production of angiotensin II (potent vasoconstrictor) is reduced, as is angiotensin II-mediated secretion of aldosterone (sodium and water retention) from the adrenal gland. These effects are believed to have a beneficial effect on the prevention of cardiac remodeling, which has been shown to have a detrimental effect on cardiac function.

9. **The answer is A (I)** *[see Table 34-3 and IV.K.5.b]*.
Dobutamine in doses of 5 to 20 mcg/kg/min is an inotropic agent that is useful in the treatment of HF. Dobutamine does not have the versatility that dopamine offers, lacking comparable effects on renal blood flow and peripheral vascular resistance. Rather, dobutamine has a peripheral dilating effect that offers a benefit to patients who have reduced cardiac output due to elevated peripheral resistance.

10. **The answer is E (I, II, III)** *[see Table 34-3]*.
The recent guidelines for the diagnosis and management of chronic HF recognize four stages in the progression of HF, and each stage is associated with clinical findings, goals of treatment, and medications that should be considered. Stage A represents patients who are merely at risk for HF owing to underlying risk factors, such as hypertension, hyperlipidemia, and smoking. ACEIs are recognized for their beneficial effects in cardiac remodeling and have been recommended as first-line therapy for select patients with stage A HF.

11. **The answer is E (I, II, and III)** *[see I.G.4.c]*.
Two sets of criteria have been used by the cardiology associations to provide a clear recommendation based on the clinical effects associated with specific interventions: The first involves a risk-to-benefit assessment; and the second is a summary of populations studied, which results in the findings on any given intervention evaluated. A class III recommendation demonstrates that the risk is greater than the benefit; and a level C of evidence would refer to case studies, expert opinion, based on very limited populations of patients studied. This would not be a treatment intervention that would be widely accepted based on peer-reviewed evidence.

Study Questions

Directions for questions 1–4: Each of the questions, statements, or incomplete statements in this section can be correctly answered or completed by **one** of the suggested answers or phrases. Choose the **best** answer.

1. A 67-year-old man who weighs 100 kg (212 lb) and is 60 inches tall presents to his physician after a transatlantic flight complaining of pain and swelling of his right lower extremity. The patient had total knee arthroplasty 2 weeks before his travel. His medical history reveals that he has an ejection fraction of 15%, he is in remission for non-Hodgkin lymphoma, and he had a previous MI. His mother, father, and sister are dead as a result of stroke, pulmonary embolism (PE), and childbirth, respectively. Given this patient's history, he is most likely suffering from which of the following?

(A) ruptured Baker cyst
(B) deep venous thrombosis (DVT) of the lower extremity
(C) torn medial meniscus
(D) septic arthritis

2. Prophylaxis against venous throboembolic disease (VTED) may include
   (A) nonpharmacological prophylaxis.
   (B) pharmacological prophylaxis.
   (C) nonpharmacological and pharmacological prophylaxis.
   (D) neither nonpharmacological nor pharmacological prophylaxis.

3. Unfractionated heparin binds to antithrombin III and inactivates clotting factor(s)
   (A) Xa
   (B) IXa
   (C) IIa
   (D) All of the above
   (E) None of the above

4. Initiation of UFH therapy for the patient described in question 1 would best be achieved with
   (A) 5000 U loading dose followed by 1000 U/hr.
   (B) 5000 U loading dose followed by 1800 U/hr.
   (C) 8000 U loading dose followed by 1800 U/hr.
   (D) 1000 U loading dose followed by 1000 U/hr.

Directions for questions 5–11: The questions and incomplete statements in this section can be correctly answered or completed by **one or more** of the suggested answers. Choose the answer, **A–E**.

A if **I only** is correct
B if **III only** is correct
C if **I and II** are correct
D if **II and III** are correct
E if **I**, **II**, **and III** are correct

Directions for questions 5–10: Upon confirmation of diagnosis, the attending physician asks you, the pharmacist, to commence low-molecular-weight-heparin (LMWH) therapy for the patient described in question 1 as mentioned earlier. The following questions pertain to your pharmaceutical care for this patient:

5. When choosing an Food and Drug Administration (FDA)-approved LMWH to treat this patient, you would administer
   I. enoxaparin 1.0 mg/kg/dose subcutaneously every 12 hrs.
   II. enoxaparin 1.5 mg/kg/dose subcutaneously every 24 hrs.
   III. tinzaparin 175 IU/kg/dose subcutaneously every 24 hrs.

6. Which of the following tests are used to monitor heparin antithrombotic therapy?
   I. international normalized ratio (INR)
   II. activated partial thromboplatin time (aPTT)
   III. heparin assay

7. A patient to be commenced on oral anticoagulant therapy for DVT would be treated with
   I. oral anticoagulant therapy with warfarin for a goal INR of 2.0 to 3.0.
   II. oral anticoagulant therapy with warfarin for a goal INR of 2.5 to 3.5.
   III. oral anticoagulant therapy with aspirin for a goal INR of 2.0 to 3.0.

8. A patient on oral anticoagulant therapy is commenced on sulfamethoxazole-trimethoprim, double-strength twice daily. One may expect to see the INR
   I. increase.
   II. decrease.
   III. remain unchanged.

9. If a patient has an INR $>$ 20 and active bleeding that is clinically significant (i.e., hematuria), the pharmacist should
   I. hold the drug therapy.
   II. administer vitamin K.
   III. administer fresh frozen plasma.

10. Compared to unfractionated heparin (UFH), LMWHs have
    I. preferential binding affinity to factor Xa relative to IIa (thrombin).
    II. shorter half-lives.
    III. dose-dependent renal clearance.

11. An 87-year-old woman who weighs 49 kg (108 lb) and is 66 inches tall has sustained a hip fracture requiring open reduction with internal fixation (ORIF) surgery. She has a documented serum creatine value recorded in the chart and in the laboratory results as 4.3 mg/dL. The orthopedic surgeon asks you, the pharmacist, about the appropriate fondaparinux dosing for this patient to prevent venous thromboembolism after the surgery. Which of the following are contraindications to the use of fondaparinux in this patient?
    I. Patient weighs $<$ 50 kg.
    II. Patient has severe renal impairment.
    III. Patient is elderly.

Answers and Explanations

1. **The answer is B** *[see I.A–C]*.
The patient has the classic triad of risk factors predisposing him to DVT injury (recent knee arthroplasty), venous stasis (transatlantic travel), and hypercoagulable state (family history of VTED). The patient has other risk factors as well, including age > 40, recent surgery, oncologic disease (although in remission), congestive heart failure, previous MI with low ejection fraction, and obesity.

2. **The answer is C** *[see IV.A–B]*.
Prophylaxis of VTED can involve a nonpharmacological approach, a pharmacological approach, or a combination of nonpharmacological and pharmacological approaches. The method of prophylaxis used is determined based on the patient's degree of risk. For example, a patient at high to extremely high risk for development of VTED requires nonpharmacological and pharmacological prophylaxis.

3. **The answer is D** *[see V.A.2]*.
Unfractionated heparin acts as an anticoagulant by catalyzing the inactivation of factor IIa, factor Xa, and factor IXa by antithrombin III.

4. **The answer is C** *[see V.A.4.b.(4)]*.
Several nomograms for dosing continuous infusion UFH exist in the medical and pharmaceutical literature. The loading dose is typically 70 to 100 units/kg. In this case, the patient weighs 100 kg (212 lb) and the loading dose is 80 units/kg. Maintenance doses of 15 to 25 units/kg/hr are typically used. In this case, the maintenance dose is 18 units/kg/hr.

5. **The answer is E (I, II, III)** *[see Table 35-10]*.
Primary literature reveals appropriate randomized prospective trials examining the role of LMWH compared to UFH. From these trials, evidence of efficacy and safety for enoxaparin and tinzaparin at the treatment doses listed exists and has been approved by FDA for treatment of established VTE.

6. **The answer is D (II, III)** *[see V.A.5.a–c]*.
UFH may be appropriately monitored by either the aPTT or heparin assay. Because different laboratories use aPTT reagents with different sensitivities, the aPTT range and its corresponding ratio must be correlated to a heparin level of 0.2 to 0.4 units/mL by whole-blood (protamine titration) assay or 0.3 to 0.7 units/mL by plasma-amidolytic assay. The safety and efficacy of LMWH cannot be reliably evaluated by aPTT determinations. LMWH safety and efficacy can be evaluated by heparin assay. Because of the reliability of dose responsiveness seen with LMWH therapy, the need to perform heparin assays is controversial.

7. **The answer is A (I)** *[see V.B.5.a–b; Table 35-8]*.
Oral anticoagulant therapy is monitored by measuring the prothrombin time (PT). The PT is responsive to depression of three of the four vitamin K–dependent procoagulant clotting factors (prothrombin or factors II, VII, and X). These respective clotting factors take approximately 96 hrs to be depleted, at which time the PT should be sufficient to arrive at an INR of 2.0 to 3.0 for patients with DVT (by appropriately converting the PT ratio to the power of the international sensitivity index [ISI]). Patients with mechanical prosthetic heart valves have INRs targeted in the 2.5 to 3.5 range. Aspirin therapy is not monitored by INR determinations.

8. **The answer is A (I)** *[see Table 35-4]*.
Oral anticoagulant therapy with warfarin may be complicated by myriad drug–drug interactions owing to the highly protein-bound state of warfarin. Such drug interactions may potentiate (prolong) PT:INR ratio, inhibit (shorten) the anticoagulant effect of warfarin, or have no effect on the actions of warfarin. Sulfamethoxazole-trimethoprim and other antibiotics have the potential to augment the anticoagulant effect of warfarin by eliminating bacterial flora and, thereby, producing vitamin K deficiency.

9. **The answer is E (I, II, III)** *[see Table 35-7]*.
Pharmacists may be called on to offer advice regarding reversal of warfarin therapy or may be empowered using Pharmacy and Therapeutics Committee or Medical Board-approved protocols to reverse warfarin's effect. In all instances, the pharmacist must critically and clinically evaluate the situation and communicate with the physician regarding management issues. A need for immediate surgery or invasive procedures will always hasten the urgency of warfarin reversal. In the setting of active bleeding, its clinical significance must be demonstrated by consultation with the patient's physician. If the INR is > 20 and the patient has active bleeding that is clinically significant, the pharmacist must hold drug therapy, consider the most appropriate dose and route of vitamin K delivery, and administer fresh frozen plasma to replete the vitamin K–dependent clotting factors.

10. The answer is A (I) *[see V.C.3.a.(1); V.C.4.b]*.
UFH has a factor Xa:IIa binding-affinity ratio of approximately 1:1 and the various commercial LMWHs have factor Xa:IIa binding-affinity ratios of 2:1 up to 4:1, depending on their molecular size distribution. This increased binding affinity for factor Xa relative to factor IIa (thrombin) is said to account for the improved ability of LMWHs to catalyze inactivation of thrombin; the smaller fragments cannot bind to thrombin and, therefore, retain their ability to inactivate factor Xa. LMWHs have longer half-lives than UFH. LMWHs are cleared primarily via the kidneys, and their biologic half-life is increased in patients with renal failure *independent* of dose.

11. The answer is C (I, II) *[see V.D.5.b; V.D.6.a.(1)–(2)]*.
The synthetic pentasaccharide fondaparinux is contraindicated in patients who have severe renal impairment and who weigh < 50 kg. Calculation of the patient's estimated Clcr by the Crockcroft–Gault method reveals an estimated clearance of approximately 8.5 mL/min, which would be defined as severe renal impairment. Her stated weight is 49 kg. Thus, this patient's severe renal impairment and low weight constitute contraindications to the use of fondaparinux. Fondaparinux is recommended for use with *precaution* in the elderly patient population.

Study Questions

Directions for questions 1–12: Each of the questions, statements, or incomplete statements in this section can be correctly answered or completed by **one** of the suggested answers or phrases. Choose the **best** answer.

1. Isoniazid is a primary antitubercular agent that

(A) requires pyridoxine supplementation.
(B) may discolor the tears, saliva, urine, or feces orange-red.
(C) causes ocular complications that are reversible if the drug is discontinued.
(D) may be ototoxic and nephrotoxic.
(E) should never be used because of hepatotoxic potential.

2. All of the following factors may increase the risk of nephrotoxicity from gentamicin therapy *except* which one?

(A) age $>$ 70 years
(B) prolonged courses of gentamicin therapy
(C) concurrent amphotericin B therapy
(D) trough gentamicin levels $<$ 2 mg/mL
(E) concurrent cisplatin therapy

3. In which of the following groups do all four drugs warrant careful monitoring for drug-related seizures in high-risk patients?

(A) penicillin G, imipenem, amphotericin B, metronidazole
(B) penicillin G, chloramphenicol, tetracycline, vancomycin
(C) imipenem, tetracycline, vancomycin, sulfadiazine
(D) cycloserine, metronidazole, vancomycin, sulfadiazine
(E) metronidazole, imipenem, doxycycline, erythromycin

4. AC is a 34-year-old male admitted with a diagnosis of peritonitis. Cultures are positive for *Bacteroides fragilis*, *Enterococcus faecalis*, and *Staphylococcus aureus*. Which of the following would be the best initial therapy to recommend?

(A) telithromycin
(B) quinupristin/dalfopristin
(C) tigecycline
(D) trimethoprim/sulfamethoxazole
(E) kanamycin

5. TJ is a 45-year-old female presenting with an *Enterobacter aerogenes* bacteremia with a low-grade fever (101.6°F). The most appropriate management of her fever would be to

(A) give acetaminophen 1000 mg orally every 6 hrs.
(B) give aspirin 650 mg orally every 4 hrs.
(C) give alternating doses of aspirin and acetaminophen every 4 hrs.
(D) withhold antipyretics and use the fever curve to monitor her response to antibiotic therapy.
(E) use tepid water baths to reduce the fever.

6. BC has an upper respiratory infection. Two years ago, she experienced an episode of bronchospasm after penicillin therapy. Current cultures are positive for a strain of *Streptococcus pneumoniae* that is sensitive to all of the following drugs. Which of these drugs would be the best choice for this patient?

(A) amoxicillin/clavulanate
(B) telithromycin
(C) ampicillin
(D) cefaclor
(E) loracarbef

7. All of the following drugs are appropriate therapies for a lower urinary tract infection owing to *Pseudomonas aeruginosa except*

(A) norfloxacin.
(B) trimethoprim–sulfamethoxazole.
(C) ciprofloxacin.
(D) tobramycin.
(E) methenamine mandelate.

8. BT is a 43-year-old female seen by her primary-care physician for a mild staphylococcal cellulitis on the arm. Which of the following regimens would be appropriate oral therapy?

(A) dicloxacillin 125 mg every 6 hrs
(B) vancomycin 250 mg every 6 hrs
(C) methicillin 500 mg every 6 hrs
(D) cefazolin 1 g every 8 hrs
(E) penicillin V 500 mg every 6 hrs

9. RC is a 33-year-old male with a history of HIV for 10 years who now presents with *Mycobacterium avium-intracellulare* (MAI). Which of the following drugs has demonstrated in vitro activity against MAI?

(A) daptomycin
(B) clarithromycin
(C) erythromycin base
(D) cloxacillin
(E) minocycline

10. All of the following statements regarding pentamidine isethionate are true *except* which one?

(A) It is indicated for treatment or prophylaxis of infection owing to *Pneumocystis carinii*.
(B) It may be administered intramuscularly, intravenously, or by inhalation.
(C) It has no clinically significant effect on serum glucose.
(D) It is effective in the treatment of leishmaniasis.

11. RE is a 23-year-old male with a history of severe asthma. An outbreak of H1N1 influenza has just been reported in his community, and he is exhibiting initial symptoms of the infection. Which agent would be the most useful to treat RE?

(A) cidofovir
(B) famciclovir
(C) oseltamivir
(D) zanamivir
(E) ribavirin

12. Dr. Jones requests your help in selecting a protease inhibitor as part of a regimen for a treatment-naive male patient. Which of the following would you recommend?

(A) darunavir/ritonavir
(B) lopinavir/ritonavir
(C) nelfinavir
(D) saquinavir/ritonavir
(E) tipranavir/ritonavir

Directions for questions 13–14: The questions and incomplete statements in this section can be correctly answered or completed by **one or more** of the suggested answers. Choose the answer, **A**–**E**.

A if **I only** is correct
B if **III only** is correct
C if **I and II** are correct
D if **II and III** are correct
E if **I, II, and III** are correct

13. Drugs usually active against penicillinase-producing *Staphylococcus aureus* include which of the following?

I. piperacillin–tazobactam
II. amoxicillin–clavulanate
III. nafcillin

14. Antiviral agents that are active against cytomegalovirus (CMV) include which of the following?

I. ganciclovir
II. foscarnet
III. acyclovir

Directions for questions 15–17: Each description listed in this section is most closely associated with **one** of the following drugs. The drugs may be used more than once or not at all. Choose the **best** answer, **A**–**E**.

A clofazimine
B itraconazole
C levofloxacin
D neomycin

15. It may be administered once per day for the treatment of urinary tract infections.

16. It may cause pink to brownish skin pigmentation within a few weeks of initiation of therapy.

17. Coadministration with astemizole or terfenadine may lead to life-threatening cardiac dysrhythmias.

Answers and Explanations

1. **The answer is A** *[see VI.B.2.d.(5)]*.
Isoniazid increases the excretion of pyridoxine, which can lead to peripheral neuritis, particularly in poorly nourished patients. Pyridoxine (a form of vitamin B_6) deficiency may cause convulsions as well as the neuritis, involving synovial tenderness and swelling. Treatment with the vitamin can reverse the neuritis and prevent or cure the seizures.

2. **The answer is D** *[see II.B.4.b]*.
Trough serum levels $<$ 2 mg/mL are considered appropriate for gentamicin and are recommended to minimize the risk of toxicity from this aminoglycoside. Because aminoglycosides accumulate in the proximal tubule of the kidney, nephrotoxicity can occur.

3. **The answer is A** *[see II.C.4.6; II.F.e.2; V.C.3.b.(4); VI.B.2.d.(5)]*.
Seizures have been attributed to the use of penicillin G, imipenem, amphotericin B, and metronidazole. Seizures are especially likely with high doses in patients with a history of seizures and in patients with impaired drug elimination.

4. **The answer is C** *[see II.K.14]*.
Although active against various gram-positive and negative organisms, tigecycline is only agent approved for the treatment of intra-abdominal infections caused by these organisms.

5. **The answer is D** *[see I.H.1]*.
The fever curve is useful for monitoring a patient's response to antimicrobial therapy. Antipyretics can be used to reduce high fever in patients at risk for complications (e.g., seizures) or, in some cases, to make the patient more comfortable.

6. **The answer is B** *[see II.K.13; II.D.4.6]*.
Amoxicillin and ampicillin are all penicillins and should be avoided in patients with histories of hypersensitivity to other penicillin compounds. Although the risk of cross-reactivity with cephalosporins (e.g., cefaclor, loracarbef) is now considered low, most clinicians avoid the use of these agents in patients with histories of type I hypersensitivity reactions (e.g., anaphylaxis, bronchospasm, giant hives).

7. **The answer is B** *[see II.B.2.b.(3); II.I.2.a; II.J.2.a; II.J.2.c.(1)]*.
Norfloxacin, ciprofloxacin, tobramycin, and methenamine mandelate achieve urine concentrations high enough to treat urinary tract infections caused by *P. aeruginosa*. Trimethoprim–sulfamethoxazole is not useful for treating infection caused by this organism, although the combination is useful for treating certain other urinary tract infections.

8. **The answer is A** *[see II.F.2.c.(4)]*.
Although vancomycin, methicillin, and cefazolin have excellent activity against staphylococci, they are not effective orally for systemic infections. Vancomycin is prescribed orally for infections limited to the gastrointestinal tract, but because it is poorly absorbed orally, it is not effective for systemic infections. Most hospital- and community-acquired staphylococci are currently resistant to penicillin. Thus, of the drugs listed, the most appropriate drug for oral therapy of staphylococcal cellulitis is dicloxacillin.

9. **The answer is B** *[see II.D.6.a–b]*.
Clarithromycin, an alternative to erythromycin, has demonstrated in vitro activity against MAI. Clarithromycin is also used against *Toxoplasma gondii* and *Cryptosporidium* spp., and it is more active than erythromycin against staphylococci and streptococci. Vancomycin and cloxacillin are used to treat staphylococci and streptococci, but has no demonstrated activity versus MAI.

10. **The answer is C** *[see V.D]*.
Pentamidine isethionate is indicated for both treatment and prophylaxis of infection from *P. carinii*. It can be administered intramuscularly, intravenously, or by inhalation. Inhalation may produce bronchospasm. Blood glucose should be carefully monitored because pentamidine may produce either hyperglycemia or hypoglycemia.

11. **The answer is C** *[see VII.B.9]*.
Cidofovir and famciclovir have little or no in vivo activity against H1N1 influenza. Ribavirin has some activity but is not used for influenza and is mainly indicated for treatment of hepatitis C in combination with interferon. Zanamivir and oseltamivir are agents that demonstrate activity against H1N1 influenza and are indicated for the treatment of influenza infections. Zanamivir is an inhaled agent that should be avoided in patients with a history of asthma or chronic obstructive pulmonary disease, due to the risk of bronchospasm and acute decline in lung function. Oseltamivir is an oral agent that is most appropriate in this case.

12. **The answer is A** *[see VII.C.5.a–i]*.
Lopinavir/ritonavir is a PI used in alternative regimens for treatment-naïve patients and is only a preferred PI in pregnant women. Nelfinavir, saquinavir/ritonavir, and tipranavir/ritonavir are not preferred PIs due to inferior virologic potency and/or adverse effects. Darunavir/ritonavir is considered a preferred PI.

13. **The answer is E (I, II, III)** *[see II.E.2–4]*.
Piperacillin and amoxicillin each include a β-lactamase inhibitor. These combinations offer activity against *S. aureus* similar to that of the penicillinase-resistant penicillins, such as nafcillin.

14. **The answer is C (I, II)** *[see VII.B.1; VII.B.7–8]*.
Only ganciclovir and foscarnet are active against CMV infections. These agents are virustatic and arrest DNA synthesis by inhibiting viral DNA polymerase. Foscarnet is a broad-spectrum antiviral agent and is used in patients with ganciclovir resistance. Acyclovir is not clinically useful for the treatment of CMV infections because CMV is relatively resistant to acyclovir in vitro.

15. **The answer is C** *[see II.I.3.c]*.
Levofloxacin is appropriate for treatment of urinary tract infections, and may be dosed once daily.

16. **The answer is A** *[see II.K.5.d.(1)]*.
Because clofazimine contains phenazine dye, it can cause pink to brown skin pigmentation. This change in pigmentation occurs in 75% to 100% of patients taking clofazimine, and it occurs within a few weeks of the initiation of therapy. The discoloration of skin has reportedly led to severe depression and even suicide in some patients. Clofazimine is used in the treatment of leprosy and several atypical *Mycobacterium* infections.

17. **The answer is B** *[see III.F.5.d]*.
Administration of itraconazole or ketoconazole with astemizole or terfenadine may increase the level of astemizole or terfenadine, which can lead to life-threatening dysrhythmias and death. Itraconazole, which is an imidazole, is a fungistatic agent. Specifically, itraconazole can be taken orally to treat aspergillosis infections and other deep fungal infections, such as blastomycosis, coccidioidomycosis, cryptococcosis, and histoplasmosis.

Study Questions

Directions: Each of the questions, statements, or incomplete statements in this section can be correctly answered or completed by **one** of the suggested answers or phrases. Choose the **best** answer.

1. Phenytoin is effective for the treatment of all of the following types of seizures *except*

(A) generalized tonic–clonic.
(B) simple partial.
(C) complex partial.
(D) absence.
(E) grand mal.

2. Which of the following anticonvulsants is contraindicated in patients with a history of hypersensitivity to tricyclic antidepressants?

(A) phenytoin
(B) ethosuximide
(C) acetazolamide
(D) carbamazepine
(E) phenobarbital

3. Which anticonvulsive drug requires therapeutic monitoring of phenobarbital serum levels as well as its own serum level?

(A) phenytoin
(B) primidone
(C) clonazepam
(D) ethotoin
(E) carbamazepine

4. Which anticonvulsive drug treatment has a higher incidence of kidney stones?
   (A) phenytoin
   (B) carbamazepine
   (C) topiramate
   (D) tiagabine

5. What are the most common adverse effects of anticonvulsive drugs?
   (A) headache and dizziness
   (B) gastrointestinal symptoms
   (C) alternation of cognition and mentation
   (D) adverse effects on appetite and body weight
   (E) all of the above

6. Which antiepileptic drug has the least effect on the efficacy of oral contraceptives?
   (A) phenytoin
   (B) tiagabine
   (C) gabapentin
   (D) lamotrigine
   (E) C and D

7. Which of the following drugs could cause hyponatremia?
   (A) carbamazepine
   (B) phenytoin
   (C) oxcarbazepine
   (D) felbamate
   (E) topiramate
   (F) A, C, and D

Answers and Explanations

1. **The answer is D** *[see II.B.2.a.(2)]*.
   Phenytoin (diphenylhydantoin) is the most commonly prescribed hydantoin for seizure disorders. It is one of the preferred drugs for generalized tonic–clonic (grand mal) seizures and for partial seizures, both simple and complex. However, phenytoin is not effective for absence (petit mal) seizures.

2. **The answer is D** *[see II.B.1.c.(2)]*.
   Carbamazepine is structurally related to the tricyclic antidepressants (e.g., amitriptyline, desipramine, imipramine, nortriptyline, protriptyline) and should not be administered to patients with hypersensitivity to any of the tricyclic antidepressants.

3. **The answer is B** *[see II.B.5–6]*.
   Primidone's antiseizure activity may be partly attributable to phenobarbital. In patients receiving primidone, serum levels of both primidone and phenobarbital should be measured.

4. **The answer is C** *[see II.B.12]*.
   There is a higher incidence of kidney stones (renal calculus) with topiramate administration.

5. **The answer is E** *[see I.B.1–9]*.
   Alternation in cognition and mentation, gastrointestinal symptoms, appetite and body weight, and headache and dizziness are all common adverse effects of anticonvulsive drugs.

6. **The answer is E** *[see IV.C.5]*.
   Gabapentin and lamotrigine do not increase the metabolism of oral contraceptives to a clinically significant level; therefore, they could be used with oral contraceptives.

7. **The answer is F** *[see II.B.1; II.B.9; II.B.16]*.
   Carbamazepine, oxcarbazepine, and felbamate all cause hyponatremia.

3. **Disadvantages.** Optimal transplant variables and target site not defined. Also, clinical studies showed development atypical dyskinesias during off period.

D. Use of genetically engineered viruses (adeno-associated virus, AAV) to carry levodopa-dopamine converting enzyme aromatic L-amino decarboxylase (AADC) to increase effectiveness of levodopa; as a result, decrease doses of levodopa and subsequently decrease dyskinesia and other side effects associated with levodopa.

E. Neuronal regeneration: delivering either growth factors or stem cells to produce dopamine-producing neurons.

Study Questions

Directions: Each of the questions, statements, or incomplete statements in this section can be correctly answered or completed by **one** of the suggested answers or phrases. Choose the **best** answer.

1. Which of the following drugs is a catechol-*O*-methyltransferase (COMT) inhibitor and has reports of fatal liver toxicity with it?

(A) tolcapone
(B) entacapone
(C) rasagiline
(D) selegiline

2. Levodopa is associated with which of the following problems?

(A) Gastrointestinal side effects
(B) Involuntary movements
(C) Decline in efficacy after 3 to 5 years
(D) All of the above

3. Amantadine has which of the following advantages over levodopa?

(A) More rapid relief of symptoms
(B) Higher success rate
(C) Better long-term effects

4. Which drug is a non-ergot dopamine agonist and has a side-effect profile different from the rest of the dopaminergic agents?

(A) entacapone
(B) levodopa/carbidopa
(C) ropinirole
(D) selegiline

5. Which of the following medications is indicated as an adjunct to carbidopa/levodopa therapy?

(A) pramipexole
(B) bromocriptine
(C) amantadine
(D) tolcapone

Answers and Explanations

1. The answer is A *[see II.E.4.a.(3).(a)–(c)]***.**
High risk of fatal liver failure use with caution with patients with liver abscess. Patients should be monitored and instructed to look for signs of liver disease such as clay-colored stool, jaundice, fatigue, loss of appetite, and lethargy.

2. The answer is D *[see II.B.3.c–d]***.**
Levodopa can cause GI side effects such as nausea and vomiting, particularly when starting treatment. Bowel irregularity and gastrointestinal bleeding can also occur. With long-term levodopa therapy, involuntary choreiform movements can develop, and the efficacy of the drug declines. Other unwanted effects of levodopa include tachycardia and cardiac arrhythmias, postural hypotension, and psychiatric disturbances such as confusion or depression.

3. The answer is A *[see II.D.2.a.(4); II.D.2.c–d]***.**
Amantadine is most efficacious within the first few weeks, whereas benefits from levodopa may not be seen for weeks to months. Amantadine is more beneficial than the anticholinergics but is less effective than levodopa. Unfortunately, the efficacy of amantadine declines after 6 to 12 months of therapy. The efficacy of levodopa declines after 3 to 5 years of therapy.

4. **The answer is C** *[see II.E.3.a–b]***.**
Non-ergot dopamine agonists such as ropinirole are indicated for both early and advanced stages of Parkinson disease. These drugs selectively bind to dopamine receptors and activate the D_2-receptor but have little or no affinity for the D_1-receptor. They have a greater affinity for the D_3-receptor than for the D_2-receptor. The incidence of adverse events (e.g., pleuropulmonary fibrosis and retroperitoneal fibrosis, coronary vasoconstriction, erythromelalgia, and Raynaud phenomenon) is low compared to nonselective dopamine agonists. Non-ergot dopamine agonists have a low potential for the devolvement of motor fluctuations and dyskinesia.

5. **The answer is D** *[see II.E.4.a.(1).(d)]***.**
Tolcapone is an inhibitor of COMT enzyme used to metabolize catecholamines, including levodopa. It is indicated as an adjunct therapy to carbidopa/levodopa therapy.

Study Questions

Directions: Each of the questions, statements, or incomplete statements in this section can be correctly answered or completed by one of the suggested answers or phrases. Choose the best answer.

For questions 1–5: DG is a 23-year-old female committed to the inpatient psychiatric ward by her parents. They state that she has recently been under a large amount of stress from college, and they have noticed over the past year that she has become more withdrawn from her friends and social activities. They also state that she angers more easily than she used to as a child, and this morning they found her with a knife trying to slit her wrists. DG states that the voices keep telling her she is bad and that she should kill herself. She does not admit to any visual hallucinations but describes multiple voices (male and female) talking to her continuously telling her that she should harm herself or that people are out to get her. She keeps telling you that her parents are trying to get rid of her, and she wants to leave. She appears to be a healthy young woman although noticeably agitated. Her medical history is significant only for smoking one pack/day since age 16. DG is diagnosed with schizophrenia.

1. Which type of schizophrenia is DG likely experiencing based upon her presenting signs and symptoms?
   (A) catatonic
   (B) disorganized
   (C) paranoid
   (D) residual

2. Which of the following of DG's symptoms is best described as a negative symptom of schizophrenia?
   (A) social withdrawal
   (B) auditory hallucinations
   (C) delusions
   (D) agitation

3. The medical team decides to initiate treatment for DG. Which of the following antipsychotic medications is the best initial treatment for this patient?
   (A) haloperidol
   (B) risperidone
   (C) thioridazine
   (D) clozapine

4. Which of the following is *not* a potential adverse effect of the medication selected for DG in question 3?
   (A) weight gain
   (B) pseudoparkinsonism
   (C) sedation
   (D) urinary retention

5. DG is stabilized on the medication prescribed and is discharged home. DG is readmitted into the psychiatric ward 1 year later for auditory and visual hallucinations secondary to noncompliance on her current treatment regimen. Which of the following treatment options is most appropriate for DG at this time?
   (A) haloperidol decanoate
   (B) long-acting risperidone
   (C) clozapine monotherapy
   (D) adjunctive clozapine with haloperidol

For questions 6–8: TW is a 52-year-old female with a history of schizophrenia and diabetes mellitus type 2. She has been treated for many years with haloperidol with good response; however, she has recently developed lip smacking and tongue chewing.

6. What type of adverse effect is TW experiencing?
   (A) akathisia
   (B) acute dystonia
   (C) pseudoparkinsonism
   (D) tardive dyskinesia

7. Which of the following medications has been used to treat the adverse effect described in question 6?
   (A) vitamin E
   (B) propranolol
   (C) diphenhydramine
   (D) amantadine

8. Now that TW is experiencing this reaction, her health care providers want to change her therapy to a different antipsychotic. Which of the following antipsychotics is the best treatment option for her?
   (A) olanzapine
   (B) risperidone
   (C) quetiapine
   (D) fluphenazine

9. Which of the following atypical antipsychotics would be the least likely to cause weight gain?

(A) risperidone
(B) olanzapine
(C) quetiapine
(D) aripiprazole

10. Which of the following statements does not describe a way in which atypical antipsychotics differ from typical antipsychotics?

(A) Atypical antipsychotics have a higher affinity for serotonin receptors than dopamine receptors.
(B) Atypical antipsychotics are more efficacious for positive symptoms than typical antipsychotics.
(C) Atypical antipsychotics are more likely to cause weight gain and hyperlipidemia than typical antipsychotics.
(D) Atypical antipsychotics are less likely to cause extrapyramidal symptoms (EPS) than typical antipsychotics.

11. Which of the following long-acting injectable antipsychotics requires a 3-week overlap with oral antipsychotic medication following the first injection?

(A) paliperidone
(B) olanzapine
(C) haloperidol
(D) risperidone

12. Which of the following antipsychotics is the only agent shown to produce benefit in WELL-DEFINED treatment-resistant schizophrenia?

(A) risperidone
(B) clozapine
(C) olanzapine
(D) chlorpromazine

13. Which of the following antipsychotics is most likely to cause anticholinergic side effects?

(A) aripiprazole
(B) olanzapine
(C) paliperidone
(D) risperidone

14. XY is currently being treated for schizophrenia and was recently started on haloperidol (Haldol) 20 mg daily 1 week ago. You notice that he is pacing the unit floors; and upon talking to him, he confesses being unable to sit still. He says he feels like he has a motor running inside him that is relieved only by walking. Your team thinks he is agitated from his hallucinations and wants to increase the haloperidol to 30 mg. You recommend which of the following?

(A) Disagree with the team, he is experiencing a manic episode and needs to have valproic acid added to his treatment regimen.
(B) Disagree with the team, he is experiencing a dystonic reaction related to the haloperidol dose. Recommend decreasing the dose and starting an IV anticholinergic medication
(C) Disagree with the team, he is experiencing akathisia related to the haloperidol dose. Recommend decreasing the dose and starting a benzodiazepine.
(D) Disagree with the team, he is experiencing tardive dyskinesia related to the haloperidol dose. Recommend decreasing the dose and stating an anticholinergic medication

15. Which of the following antipsychotics acts as a partial agonist at 5-HT_{1A} receptors?

(A) aripiprazole
(B) olanzapine
(C) haloperidol
(D) risperidone

Answers and Explanations

1. The answer is C *[see Table 39-1]*.
DG's prominent symptoms include well-formed hallucinations and delusions. These hallucinations and delusions are characteristics of paranoid schizophrenia. DG also does not meet the criteria for any other type of schizophrenia.

2. The answer is A *[see Table 39-2]*.
Social withdrawal or asocial behavior is a negative symptom of schizophrenia. Hallucinations, delusions, and agitation are all positive symptoms of schizophrenia.

3. The answer is B *[see IV.A.2; IV.C.1; IV.C.6]*.
The American Psychiatric Association currently recommends using atypical antipsychotics first over typical antipsychotics, unless the patient has a preference. Haloperidol and thioridazine are typical antipsychotics. Clozapine should be used only for treatment refractory patients because of its adverse effect profile.

4. The answer is D *[see Table 39-4; Table 39-6]*.
Risperidone has been associated with moderate weight gain, low to moderate risk of EPS, and low risk of sedation. It has not been associated with anticholinergic effects such as urinary retention.

5. **The answer is B** *[see IV.D.3]*.
DG has a history of response with risperidone; however, she is experiencing a relapse of symptoms owing to noncompliance. A long-acting formulation is indicated to assist with medication compliance. As she has not failed multiple antipsychotics, DG is not a candidate for clozapine or adjunctive clozapine. Long-acting risperidone is preferred in this patient over haloperidol decanoate owing to the patient's response history and its preferable adverse effect profile.

6. **The answer is D** *[see IV.B.4.b.(1)–(4)]*.
TW is experiencing lip smacking and tongue chewing of a late onset, which is best described as tardive dyskinesia.

7. **The answer is A** *[see IV.B.4.b.(4).(d)]*.
Vitamin E, benzodiazepines, baclofen, and reserpine have all been used in the treatment of tardive dyskinesia, although none has been definitively proven to be effective.

8. **The answer is C** *[see Table 39-3; Table 39-6]*.
Because TW is experiencing tardive dyskinesia, her therapy should be changed to an atypical antipsychotic. Her medical history is significant for type 2 diabetes mellitus. Olanzapine is associated with a high risk of causing weight gain, and other metabolic symptoms and should not be used in this patient. Risperidone has a low to moderate risk of EPS. Other atypical antipsychotics, such as quetiapine, that carry a lower risk of EPS would be preferable.

9. **The answer is D** *[see Table 39-6]*.
Olanzapine has a high risk of causing weight gain. Risperidone and quetiapine have a moderate risk of causing weight gain. Aripiprazole is associated with a low risk of weight gain.

10. **The answer is B** *[see IV.C.2–5.a; Table 39-4]*.
Atypical antipsychotics have a higher affinity for serotonin receptors than dopamine receptors, whereas typical antipsychotics have no activity at serotonin receptors. Atypical and typical antipsychotics have similar efficacy for positive symptoms of schizophrenia; however, atypical antipsychotics have increased efficacy against negative symptoms. Atypical antipsychotics are more likely to cause significant weight gain and hyperlipidemia and less likely to cause EPS than typical antipsychotics.

11. **The answer is D** *[see IV.D.3]*.
Risperdal Consta is the only injectable that requires a 3-week overlap with oral risperidone following the first injection. The other injectables either do not require an oral overlap or it is less/greater than 3 weeks.

12. **The answer is B** *[see IV.C.6]*.
Clozapine is the only antipsychotic to be effective in treatment-resistant schizophrenics.

13. **The answer is B** *[see Table 39-6]*.
Olanzapine is the only antipsychotic listed that is a strong antagonist of cholinergic receptors. The other three agents have no to minimal blockage of the cholinergic receptors.

14. **The answer is C** *[see IV.B.4.b.(2)]*.
The patient is experiencing akathisia from too high of a haloperidol dose. The haloperidol dose should be decreased and a benzodiazepine should be started. Akathisia is described as an inner restlessness coupled with an inability to sit still or a need to move.

15. **The answer is A** *[see IV.C.2]*.
Aripiprazole is the only antipsychotic listed that in addition its blocking of 5-HT and dopamine receptors, it also acts as an agonist at 5-HT1A receptors.

(2) Tricyclic antidepressants have limited data supporting their use. This medication class may be most effective in patients with insomnia who have a comorbid depression or substance use disorder or in patients who have a contraindication or a poor response to benzodiazepine agents. See Chapter 38 for side effects of this medication class.

(3) The use of antipsychotics may best most effective in insomnia patients with a comorbid psychiatric disorder. See Chapter 37 for side effects of this medication class.

e. OTC medications and natural remedies

(1) Antihistamines such as diphenhydramine and doxylamine are found in nonprescription sleeping aids. There is a paucity of data supporting their use.

(a) Adverse effects include a hangover effect, dizziness, dry mouth, and constipation. Tolerance to these agents develops quickly.

(2) **Natural remedies**

(a) Melatonin and valerian are two commonly used natural remedies. There is minimal data to support the use of these two products for insomnia. The FDA does not strictly regulate nutritional supplements and herbal products therefore ingredients are not standardized.

D. Evaluation of treatment

1. Choice of a sleep agent should be based on a number of patient-specific factors including age, length of treatment, sleep complaint, substance use history, and cost. Pharmacological treatment may be most appropriate for patients with significant impairment and distress.
2. Treatment should focus on both quantitative and qualitative aspects of patient's sleep and daytime function.
3. Short half-life agents may work best in reducing sleep latency, whereas long-acting agents work may work best in improving total sleep time.
4. Ramelteon and doxepin may be best for patients with insomnia and a comorbid substance use disorder.
5. Sedating antidepressants and antipsychotics may work best for patients with insomnia and a comorbid psychiatric disorder.
6. Antihistamines may work best for patients with infrequent symptoms.

E. Pregnancy

1. Benzodiazepines FDA approved for insomnia are all pregnancy category X.
2. Benzodiazepine-receptor agonists are all pregnancy category C.
3. Ramelteon and doxepin are both pregnancy category C.
4. See Chapters 37 and 38 for the pregnancy category ratings for sedating antidepressants and antipsychotics.

Study Questions

Directions: Each of the questions, statements, or incomplete statements in this section can be correctly answered or completed by **one** of the suggested answers or phrases. Choose the **best** answer.

1. Which of the following is correct regarding the *DSM-IV* diagnosis of major depressive disorder?

(A) Patients must have 10 or more symptoms.
(B) Symptoms must be present for at least 2 weeks.
(C) Symptoms do not cause significant social or occupational impairment.
(D) Diagnosis requires a history of mania.

2. A patient with major depression should receive antidepressant therapy for at least

(A) 2 weeks.
(B) 6 weeks.
(C) 2 months.
(D) 6 months.

For questions 3–4: A 36-year-old woman presents with a 2-month history of depressed mood, anhedonia, increased appetite, weight gain, hypersomnolence, and suicidal ideation. This is the patient's first episode of major depression.

3. Which of the following antidepressants would be most appropriate in the treatment of this patient?

(A) amitriptyline
(B) sertraline
(C) phenelzine
(D) mirtazapine

4. Which of the following is *not* a potential adverse effect of the medication selected for the patient in question 3?

(A) sexual dysfunction
(B) nausea
(C) urinary retention
(D) insomnia

5. Which of the following medications would most likely exacerbate a preexisting seizure disorder?

(A) venlafaxine
(B) trazodone
(C) bupropion
(D) paroxetine

6. A patient who has received citalopram 40 mg/day for 2 weeks for the treatment of major depression complains that the medication is not working and would like to be switched to another agent. What is the appropriate recommendation?

(A) Provide the patient with some information on monoamine oxidase inhibitors (MAOIs) and call the physician to recommend switching the patient to phenelzine.
(B) Encourage the patient to continue with the current regimen and inform him or her that it may take 4 to 6 weeks before the full response is evident.
(C) Recommend adding lithium to augment the current regimen.
(D) Recommend switching to mirtazapine because of therapeutic failure with citalopram.

7. A patient diagnosed with depression was unsuccessfully treated with fluoxetine. Fluoxetine was discontinued, and 14 days later, the patient started therapy with phenelzine. Then, 3 days after phenelzine was started, the patient presented with hyperreflexia, fever, elevated blood pressure, confusion, and diarrhea. What is the most likely cause of this clinical presentation?

(A) serotonin syndrome
(B) serotonin withdrawal syndrome
(C) hypertensive crisis
(D) neuroleptic malignant syndrome

8. A patient presents with pressured speech, inability to sleep for 72 hrs, bizarre dress, inappropriate makeup, and grandiose delusions that interfere with social functioning. Which of the following is the most likely diagnosis?

(A) depression
(B) euthymia
(C) hypomania
(D) mania

9. Which of the following medications would be considered first-line monotherapy for an acute episode of mania?

(A) gabapentin
(B) lithium
(C) lamotrigine
(D) haloperidol

10. Which of the following is the appropriate therapeutic range for lithium in the treatment of mania?

(A) 0.4 to 0.6 mEq/L
(B) 0.6 to 1.5 mEq/L
(C) 1.0 to 2.0 mEq/L
(D) 0.5 to 1.2 mEq/L

11. Which of the following mood stabilizers would be most appropriate in a patient with liver disease?

(A) lithium
(B) valproic acid
(C) carbamazepine
(D) none of the above

12. A 32-year-old, 70-kg man diagnosed with bipolar I disorder is being treated with valproic acid (VPA). Which of the following is a reasonable loading dose for VPA in this patient?

(A) 250 mg twice a day
(B) 500 mg twice a day
(C) 250 mg three times a day
(D) 500 mg three times a day

13. Which of the following factors may increase lithium concentration?

(A) caffeine
(B) osmotic diuretics
(C) increased fluid intake
(D) nonsteroidal anti-inflammatory drugs

14. Which of the following is a late adverse effect of lithium?

(A) nausea
(B) hand tremor
(C) seizures
(D) hypothyroidism

15. Which of the following antidepressants is a potent inhibitor of CYP2D6 liver enzyme?

(A) citalopram (Celexa)
(B) paroxetine (Paxil)
(C) trazodone (Desyrel)
(D) venlafaxine (Effexor)

16. The dosage range for selegiline (Emsam) patch is which of the following?

(A) 6 to 12 mg
(B) 12 to 15 mg
(C) 3 to 6 mg
(D) 20 to 40 mg

17. Which of the following tricyclic amine antidepressants (TCAs) causes the most anticholinergic side effects?

(A) nortriptyline (Pamelor)
(B) desipramine (Norpramin)
(C) amitriptyline (Elavil)
(D) protriptyline (Vivactil)

18. Which of the following medications for bipolar disorder is recommended as maintenance treatment?

(A) aripiprazole (Abilify)
(B) carbamazepine (Tegretol)
(C) lamotrigine (Lamictal)
(D) iloperidone (Fanapt)

19. Which of the following medications would have the quickest onset of symptom relief in a patient presenting with generalized anxiety disorder (GAD)?

(A) fluoxetine (Prozac)
(B) buspirone (Buspar)
(C) lorazepam (Ativan)
(D) venlafaxine XR (Effexor XR)

20. Buspirone (Buspar) mechanism of action can best be described as which of the following?

(A) Norepinephrine reuptake inhibitor
(B) 5-HT_2-receptor antagonist
(C) D_2-receptor antagonist
(D) Partial agonist at 5-HT_{1A}-receptors

21. Duration of treatment for panic disorder should be continued for a period of how long after symptom remission?

(A) 3 months
(B) 6 months
(C) 12 months
(D) 12 to 24 months

22. Which of the following medication classes is considered a first-line treatment option for social anxiety disorder?

(A) Atypical antipsychotics
(B) Anticonvulsants
(C) Selective serotonin reuptake inhibitors (SSRIs)
(D) Tricyclic antidepressants

23. Which benzodiazepine is FDA approved for the treatment of panic disorder?

(A) diazepam (Valium)
(B) clonazepam (Klonopin)
(C) lorazepam (Ativan)
(D) chlordiazepoxide (Librium)

Answers and Explanations

1. The answer is D *[see I.A.1]***.**
The *DSM-IV-TR* criteria provide the diagnostic guidelines for MDD require a patient have five or more symptoms present for a period of at least 2 weeks. These symptoms must cause significant social and occupational impairment. If a patient had a history of mania as part of his or her symptoms presentation, this patient would be diagnosed as bipolar rather than as unipolar MDD.

2. The answer is D *[see I.B.1]***.**
Patients should receive antidepressant therapy through the continuation phase, which is generally 6 to 9 months.

3. The answer is B *[see I.B.1.c]***.**
Sertraline, an SSRI, is a good first-line agent, particularly in patients who would benefit from the stimulatory side effects. Amitriptyline and mirtazapine would not be good alternatives because of this patient's hypersomnolence and weight gain. In addition, a TCA (amitriptyline) is not recommended in patients at risk for suicide. Although some aspects of this patient's depression may be considered atypical, an MAOI would not be selected as first-line therapy, given that it is the patient's first episode of depression.

4. **The answer is C** *[see I.B.1.c]*.
Sertraline has been associated with nausea, sexual dysfunction, and insomnia. Sertraline does not express anticholinergic activity and would, therefore, not cause urinary retention. Of the SSRIs, only paroxetine has been associated with causing anticholinergic adverse effects.

5. **The answer is C** *[see I.B.1.e]*.
Although all antidepressants can lower the seizure threshold, bupropion is contraindicated in patients with seizure disorder. Bupropion is specifically contraindicated in patients with a seizure disorder. Paroxetine was associated with a 0.1% incidence of seizures during clinical trials. Seizure associated with venlafaxine occurs infrequently (1/100 to 1/1000 patients). The overdosage of trazodone may be associated with seizures; but at normal doses, trazodone is not thought to alter the seizure threshold.

6. **The answer is B** *[see I.B.1.i]*.
An antidepressant must be given at the maximum tolerated dose for 4 to 6 weeks before it is considered a therapeutic failure; therefore, the best recommendation is to continue with the current regimen for at least 2 more weeks. MAOIs are reserved for refractory depressed patients and are not indicated in this patient scenario. Lithium is an appropriate augmentative agent but is not indicated until the patient has failed two or three different antidepressant trials.

7. **The answer is A** *[see Table 40-2]*.
Serotonin syndrome may result when starting an MAOI immediately after another agent that increases serotonin levels. Generally, a 2-week washout period is recommended; however, fluoxetine requires a 5-week washout period because of norfluoxetine (active metabolite).

8. **The answer is D** *[see II.B.1]*.
The clinical presentation described is consistent with mania. Hypomania generally does not impair functioning. Euthymia implies normal mood, whereas depression typically involves more neurovegetative symptoms.

9. **The answer is B** *[see Table 40-6]*.
Lithium is considered to be first-line monotherapy for euphoric mania. Gabapentin has demonstrated utility as a mood stabilizer but is considered only an adjunctive therapy. Lamotrigine is an anticonvulsant that currently has data supporting its use in depressive episodes of bipolar disorder but not as first-line monotherapy for mania. Haloperidol is a traditional antipsychotic that may be used parenterally to manage acute agitation but is not appropriate as first-line monotherapy.

10. **The answer is D** *[see II.D.1.a.(4)]*.
The therapeutic range of lithium is 0.5 to 1.2 mEq/L. When using lithium in the treatment of acute mania, the upper end of the therapeutic range is typically used.

11. **The answer is A** *[see II.D.1.a.(2)]*.
Lithium is not known to cause hepatic dysfunction, nor is it metabolized via the liver. However, both valproic acid and carbamazepine can impair liver function.

12. **The answer is D** *[see II.D.3]*.
The appropriate loading dose for VPA in acute mania is 20 mg/kg/day; therefore, in this patient, the appropriate loading dose is 1400 mg/day. This equation approximates the need for the patient, and it is appropriate to round up to available dosage forms.

13. **The answer is D** *[see Table 40-8]*.
Caffeine, osmotic diuretics, and increased fluid intake all decrease lithium concentrations. Nonsteroidal anti-inflammatory drugs decrease renal blood flow and decrease lithium clearance, resulting in increased lithium concentrations.

14. **The answer is D** *[see Table 40-7]*.
Hypothyroidism is a late side effect of lithium therapy usually occurring after 18 months of treatment. Thyroid function panel should be checked at baseline and on follow-up to monitor for this adverse effect.

15. **The answer is B** *[see Table 40-4]*.
Paroxetine is a potent inhibitor of CYP2D6. The other antidepressants listed are only mildly potent inhibitors of CYP2D6.

16. **The answer is A** *[see Table 40-1]*.
The recommended dosage range for selegiline patch is 6 to 12 mg/day. Patients should be started on 6 mg and slowly titrated up in dose to a maximum dose of 12 mg/day.

17. **The answer is C** *[see Table 40-3]*.
Tertiary amine TCAs cause more anticholinergic adverse effects than secondary amine TCAs. Of the antidepressants listed, only amitriptyline is a tertiary amine TCA.

18. **The answer is C** *[see Table 40-6]*.
Lamotrigine has been shown to be an effective agent in the preventing relapse into both mania and depression. Therefore, lamotrigine is FDA approved for maintenance treatment of bipolar disorder.

19. **The answer is C** *[see III.E.1]*.
Lorazepam is a benzodiazepine and these agents produce symptom relief in GAD within days to 1 week of treatment. All other medications listed require a period of at least up to 2 weeks or longer for GAD symptom relief.

20. The answer is D *[see III.D.2.a]*.
Buspirone main mechanism of action is through partial agonism of 5-HT_{1A}-receptors. Buspirone does not act at all by the other mechanisms of action listed.

21. The answer is D *[see III.E.2]*.
Treatment of panic disorder should be continued for a period of 12 to 24 months in order to ensure patients do not have a relapse of symptoms.

22. The answer is C *[see III.D.1.c]*.
SSRIs are the first-line treatment option for SAD. These other treatments listed may be used as possible second-line treatments.

23. The answer is B *[see III.D.2.b]*.
Clonazepam and alprazolam XR (Xanax XR) are the only benzodiazepines FDA approved for the treatment of panic disorder.

Study Questions

Directions for questions 1–7: Each of the questions, statements, or incomplete statements in this section can be correctly answered or completed by **one** of the suggested answers or phrases. Choose the **best** answer.

1. The symptoms of allergen-mediated asthma result from which of the following?

(A) Increased release of mediators from mast cells
(B) Increased adrenergic responsiveness of the airways
(C) Increased vascular permeability of bronchial tissue
(D) Decreased calcium influx into the mast cells
(E) Decreased prostaglandin production

2. Acute exacerbations of asthma can be triggered by all of the following *except*

(A) bacterial or viral pneumonia.
(B) hypersensitivity reaction to penicillin.
(C) discontinuation of asthma medication.
(D) hot, dry weather.
(E) stressful emotional events.

3. A 45-year-old male with a history of asthma has a peak expiratory flow rate (PEFR) of 65%, nocturnal wheezing once a month, and daytime wheezing usually less than twice a week. According to the National Institutes of Health (NIH) guidelines for the treatment of asthma, he has which type?

(A) Mild intermittent
(B) Mild persistent
(C) Moderate persistent
(D) Severe persistent

4. The patient in question 3 should be treated with which *two* agents?

(A) Inhaled steroid and ipratropium
(B) Inhaled steroid and albuterol MDI (as needed)
(C) Inhaled steroid and aspirin

5. A 15-year-old female is brought to the emergency department. She is breathing 30 times per minute, is unable to speak in full sentences, and has a peak expiratory flow rate (PEFR) < 50% predicted. The preferred first-line therapy for her asthma exacerbation is

(A) theophylline.
(B) β-agonist.
(C) corticosteroid.
(D) cromolyn sodium.
(E) A and B
(F) B and C

6. The primary goals of asthma therapy in an adult patient include all of the following *except*

(A) maintain normal activity levels.
(B) maintain control of symptoms.
(C) avoid adverse effects of asthma medications.
(D) prevent acute exacerbations and chronic symptoms.
(E) prevent destruction of lung tissue.

7. Which of the following tests is used at home to assess therapy and determine if a patient with asthma should seek emergency care?

(A) Forced expiratory volume in 1 sec (FEV_1)
(B) Forced vital capacity (FVC)
(C) Total lung capacity (TLC)
(D) Peak expiratory flow rate (PEFR)
(E) Residual volume (RV)

Directions for question 8: The incomplete statement in this section can be correctly answered or completed by **one or more** of the suggested answers. Choose the answer, **A–E**.

(A) if **I only** is correct
(B) if **III only** is correct
(C) if **I and II** are correct
(D) if **II and III** are correct
(E) if **I**, **II**, **and III** are correct

8. The disease process of chronic bronchitis is characterized by

I. the destruction of central and peripheral portions of the acinus.
II. an increased number of mucous glands and goblet cells.
III. edema and inflammation of the bronchioles.

Directions for questions 9–11: Each description in this section is most closely associated with **one** of the following agents. The agents may be used more than once or not at all. Choose the **best** answer, **A–E**.

(A) cimetidine
(B) albuterol
(C) ipratropium bromide
(D) epinephrine
(E) atropine

9. Decreases theophylline clearance

10. Has anticholinergic activity with few side effects

11. Has high β_2-adrenergic selectivity

Answers and Explanations

1. The answer is A *[see I.F; Figure 41-1].*
In asthma, airborne antigen binds to the mast cell, activating the IgE-mediated process. Mediators (e.g., histamine, leukotrienes, prostaglandins) are then released, causing bronchoconstriction and tissue edema.

2. The answer is D *[see I.D; Figure 41-1].*
Exacerbations of asthma can be triggered by allergens, respiratory infections, occupational stimuli (e.g., fumes from gasoline or paint), emotions, and environmental factors. Studies have shown that cold air can cause release of mast cell mediators by an undetermined mechanism. Hot, dry air does not cause this release.

3. The answer is C *[see Table 41-3].*
The patient has moderate persistent asthma. All three parameters are consistent with mild persistent asthma. If any one of the three parameters indicated moderate persistent asthma, then the patient would be classified as moderate asthma (PEFR = 65%).

4. The answer is B *[see Figure 41-3].*
Inhaled steroids are the anti-inflammatory drug of choice owing to proven efficacy. All patients should be prescribed a short-acting β_2-agonist to use as rescue therapy for worsening symptoms. If chronic symptoms worsen, a long-acting β_2-agonist can be added (e.g., Advair). Remember that increasing the dose of the inhaled steroid may not improve symptoms, a long-acting bronchodilator is more likely to do so.

5. **The answer is F** *[see Figure 41-3].*
Patient is obviously in respiratory distress. Aggressive treatment with oxygen, systemic steroids, and short-acting bronchodilators is indicated. Ipratropium could also be added to the albuterol in the acute setting.

6. **The answer is E** *[see I.F; I.H.1; II.D].*
Asthma is characterized by reversible airway obstruction in response to specific stimuli. Mast cells release mediators, which trigger bronchoconstriction. After an acute attack, in most cases symptoms are minimal and pathological changes are not permanent. Unlike asthma, COPD does cause progressive airway destruction, chronic bronchitis by excessive mucus production and other changes, and emphysema by destruction of the acinus.

7. **The answer is D** *[see I.G.2.a.(3)].*
For home monitoring, PEFR is the best test for assessment of therapy, trigger identification, and the need for referral to emergency care. It is recommended for patients who have had severe exacerbations of asthma, who are poor perceivers of asthma symptoms, and those with moderate-to-severe disease.

8. **The answer is D (II, III)** *[see II.D.1–2].*
Chronic bronchitis is characterized by an increase in the number of mucous and goblet cells owing to bronchial irritation. This results in increased mucus production. Other changes include edema and inflammation of the bronchioles and changes in smooth muscle and cartilage. Emphysema is a permanent destruction of the central and peripheral portions of the acinus distal to the bronchioles. In this disease, adequate oxygen reaches the alveolar duct, owing to increased rate of breathing, but perfusion is abnormal.

9. **The answer is A** *[see Table 41-8].*

10. **The answer is C** *[see II.G.1.a].*

11. **The answer is B** *[see Table 41-4].*
Cimetidine, an H_2-receptor antagonist, decreases theophylline clearance by inhibiting hepatic microsomal mixed-function oxidase metabolism, thus increasing serum theophylline concentrations. Theophylline clearance can be decreased by 40% during the first 24 hrs of concurrent therapy. Anticholinergic agents such as atropine and ipratropium bromide produce bronchodilation by competitively inhibiting cholinergic receptors. The disadvantages of atropine include dry mouth, tachycardia, and urinary retention. Ipratropium bromide is three to five times more potent than atropine and does not have these side effects. Albuterol is one of the most β_2-selective adrenergic agents available. Other such agents include terbutaline, bitolterol, and pirbuterol. Agents with β_2-selectivity dilate bronchioles without causing side effects related to β_1-stimulation (e.g., increased heart rate).

Study Questions

1. Which of the following statements best characterizes osteoarthritis (OA)?
   - **(A)** OA is a common disorder characterized by diffuse inflammation leading to increased disability.
   - **(B)** OA is a systemic disorder characterized by degenerative changes in the joint(s) and typically exhibits extra-articular involvement.
   - **(C)** OA is a common disorder that affects the normal synthesis and degradation of cartilage.
   - **(D)** OA is a common disorder that adversely affects bone density and leads to falls and fractures.
   - **(E)** OA is a systemic disorder frequently associated with localized inflammation and pannus formation.

2. Which of the following agents is recommended as first-line drug therapy by the American College of Rheumatology for patients with mild to moderate osteoarthritis?
   - **(A)** Ibuprofen (Motrin)
   - **(B)** Celecoxib (Celebrex)
   - **(C)** Diclofenac gel (Voltaren Gel)
   - **(D)** Tramadol (Ultram)
   - **(E)** Acetaminophen (Tylenol)

3. When consideration is given to diagnosing osteoarthritis, which of the following statements is FALSE?
   (A) Joint tenderness, diminished range of motion, and/or articular crepitus can be assessed
   (B) Radiographical evidence will show joint space narrowing
   (C) Common patient complaints include a deep, localized ache in a joint
   (D) Laboratory evidence reveals a high sedimentation rate, positive rheumatoid factor, and anti-cyclic citrullinated peptide antibody
   (E) Morning stiffness lasts < 30 mins

4. Which of the following disease modifying anti-rheumatic drugs are recommended by the American College of Rheumatology for all patients with rheumatoid arthritis regardless of disease duration and degrees of disease activity?
   (A) Methotrexate and sulfasalazine
   (B) Methotrexate and hydroxychloroquine
   (C) Methotrexate and etanercept
   (D) Methotrexate and leflunomide
   (E) Methotrexate and minocycline

5. In order to reduce toxicity with methotrexate, concomitant administration with what vitamin is recommended?
   (A) Folic acid
   (B) Thiamine
   (C) Ascorbic acid
   (D) Pyridoxine
   (E) Riboflavin

6. All of the following statements are true about the use of hyaluronic acid derivatives in osteoarthritis (OA) *except*:
   (A) Should be considered in those not responding to simple analgesics
   (B) Should be considered for the treatment of knee OA
   (C) Should be considered as disease-modifying agents
   (D) Should be considered if no allergies exist to feathers or egg products
   (E) Should be considered to improve elasticity of synovial fluid

7. Which of the following agents used for osteoarthritis or rheumatoid arthritis require dosage adjustment in patients with renal impairment?
   (A) Prednisone
   (B) Acetaminophen
   (C) Oxycodone
   (D) Glucosamine
   (E) Tramadol

8. Which of the following disease modifying antirheumatic drugs can be administered orally?
   (A) Certolizumab (Cimzia)
   (B) Anakinra (Kineret)
   (C) Abatacept (Orencia)
   (D) Leflunomide (Arava)
   (E) Etanercept (Enbrel)

9. What is the recommended starting dose of methotrexate when used for rheumatoid arthritis?
   (A) 2.5 mg PO daily
   (B) 2.5 mg PO weekly
   (C) 7.5 mg PO daily
   (D) 7.5 mg PO weekly
   (E) 25 mg PO weekly

10. Ocular toxicity is associated with
    (A) leflunomide (Arava)
    (B) methotrexate (Rheumatrex)
    (C) hydroxychloroquine (Plaquenil)
    (D) infliximab (Remicade)
    (E) adalimumab (Humira)

11. A baseline PPD is recommended to rule-out latent tuberculosis before initiating:
    (A) leflunomide, etanercept, infliximab
    (B) methotrexate, sulfasalazine, hydroxychloroquine
    (C) leflunomide, methotrexate, etanercept
    (D) methotrexate, infliximab, anakinra
    (E) abatacept, leflunomide, sulfasalazine

12. Before initiating therapy with a nonsteroidal anti-inflammatory drug, it is important to evaluate:
    (A) hematocrit, sodium, triglycerides
    (B) serum creatinine, hematocrit, blood pressure
    (C) blood pressure, serum folate, potassium
    (D) liver function tests, serum creatinine, and serum folate
    (E) sodium, hematocrit, respiration

13. All of the following statements are true about disease modifying antirheumatic drugs *except*:
    (A) Should be started within 3 to 4 months of diagnosis of RA
    (B) Can reduce or prevent joint damage
    (C) Shown to work within 1 to 2 days of starting therapy
    (D) Classified as nonbiological or biological
    (E) Can preserve joint function

Answers and Explanations

1. **The answer is C** *[see III.C]*.
Inflammation is generally not present in osteoarthritis. It is a localized (not systemic) disorder that affects the cartilage and can eventually affect the underlying bone causing severe pain and disability.

2. **The answer is E** *[see III.E.3.a]*.
The ACR recommends acetaminophen (≤ 4 gm/day) as the first drug treatment option in patients with mild to moderate OA pain.

3. **The answer is D** *[see III.D.2]*.
No specific lab tests are diagnostic for OA.

4. **The answer is D** *[see IV.I.2.a & b]*.
Based on the ACR's 2008 RA Treatment Guidelines, both MTX and leflunomide are recommended for all patients with RA regardless of disease duration, disease burden, or prognostic factors.

5. **The answer is A** *[see IV.I.2.a]*.
MTX inhibits dihydrofolate reductase. Research has shown supplemental doses of folic acid (e.g., 1 mg/day) can reduce side effects.

6. **The answer is C** *[see III.E.3.c.(4)(b)]*.
To date, no drug treatment (including hyaluronic acid derivatives) has demonstrated

7. **The answer is E** *[see III.E.3]*.
Tramadol's maximum daily dose is 200 mg and should be given every 12 hrs if creatinine clearance is ≤ 30 mL/min.

8. **The answer is D** *[see Table 42-2]*.
Leflunomide is available for oral administration. The other agents must be given SC or IV.

9. **The answer is D** *[see Table 42-2]*.
The initial starting dose of MTX when treating RA is 7.5 mg PO weekly.

10. **The answer is C** *[see Table 42-2]*.
An ophthalmic exam is recommended when patients are receiving hydroxychloroquine.

11. **The answer is A** *[see Table 42-2]*.
Some biological DMARDs have been linked with re-activating latent TB; therefore, before starting therapy with leflunomide, etanercept, or infliximab, patients should have a PPD placed.

12. **The answer is B** *[see III.E.3.b.(4)]*.
Common side effects of NSAIDs include GI toxicity (e.g., bleeding), acute renal failure, and fluid retention (leading to hypertension).

13. **The answer is C** *[see IV.I.3; Table 42-2]*.
The main disadvantage to DMARD therapy is the time it takes for the medication to work. In general, nonbiological agents can take 3 to 4 months for affect; whereas biological agents can take 1 to 2 months (or more).

Study Questions

Directions for questions 1–3: Each of the questions, statements, or incomplete statements in this section can be correctly answered or completed by **one** of the suggested answers or phrases. Choose the **best** answer.

1. All of the following statements concerning an acute gouty arthritis attack are correct *except* which one?

(A) The diagnosis of gout is ensured by a good therapeutic response to colchicine because no other form of arthritis responds to this drug.
(B) To be ensured of the diagnosis, monosodium urate crystals must be identified in the synovial fluid of the affected joint.
(C) Attacks frequently occur in the middle of the night.
(D) An untreated attack may last up to 2 weeks.
(E) The first attack usually involves only one joint, most frequently the big toe (first metatarsophalangeal joint).

2. A 42-year-old obese man has been diagnosed with gout. He has had three acute attacks this year, and his uric acid level is presently 11.5 mg/dL (upper limit of normal is 7.0 mg/dL). He has no other diseases. Rational treatment of this patient during the interval period between gouty attacks might include any of the following *except*

(A) acetaminophen or aspirin 650 mg as needed for joint pain.
(B) probenecid.
(C) colchicine.
(D) allopurinol.
(E) a decrease in caloric intake.

3. A 45-year-old man is admitted to the hospital with the diagnosis of an acute attack of gout. His serum uric acid is 10.5 mg/dL (normal is 3 to 7 mg/dL). Which of the following would be the most effective initial treatment plan?
   (A) Before treating this patient, immobilize the affected joint and obtain a 24-hr urinary uric acid level to determine which drug, either allopurinol or probenecid, would be the best agent to initiate therapy.
   (B) Begin oral colchicine 1.2 mg initially, followed by 0.6 mg every 2 hrs until relief is obtained, gastrointestinal distress occurs, or a maximum of 8 mg has been taken; also, begin probenecid 250 mg twice a day concurrently.
   (C) Administer oral indomethacin 50 mg three times a day for 2 days; then gradually taper the dose over the next few days.
   (D) Administer oral naproxen 750 mg, followed by 250 mg every 8 hrs for 3 weeks.
   (E) Give colchicine 0.5 mg intramuscularly followed by 1.0 mg intravenous piggyback every 12 hrs for 2 weeks.

Directions for question 4: The question in this section can be correctly answered or completed by **one or more** of the suggested answers. Choose the answer, **A–E**.

(A) if **I only** is correct
(B) if **III only** is correct
(C) if **I and II** are correct
(D) if **II and III** are correct
(E) if **I, II, and III** are correct

4. Allopurinol is recommended instead of probenecid in the treatment of hyperuricemia in which of the following situations?
   (I) When the patient has several large tophi on the elbows and knees
   (II) When the patient has an estimated creatinine clearance of 15 mL/min
   (III) When the patient has leukemia and there is concern regarding renal precipitation of urate

Directions for question 5: The incomplete statement in this section can be correctly answered or completed by **one** of the suggested answers or phrases. Choose the **best** answer.

5. In a patient who has had documented gouty arthritis and hyperuricemia and who also has hypertension, a preferred antihypertensive agent would be
   (A) hydrochlorothiazide
   (B) losartan
   (C) clonidine
   (D) lisinopril
   (E) irbesartan

6. Which of the following ***best describes*** a current important point about the use of allopurinol in the treatment of intercritical gout?
   (A) It is best dosed in a "2 months on and 2 months off" pattern
   (B) It needs to be dosed twice daily because of its short half-life.
   (C) It is the only currently available FDA-approved xanthine oxidase inhibitor on the market.
   (D) It should be used in reduced doses if the patient has significant renal impairment.
   (E) It can only be used in patients who are overproducers of uric acid.

Answers and Explanations

1. **The answer is A** *[see III.B.1–2; III.C.1; III.C.3]***.** Other forms of acute arthritis may respond to colchicine, so that the diagnosis of gout cannot be established unequivocally by a good response to this agent. A definitive diagnosis requires the presence of urate crystals in the affected joint, although the presence of other symptoms or laboratory findings may suggest a probable diagnosis of gout.

2. **The answer is A** *[see I.D.2.c.(1); IV.C]***.** Aspirin in doses < 2 g/day can inhibit uric acid secretion. Weight reduction, allopurinol or probenecid to lower the serum uric acid levels, and prophylactic colchicine are all appropriate interventions in the interval phase to reduce the incidence of acute gouty attacks.

3. **The answer is C** *[see III.E.1.c; III.E.2.a; III.E.2.b; IV.C]***.** Of the selections, the most effective initial plan in treating an acute attack of gout is to administer indomethacin orally, giving 50 mg three times a day for 2 to 3 days, then gradually tapering the dosage over the next few days. Although joint immobilization is an appropriate initial step, drugs for pain relief should be administered as soon as possible. Uric acid modification therapy (allopurinol or probenecid) should not be initiated until the acute attack is under control. Initiating therapy with probenecid at this point may prolong the resolution of an acute attack of gouty arthritis, which can usually be accomplished within 7 days of NSAID therapy. Colchicine should never be given intramuscularly because it causes tissue irritation. The IV form of this drug has been removed from the market.

4. **The answer is E (I, II, III)** *[see IV.C]*.
In the treatment of hyperuricemia, allopurinol is indicated rather than probenecid when large tophi are present, when the creatinine clearance is < 50 to 60 mL/min (probenecid would be ineffective, but the allopurinol dosage would have to be decreased), when the patient is an overproducer of uric acid, and when there is a need to prevent the formation of large amounts of uric acid (e.g., when conditions such as leukemia are present).

5. **The answer is B** *[see IV.C.3.b.(5).(a)]*.
Losartan, an angiotensin II receptor blocker has been shown to increase urinary uric acid secretion and can, therefore, lower serum uric acid levels. Hydrochlorothiazide actually decreases urinary uric acid excretion and must be used cautiously in gout patients, if at all. The other antihypertensive agents mentioned have minimal or no effects on the serum uric acid.

6. **The answer is D** *[IV.C.3.b.(1)]*.
Allopurinol must be given daily without interruption, its principal metabolite (oxypurinol) has a long half-life so once a day dosing is appropriate, febuxostat is another xanthine oxidase inhibitor on the market, it can be used for both overproducers and hypoexcreters of uric acid. D. is correct because doses do need to be reduced if the patient has renal impairment.

Study Questions

Directions for questions 1–6: Each of the questions, statements, or incomplete statements in this section can be correctly answered or completed by **one** of the suggested answers or phrases. Choose the **best** answer.

1. ZZ is a 43-year-old female with a chief complaint of hematemesis and abdominal pain. Serology is positive for *H. pylori*. Which of the following would be the best regimens to treat ZZ?

(A) Omeprazole 20 mg daily plus clarithromycin 500 mg b.i.d. × 14 days
(B) Lansoprazole 30 mg b.i.d. plus tetracycline 500 mg q.i.d. × 14 days
(C) Rabeprazole 20 mg b.i.d. plus amoxicillin 1 g b.i.d. plus clarithromycin 500 mg b.i.d. × 7 days
(D) Esomeprazole 40 mg b.i.d. plus amoxicillin 500 mg b.i.d. plus clarithromycin 500 mg b.i.d. × 7 days
(E) Pantoprazole 40 mg b.i.d. plus amoxicillin 1 g b.i.d. plus clarithromycin 500 mg t.i.d. × 10 days

2. All of the following statements concerning antacid therapy used in the treatment of duodenal or gastric ulcers are correct *except* which one?

(A) Antacids may be used to heal the ulcer but are ineffective in controlling ulcer pain.
(B) Antacids neutralize acid and decrease the activity of pepsin.
(C) If used alone for ulcer therapy, antacids should be administered 1 hr and 3 hrs after meals and before bedtime.
(D) If diarrhea occurs, the patient may alternate the antacid product with aluminum hydroxide.
(E) Calcium carbonate should be avoided because it causes acid rebound and induces constipation.

3. As part of a comprehensive management strategy to treat peptic ulcer disease, patients should be encouraged to do all of the following *except*

(A) decrease caffeine ingestion.
(B) eat only bland foods.
(C) stop smoking.
(D) avoid alcohol.
(E) avoid the use of milk as a treatment modality.

4. A gastric ulcer patient requires close follow-up to document complete ulcer healing because

(A) perforation into the intestine is common.
(B) spontaneous healing of the ulcer may occur in 30% to 50% of cases.
(C) there is the risk of the ulcer being cancerous.
(D) symptoms tend to be chronic and recur.
(E) weight loss may be severe in gastric ulcer patients.

5. IT is a 58-year-old male admitted to the intensive care unit with acute respiratory failure and thrombocytopenia. He is at high risk for an upper gastrointestinal bleed. Which of the following agents are approved by the U.S. Food and Drug Administration (FDA) for the prevention of this type of bleed?

(A) Sucralfate
(B) Famotidine
(C) Esomeprazole
(D) Lansoprazole
(E) Omeprazole

6. All of the following provide acid suppression similar to omeprazole 20 mg every day *except*

(A) dexlansoprazole 30 mg every day.
(B) pantoprazole 40 mg every day.
(C) rabeprazole 20 mg every day.
(D) ranitidine 150 mg twice a day.
(E) all provide equivalent acid suppression.

Directions for questions 7–8: The questions and incomplete statements in this section can be correctly answered or completed by **one or more** of the suggested answers. Choose the answer, **A–E**.

A if **I only** is correct
B if **III only** is correct
C if **I and II** are correct
D if **II and III** are correct
E if **I**, **II**, **and III** are correct

7. Correct statements concerning cigarette smoking and ulcer disease include which of the following?

(I) Smoking delays healing of gastric and duodenal ulcers.
(II) Nicotine decreases biliary and pancreatic bicarbonate secretion.
(III) Smoking accelerates the emptying of stomach acid into the duodenum.

8. When administered at the same time, antacids can decrease the therapeutic efficacy of which of the following drugs?

(I) sucralfate
(II) ranitidine
(III) cimetidine

Directions for questions 9–13: Each description in this section is most closely associated with **one** of the following agents. Each agent is used only **once**. Choose the **best** answer, **A–E**.

A Sodium bicarbonate
B Aluminum hydroxide
C Calcium carbonate
D Magnesium hydroxide
E Propantheline

9. May cause diarrhea

10. Cannot be used by patients with heart failure

11. If used with milk and an alkaline substance can cause milk-alkali syndrome

12. May cause dry mouth

13. Can be alternated with an antacid mixture to control diarrhea.

Answers and Explanations

1. The answer is C *[see Table 44-4]***.**
Though all agents are useful in the treatment of *Helicobacter pylori*, only the combination of rabeprazole with amoxicillin and clarithromycin for 7 days is correct. The other doses and duration of therapy are incorrect.

2. The answer is A *[see II.A.1]***.**
Antacids have been shown to heal peptic ulcers, and their main use in modern therapy is to control ulcer pain. Antacids should be taken 1 hr and 3 hrs after meals because the meal prolongs the acid-buffering effect of the antacid. If diarrhea becomes a problem with antacid use, an aluminum hydroxide product can be alternated with the antacid mixture; this takes advantage of the constipating property of aluminum. Because calcium carbonate causes acid rebound and constipation, its use should be avoided.

3. The answer is B *[see II.B.1.a.(1)]***.**
Bland food diets are no longer recommended in the treatment of ulcer disease because research indicates that bland or milk-based diets do not accelerate ulcer healing. Studies show that patients can eat almost anything; however, they should avoid foods that aggravate their ulcer symptoms.

4. The answer is C *[see I.D.6]***.**
Between 5% and 10% of gastric ulcers may be the result of cancer. The ulcer may respond to therapy; however, failure of the ulcer to decrease satisfactorily in size and to heal with therapy may suggest cancer. Close follow-up is necessary to document complete ulcer healing.

5. The answer is E *[see II.6.B]***.**
Though all of these agents have been used with success in the prevention of GI bleeds in critically ill patients, only omeprazole (as a powder for oral suspension) has been FDA approved for this indication.

6. The answer is D *[see II.A.6.b.(1)]***.**
Doses of omeprazole 20 mg, dexlansoprazole 30 mg, pantoprazole 40 mg, and rabeprazole 20 mg administered once daily provide similar levels of acid suppression. All provide significantly better acid inhibition than ranitidine, even at doses of 150 mg twice a day or more.

7. **The answer is E** *(I, II, III) [see I.E.3; II.B.1.c]*.
Clinical studies have shown that smoking increases susceptibility to ulcer disease, impairs spontaneous and drug-induced healing, and increases the risk and rapidity of recurrence of the ulcer. These findings may result in part from nicotine's ability to decrease biliary and pancreatic bicarbonate secretion, thus decreasing the body's ability to neutralize acid in the duodenum. Also, the accelerated emptying of stomach acid into the duodenum may predispose to duodenal ulcer and may decrease healing rates.

8. **The answer is E** *(I, II, III) [see II.A.1.e.(3); II.A.3.d]*.
The mean peak blood concentration of cimetidine and the area under the 4-hr cimetidine blood concentration curve were both reduced significantly when cimetidine was administered at the same time as an antacid. The absorption of ranitidine is also reduced when it is taken concurrently with an aluminum-magnesium hydroxide antacid mixture. To avoid this interaction, the antacid should be administered 1 hr before or 2 hrs after the administration of cimetidine or ranitidine. Antacids may reduce mucosal binding of sucralfate, decreasing its therapeutic efficacy. Antacids should, therefore, be given 30 to 60 mins before or after sucralfate.

9. **The answer is D** *[see II.A.1.b.(3)]*.

10. **The answer is A** *[see II.A.1.d.(2)]*.

11. **The answer is C** *[see II.A.1.d.(5)]*.

12. **The answer is E** *[see II.A.4.c.(1)]*.

13. **The answer is B** *[see II.A.1.b.(3)]*.
Magnesium-containing products tend to cause diarrhea, possibly because of magnesium's ability to stimulate the secretion of bile acids by the gallbladder. Because of its sodium content, sodium bicarbonate is contraindicated in patients with CHF, hypertension, severe renal disease, and edema. Sodium bicarbonate is no longer used in peptic ulcer therapy. In addition to causing acid rebound, calcium carbonate, if taken with milk and an alkaline substance for long periods, may cause milk-alkali syndrome. It also may cause adverse effects such as hypercalcemia, alkalosis, azotemia, and nephrocalcinosis. Propantheline, like other anticholinergic agents, may cause dry mouth, blurred vision, urinary retention, and constipation. These agents sometimes are used as adjuncts to relieve duodenal ulcer pain. They are contraindicated in gastric ulcer because they delay gastric emptying. Aluminum hydroxide is constipating and can be alternated with the patient's current antacid when that antacid product is causing diarrhea.

Study Questions

For questions 1–2: A 35-year-old male presents to his physician with a primary complaint of abdominal pain and frequent bowel movements over the past few weeks. Upon examination and routine laboratory testing, he is found to have a low-grade fever and an elevated erythrocyte sedimentation rate. Further questioning reveals he is having four to five loose bowel movements each day. The patient is a past smoker. Stool antigen tests are negative for known GI pathogens. Physical examination and colonoscopy reveal contiguous inflammation of the rectum and most of the descending colon. The physician diagnosis is mild to moderate ulcerative colitis.

1. Which therapy would be the most effective for inducing remission?
   - **(A)** Topical corticosteroids
   - **(B)** Topical 5-ASA
   - **(C)** Oral budesonide
   - **(D)** Topical 5-ASA plus oral 5-ASA
2. Once remission is achieved, which therapy is most appropriate for maintenance?
   - **(A)** Sulfasalazine 2 g/day
   - **(B)** Balsalazide 2 g/day
   - **(C)** Olsalazine 4 g/day
   - **(D)** Topical corticosteroids

For questions 3–4: An 18-year-old female with newly diagnosed mild Crohn's disease within the ileum returns to her physician for her first follow-up since starting treatment. Three weeks ago she started oral sulfasalazine 4 g/day and azathioprine 25 mg/day. Since starting these meds, her symptoms have not improved. If anything, they are slightly worse. She is ambulatory with no signs of toxicity (blood per rectum, pain, anemia, etc.) or weight loss.

3. What would be a logical next step in therapy?
   - **(A)** Stop azathioprine and begin IV corticosteroids
   - **(B)** Stop sulfasalazine and begin oral budesonide 9 mg/day
   - **(C)** Stop azathioprine and begin prednisone 40 mg orally per day
   - **(D)** Stop sulfasalazine and begin Lialda® 4.8 gm/day
4. Remission of her first episode was successful. Unfortunately, fulldose azathioprine alone has been unable to maintain effective control of her CD. Over the past 18 months she has had numerous flare-ups. They resolve with each burst of acute therapy but return with azathioprine alone. Her symptoms are increasing (moderate disease) and her schooling is beginning to suffer. What would be a logical next step in therapy?
   - **(A)** Change azathioprine to 6-MP at 1.5 mg/kg/day
   - **(B)** Add metronidazole 750 mg/day
   - **(C)** Surgical resection with ostomy
   - **(D)** Add infliximab 5 mg/kg every 8 weeks

For question 5: A man with diarrhea-predominant IBS is experiencing interruption of his work as a truck driver secondary to frequent bouts of diarrhea. He states his symptoms are worse after eating, especially fried foods. His physician discusses the possible benefit of avoiding fat in his diet. The patient agrees to try but also asks for something to uses in emergencies.

5. What would be the most appropriate therapy to use?
   - **(A)** Alosetron 0.5 mg b.i.d.
   - **(B)** Hyoscyamine 0.15 mg PO p.r.n.
   - **(C)** Loperamide 4 mg then 2 mg p.r.n. up to 16 mg/day
   - **(D)** Fluoxetine 40 mg q.d.
6. Which of the following is the most appropriate initial therapy for a woman with severe constipation-predominant IBS?
   - **(A)** A restrictive bland diet
   - **(B)** Tegaserod 6 mg PO b.i.d.
   - **(C)** Alosetron 1 mg PO b.i.d.
   - **(D)** Psyllium 2.5 g in divided doses

7. Ulcerative colitis and Crohn's disease present in very similar ways. There are several clinical differences between the diseases that can help differentiate them. Which of the following clinical features is more common in Crohn's disease than in ulcerative colitis?
   (A) abnormal bowel movements
   (B) slow onset of disease
   (C) joint pain
   (D) fistula formation

8. Patient prescribed anti-TNF-α agents such as adalimumab should be monitored carefully for which of the following adverse events according to black box warnings included in prescribing information?
   (A) Increased risk of severe loss of bone density
   (B) Increased risk of critically high potassium levels
   (C) Increased risk of toxic megacolon
   (D) Increased risk of pneumonia

Answers and Explanations

1. **The answer is D** *[see II.B.2]***.**
   Topical 5-ASA therapy plus oral 5-ASA therapy has been shown to be superior to either alone or topical steroids at inducing remission in mild to moderate UC. Budesonide ileal release will not likely reach the site of disease in this patient as he has left-sided disease.

2. **The correct answer is A** *[see II.B.3]***.**
   The correct doses for balsalazide would be 3 to 6 g/day and for olsalazine would be 1 g/day. Topical steroids have no place in maintenance of UC.

3. **The correct answer is B** *[see II.C.1]***.**
   This patient has not responded to 5-ASA therapy for inducing remission of her mild disease. Additionally, recent evidence indicates there are more effective treatments than 5-ASA for acute CD. As such, Lialda would not be an effective treatment either. The patient is not showing signs of severe disease or toxicity and as such neither IV or oral therapy with systemic corticosteroids is warranted at this time. Azathioprine is an appropriate agent for CD maintenance but not acute CD as it may take several months to induce remission. Continuing azathioprine is a reasonable approach to transition the patient to maintenance therapy. Budesonide is an ileal release therapy and her disease is mainly confined to the ileum. Budesonide has been shown to be effective in acute mild and moderate CD. Budesonide will help control the acute disease and then it can be withdrawn as she transitions to the maintenance phase.

4. **The correct answer is D** *[see II.C.4]***.**
   Azathioprine is a first-line therapy for maintenance of CD but in this case is not working. Switching to 6-MP will not be effective as the two agents are mechanistically similar. Broad-spectrum antibiotics such as metronidazole are unlikely to be of any benefit in this patient and should not be used. In addition, long-term adverse effects associated with metronidazole may not be tolerable. While likely to be beneficial, surgery with a permanent ostomy would also be severely limiting to a young patient due to social and QOL concerns. Infliximab has been shown to be effective for refractory CD and maintenance of CD.

5. **The correct answer is C** *[see II.D.3]***.**
   This patient is male and as such alosetron is not an appropriate option for him. Hyoscyamine is an effective antispasmodic but will likely do little for his diarrhea. The patient makes no complaint of serious impact on his life and does not show signs of severe disease. Full dose antidepressant fluoxetine dosing is not warranted. Loperamide can be of use in managing mild to moderate symptoms of IBS.

6. **The correct answer is B** *[see II.D.4]***.**
   Tegaserod has been withdrawn from the market and is available only for emergency use upon appeal to the FDA. Alosetron is effective in women with diarrhea-predominant IBS. Restrictive diets are not normally of benefit. Increasing dietary fiber is a reasonable choice prior to prescription therapy. Dietary fiber may increase bloating symptoms with IBS-C, these can be lessened by starting with smaller doses and titrating to effect. If fiber fails, laxative or lubiprostone (Amitiza) could be tested.

7. **The correct answer is D** *[see Table 45.1]***.**
   While the overlap of clinical presentation of these two diseases is substantial, fistula formation is extremely rare in ulcerative colitis.

8. **The correct answer is D** *[see II.A.6.c]***.**
   Black box warnings for all of the anti-TNF-α therapies include increased risk of serious infections such as pneumonia or reactivation of tuberculosis or hepatitis and increased risk of malignancies such as lymphoma. Changes in potassium or bone density are not adverse effects commonly associated with anti-TNF-α therapies and are not included in black box warnings. Toxic megacolon is a complication usually associated with UC and also is not included in black box warnings with anti-TNF-α use.

Study Questions

Directions: Each of the questions, statements, or incomplete statements in this section can be correctly answered or completed by **one** of the suggested answers or phrases. Choose the **best** answer.

1. Which patient meets the diagnostic criteria for diabetes, assuming tests were taken on separate visits?

(A) An elderly female with fasting blood glucose values of 102 mg/dL and 132 mg/dL.
(B) A teenage boy with a fasting blood glucose of 128 mg/dL and an A1c of 6.6%.
(C) A 10-year-old girl with a random blood glucose value of 180 mg/dL and 190 mg/dL.
(D) A morbidly obese male with a random blood glucose value of 102 mg/dL and an oral glucose tolerance test result of 160 mg/dL.

2. A 45-year-old obese female has just been diagnosed with diabetes. Otherwise, she is healthy with no other medical conditions. Her blood pressure today is 110/75 mm Hg; spot urine microalbumin < 30; TC 180; HDL 32; LDL 122; TG 150. Based on ADA guidelines, which should be started today?

(A) Aspirin 81 mg daily
(B) Pravastatin 10 mg daily
(C) Lisinopril 10 mg daily
(D) Irbesartan 150 mg daily

3. A patient is currently on a regimen of Humalog Mix 70/30, 24 units in the morning and 12 units in the evening. Based on the following averages obtained from his blood glucose meter, which would be the most appropriate recommendation for his glycemic control today?

Pre-Breakfast: 220 mg/dL
Pre-Lunch: 110 mg/dL
Pre-Supper: 90 mg/dL
Bedtime: 108 mg/dL
3 AM: 62 mg/dL

(A) Increase evening dose of Humalog Mix to 15 units
(B) Decrease evening dose of Humalog Mix to 10 units
(C) Continue current regimen without changes
(D) Increase morning dose of Humalog Mix to 28 units
(E) Decrease morning dose of Humalog Mix to 20 units

4. A 222-lb male presents to the diabetes care team for routine diabetes management. His fingerstick blood glucose value is 452 mg/dL (445 mg/dL on repeat) and his urine is negative for ketones. Per clinic protocol, he may be treated in the office for hyperglycemia. Which is the most appropriate treatment to bring his blood glucose to a target of 120 mg/dL?

(A) Glargine 20 units
(B) Lispro 60 units
(C) Aspart 30 units
(D) Glulisine 11 units
(E) Detemir 24 units

5. A 400-lb male has just been diagnosed with type 2 diabetes. His A1c is greater than 15% and his kidney and liver function are normal. Which would be the most appropriate initial agent for monotherapy?

(A) Metformin 850 mg q.d.
(B) Pioglitazone 30 mg q.d.
(C) Glargine 36 units q.d.
(D) Liraglutide 0.6 mg q.d.
(E) Glimepiride 4 mg q.d.

6. An individual with T2DM currently takes metformin XR 500 mg 2 b.i.d., pioglitazone 45 mg, and glimepiride 4 mg b.i.d. He takes his morning medications at 8 A.M. with breakfast and his evening medications at 6 P.M. with supper. He does not eat lunch. He brings in his log book and meter today, which reveal multiple hypoglycemic events (45 to 62 mg/dL) around 1 P.M. to 2 P.M. His A1c today is 6.0%. Which would be the most appropriate recommendation for glycemic control at this time?

(A) Discontinue morning dose of metformin
(B) Discontinue evening dose of metformin
(C) Discontinue daily dose of pioglitazone
(D) Discontinue morning dose of glimepiride
(E) Discontinue evening dose of glimepiride

7. A 64-year-old female is taking metformin, pioglitazone, and sitagliptin for T2DM. Her liver function tests were elevated (AST 132 u/L and ALT 140 u/L) and she tested positive for Hepatitis C. Which is the best recommendation at this time?

(A) Discontinue metformin only
(B) Discontinue pioglitazone only
(C) Discontinue sitagliptin only
(D) Discontinue metformin and pioglitazone
(E) Discontinue all agents for glycemic control

8. Which best describes the mechanism of action of repaglinide?

(A) Insulin secretagogue
(B) Insulin sensitizer
(C) DPP-IV inhibitor
(D) GLP-1 agonist
(E) α-glucosidase inhibitor

9. A patient has been hospitalized for the past 3 days following a severe asthma exacerbation, but is being discharged today. He weighs 228 lb, but he has no previous history of diabetes. Blood work today shows a random blood glucose of 320 mg/dL and an A1c of 5.2%. His current medication list includes albuterol nebules, prednisone, pulmicort, and oxygen. Which statement is most appropriate?

(A) The patient has diabetes and should be discharged on an insulin regimen.
(B) The patient has hyperglycemia induced by his inhaled corticosteroid.
(C) The patient has hyperglycemia induced by his β agonist.
(D) The patient has hyperglycemia induced by his oral glucocorticoid.

10. A patient currently takes Amaryl, Actos, Januvia, and Lantus. He presents to the clinic today concerned about the swelling in his lower extremities, significant weight gain, and shortness of breath. Which is the most likely cause of presenting symptoms?

(A) Amaryl
(B) Actos
(C) Januvia
(D) Lantus

11. A person newly diagnosed with T1DM will need to start an insulin regimen. Based on her weight of 100 lb, which would be the most appropriate *basal* regimen?

(A) Levemir 13 units daily
(B) Lantus 27 units daily
(C) Novolog 4 units three times daily
(D) NPH 15 units once daily
(E) U-500 1.5 mL twice daily

12. Which formulation is the best recommendation for a patient needing an intravenous insulin infusion?

(A) Regular insulin, U-500
(B) Regular insulin, U-100
(C) NPH insulin, U-100
(D) Aspart insulin, U-100
(E) Aspart insulin, U-400

13. A patient presents for treatment of his type 2 diabetes mellitus (T2DM). His A_{1C} is 7.2% and he has hepatitis C (AST = 150 units/L; ALT = 132 units/L), hypertension, dyslipidemia, rheumatoid arthritis, and mild renal impairment (SCr = 1.6). Which would be the best initial agent at this time?

(A) saxagliptin
(B) metformin
(C) pioglitazone
(D) glulisine

14. An obese woman (350 lb) has used metformin 1000 mg bid to control her T2DM for the past 2 years. Her A_{1C} today is 8%. Which would be the most appropriate recommendation to improve glycemic control without providing further weight gain?

(A) sulfonylurea
(B) thiazolidinedione
(C) GLP-1 agonist
(D) amylin agonist

15. All of the following are correct statements about metformin *except*

(A) metformin may cause renal impairment.
(B) metformin should not be used in patients who are alcoholic.
(C) metformin should be discontinued in women with a SCr > 1.4.
(D) metformin may cause vitamin B_{12} depletion.

16. A patient takes neutral protamine Hagedorn (NPH) 16 units bid and regular insulin 6 units bid. Based on her average blood glucose values below, what is the best recommendation for adjusting her insulin regimen?

(A) fasting: 82 mg/dL
(B) pre-lunch: 180 mg/dL
(C) pre-supper: 110 mg/dL
(D) bedtime: 98 mg/dL

17. A patient has been using continuous intravenous insulin infusion at 0.8 units/hr with steady control after being diagnosed with type 1 diabetes mellitus (T1DM). He is to be discharged from the hospital with prescriptions for detemir and glulisine. When is the most appropriate time to initiate the detemir?

(A) 30 minutes prior to discontinuing the continuous insulin infusion
(B) 1 hour prior to discontinuing the continuous insulin infusion
(C) 2 hours prior to discontinuing the continuous insulin infusion
(D) 1.5 hours after discontinuing the continuous insulin infusion
(E) 3 hours after discontinuing the continuous insulin infusion

Answers and Explanations

1. **The answer is B** *[see III.B]*.
Regardless of age or gender, diagnostic criteria for diabetes in the nonpregnant individual is a positive of at least two of the following values: random blood glucose > 200 mg/dL; fasting blood glucose ≥ 126 mg/dL; OGTT ≥ 200; A1c ≥ 6.5%.

2. **The answer is B** *[see X.A.1]*.
Based on ADA guidelines, aspirin should be initiated for primary prevention in women greater than age 60; statin therapy should be initiated in patients with overt CVD or any patient over the age of 40 without overt CVD, but with other CVD risk factors; ACEI and ARBs are recommended for blood pressure control if necessary (not needed here) and when urine microalbumin is > 30.

3. **The answer is B** *[see Table 46-2; V.A.8.b]*.
Increasing the morning dose will only lower the lunch and supper readings further. Increasing the evening dose will lower the 3 A.M. even more. This patient is most likely experiencing rebound hyperglycemia (Symogyi) as evidenced by the hypoglycemia at the 3 A.M. readings and elevated fasting readings pre-breakfast.

4. **The answer is D** *[see V.A.7.a]*.
The blood glucose needs to come down rapidly in-office, thus he would not choose glargine or detemir as agents due to their longer onset of action. Lispro, aspart, and glulisine would all be appropriate choices, but the dose should be based on the point-of-care correction equation ([Current blood glucose-Target blood glucose]/CF). Steps to solve:
    1. Weight in kg: Weight is 222lb = 101 kg
    2. Determine TDD: (101)(0.6) = 60
    3. Determine CF: 1800/60 = 30
    4. Plug into equation: (452–120)/30 = 11 units

5. **The answer is C** *[see VI.A.1.c]*.
Metformin would typically be the initial agent of choice in a patient diagnosed with type 2 diabetes. However, with this patient's A1c greater than 15%, insulin is the most appropriate choice. Metformin can be started in addition to the insulin, but not as monotherapy. Oral agents and non-insulin injections will bring the A1c down no greater than 1%.

6. **The answer is D** *[see V.B.1.a; Table 46-3]*.
The pharmacologic agent most responsible for causing hypoglycemia is the sulfonylurea (glimepiride), which is compounded by the fact that the patient does not eat lunch. The morning dose of glimepiride would peak around lunch time when food intake should be occurring. In the absence of lunch, hypoglycemia results.

7. **The answer is D** *[see V.C.3.b; V.D.3.a; V.F]*.
Metformin and pioglitazone should not be used in a patient with liver disease and elevated LFTs. Sitagliptin may be used in hepatic impairment. When the LFTs go back to a normal range, it can be considered to reinitiate metformin and pioglitazone.

8. **The answer is A** *[see V.B.1.b]*.
Repaglinide is a meglitinide, which works to produce a rapid burst of insulin secretion from the pancreas.

9. **The answer is D** *[see III.B; XIII.A]*.
Inhaled corticosteroids have no effect on the blood glucose of an individual without diabetes and β agonists have no effect. However, oral steroids, such as prednisone can induce significant hyperglycemia, particularly in the midafternoon when dosed in the morning.

10. **The answer is B** *[see V.D.6.a; Table 46-3]*.
Patients taking a TZD such as Actos should be monitored for peripheral edema, weight gain, and shortness of breath due to its propensity to cause or worsen heart failure.

11. **The answer is A** *[see V.A.6.a]*.
NovoLog is not a basal insulin and U-500 is reserved for patients with severe insulin resistance. NPH is dosed twice daily. Basal insulin should be initiated at 50% of TDD. TDD is 27 units, which gives 13.5 units as basal.

12. **The answer is B** *[see V.A.9.b]*.
Regular insulin, U-100 is the most logical choice for an IV infusion. Aspart may be given in an emergency preparedness situation, but should not be given routinely due to the additional cost above that of regular U-100 insulin.

13. **The answer is A** *[see V.F.2; VI.A.1.a]*.
Metformin and pioglitazone should not be used in liver impairment and metformin must be used cautiously in renal impairment. Rapid acting insulin would help with postprandial blood glucose values, but is not considered a standard recommendation for initial insulin therapy in T2DM. Saxagliptin may be used in patients with hepatic and renal impairment.

14. **The answer is C** *[seeV.B.6.b; V.D.6.a; Table 46-3]*.
Both sulfonylureas and TZDs have the potential to increase weight, whereas GLP-1 agonists and amylin agonists can provide weight loss. Amylin agonist is not appropriate because it should only be added after a basal and bolus insulin have been added.

15. **The answer is A** *[see V.C.3.a]*.
Metformin should not be used in patients with renal disease, but the metformin itself does not cause renal impairment.

16. **The answer is B** *[see V.A.8; Table 46-2]*.
Increasing morning NPH will cause further decrease of pre-supper reading. Increasing evening doses of insulin will cause fasting blood glucose to be too low.

17. **The answer is C** *[see V.A.9.b.(2)]*.
Long-acting insulin should be injected 2 hours prior to discontinuation of a continuous insulin infusion to allow adequate onset time.

Study Questions

Directions for questions 1–16: Each of the questions, statements, or incomplete statements in this section can be correctly answered or completed by **one** of the suggested answers or phrases. Choose the **best** answer.

1. What is the correct formula to use for calculating the FTI?

(A) $T_4 \times RT_3U$/mean serum RT_3U
(B) $T_3 \times T_3$/mean serum RT_3U
(C) $T_3 \times RT_3U$/mean serum RT_3U
(D) $T_4 \times RT_3U \times$ mean serum RT_3U
(E) $T_3 \times RT_3U \times$ mean serum RT_3U

2. What is the necessary precursor besides dietary iodine required for thyroxine biosynthesis?

(A) T_3
(B) threonine
(C) tyrosine
(D) TSH
(E) TBG

3. All of the following conditions are causes of hyperthyroidism *except*

(A) Graves disease
(B) Hashimoto thyroiditis
(C) toxic multinodular goiter
(D) triiodothyronine toxicosis
(E) Plummer disease

4. Which of the following preparations is used to attain remission of thyrotoxicosis?

(A) propranolol
(B) liotrix
(C) levothyroxine
(D) PTU
(E) desiccated thyroid

5. The thyroid gland normally secretes which of the following substances into the serum?

(A) TRH
(B) TSH
(C) DIT
(D) thyroglobulin
(E) T_4

6. All of the following conditions are causes of hypothyroidism *except*

(A) endemic goiter
(B) surgical excision
(C) Hashimoto thyroiditis
(D) goitrin-induced iodine deficiency
(E) Graves disease

7. Common tests to monitor patients receiving replacement therapy for hypothyroidism include all of the following *except*

(A) TSH stimulation test
(B) serum TSH assay
(C) FTI
(D) RT_3U
(E) TT_4

8. The FTI allows the clinician to evaluate all of the following *except*?

(A) TT_4
(B) THBI
(C) Estimated Free T_4
(D) Exact Free T_4
(E) RT_3U

9. The inhibition of pituitary thyrotropin secretion is controlled by which of the following?

(A) free T_4
(B) TRH
(C) FTI
(D) reverse triiodothyronine (rT_3)
(E) TT_4

10. Which of the following agents has been shown to interact with oral T_4 replacement therapy?

(A) PTU
(B) Cholestyramine
(C) Thyrotropin
(D) Levothyroxine
(E) Lovastatin

11. What laboratory tests are currently recommended by the ATA to diagnose thyroid disease?

(A) RT_3U and TT_4
(B) TSH and FTI
(C) TT_4 and sensitive TSH assay
(D) free T_4 and sensitive TSH assay
(E) free T_4 and RT_3U

12. Which of the following patient populations should not routinely be screened for thyroid disease?

(A) Pregnant women
(B) Patients with type I diabetes
(C) Patients with a family history of thyroid disease
(D) College students
(E) Women $>$ 60 years old

13. What is the average replacement dose of levothyroxine for an otherwise healthy adult?

(A) 25 to 50 mcg/day
(B) 50 to 100 mcg/day
(C) 75 to 150 mcg/day
(D) 100 to 200 mcg/day
(E) 200 to 400 mcg/day

14. What factors affect the optimal replacement dose of levothyroxine?

(A) Age, height, and weight
(B) Duration of hypothyroidism
(C) Pretreatment TSH level
(D) Presence of chronic illness
(E) All of the above

15. Which of the values represents the lower level of detection for the fourth-generation sensitive TSH assay as established by the ATA?

(A) 0.5 to 5.0 mIU/L
(B) 1 to 2 mIU/L
(C) 0.01 to 0.02 mIU/L
(D) 0.001 to 0.002 mIU/L
(E) 0.0001 to 0.0002 mIU/L

16. In which of the following clinical presentations should the TSH assay be used?

(A) Population screening for thyroid disease
(B) Screening hospitalized patients
(C) Patients receiving thyroid replacement after 6 to 8 weeks of therapy
(D) Patients who are HIV positive
(E) Screening patients with psychiatric illness

Directions for question 17: The question in this section can be correctly answered or completed by **one or more** of the suggested answers. Choose the answer, **A–E**.

A If **I only** is correct
B If **III only** is correct
C If **I and II** are correct
D If **II and III** are correct
E If **I, II, and III** are correct

17. A 62-year-old woman with a 5-year history of well-managed hypothyroidism was recently started on raloxifene 60 mg daily in the morning for the prevention of postmenopausal osteoporosis. Her thyroid disease had been well-controlled on 150 mcg levothyroxine (Synthroid) daily in the morning. Her TSH has remained within the normal range while on treatment. Her most recent TSH of 2.5 mIU/L and normal FT_4 values where noted last year. She presents today with an elevated TSH 15.5 mIU/L after 4 months of raloxifene therapy and symptoms of hypothyroidism. What change in therapy would be best for this patient?

(I) Repeat the TSH test and FT_4 Tests
(II) Increase the dose of levothyroxine to 200 mcg daily
(III) Switch the dosing of the raloxifene to the evening

Directions for question 18: The question in this section can be correctly answered by **one** of the suggested answers. Choose the **best** answer.

18. A 69-year-old woman with hypertension and hypothyroidism is being treated for a wound infection. In the past, she was maintained on 125 mcg levothyroxine (Levoxyl) daily with a normal TSH of 2.0 mIU/L. After 6 weeks of treatment with oral ciprofloxacin (500 mg twice a day) she complains of fatigue and sensitivity to cold. Her serum TSH level was 14 mIU/L and FT_4 was below normal. What is the best management for this patient.

(A) Increase the dose of levothyroxine
(B) Switch the patient from Levoxyl to Synthroid
(C) Discontinue levothyroxine until the wound is healed
(D) Continue therapy without any changes
(E) Separate the administration of ciprofloxacin and levothyroxine by at least 6 hrs

Directions for question 19: The questions in this section can be correctly answered or completed by **one or more** of the suggested answers. Choose the answer, **A–E**.

(A) If **I only** is correct
(B) If **IV only** is correct
(C) If **I and IV** are correct
(D) If **I**, **II**, **III**, **and IV** are correct
(E) If **II**, **III**, **and V** are correct

19. Which of the following agents have been shown to interact with oral T_4 replacement therapy?

I Atenolol
II Calcium carbonate
III Ciprofloxacin
IV Levothyroxine
V Raloxifene

20. What is the effect of amiodarone therapy on thyroid function?

(A) Patients with underlying thyroid dysfunction are at an increase risk of developing hypothyroidism within 6 months of therapy.
(B) Patients without underlying thyroid dysfunction routinely develop subclinical hyperthyroidism with amiodarone therapy.
(C) Amiodarone interacts directly with circulating serum thyrotropin.
(D) Amiodarone has no effect on thyroid function.
(E) None of the above.

21. A 33-year-old underweight woman presents to you. She is currently taking levothyroxine (Synthroid) 200 mcg daily. Her TSH level is reported to be 0.15 mIU/L. What would be the most appropriate change to make to her therapy?

(A) Continue current therapy
(B) Repeat TSH, continue levothyroxine 200 mcg daily
(C) Decrease levothyroxine to 175 mcg daily and recheck TSH in 6 weeks
(D) Decrease levothyroxine to 150 mcg daily, recheck TSH in 6 weeks
(E) Repeat TSH, TT_4, continue levothyroxine 200 mcg daily

22. What is the correct formula to use for calculating THBI?

(A) RT_3U/mean serum RT_3U
(B) $RT_3U \times$ mean serum RT_3U
(C) $TT_4 \times RT_3U$/mean serum RT_3U
(D) $T_4 \times RT_3U \times$ mean serum RT_3U
(E) $T_3 \times RT_3U \times$ mean serum RT_3U

Directions for question 23: The question in this section can be correctly answered or completed by **one or more** of the above suggested answers. Choose the answer, **A–E**.

(A) If **I only** is correct
(B) If **III only** is correct
(C) If **I and II** are correct
(D) If **II and III** are correct
(E) If **I, II, and III** are correct

23. Which of the following drugs are possible treatment options for primary hypothyroidism?

I Desiccated Thyroid (Armour Thyroid)
II Levothyroxine (Levoxyl)
III PTU

Questions 24 and 25 are based on the following case:

AB is a 58-year-old female with a history of Graves disease who has been suffering from severe emotion distress from a recent divorce. She began to develop heart palpitations, a fever, and delirium. She is transported to the emergency department where she admits to stopping her methimazole 2 weeks prior.

24. Which of the following disease states is most likely related to AB's clinical presentation?

(A) Hashimoto thyroiditis
(B) Thyrotoxic crisis
(C) Jod-Basedow phenomenon
(D) Factitious hyperthyroidism
(E) Plummer disease

25. Which of the following is part of the normal therapy for thyroid storm?

(A) Quetiapine to treat delirium
(B) A β-blocker like lisinopril
(C) PTU to inhibit the synthesis of thyroid hormones
(D) Levothyroxine to help augment the negative feedback mechanism and decrease production of thyroid hormone
(E) Methimazole because it is a thioamide and also prevents peripheral deiodination of T_4 to T_3

26. The FDA black box warning for thyroid hormone replacement therapy is:

(A) May cause life-threatening toxicity if used for weight loss
(B) Risk of hepatotoxicity
(C) Risk of nephrotoxicity
(D) May cause tendon ruptures
(E) May cause lactic acidosis

Answers and Explanations

1. The answer is A *[see II.F.5.c]*.
The FTI is a mathematical interpretation of the relationship between the rRT_3U and T_4 levels, compared to the mean population value for RT_3U. The FTI is calculated using reported values for TT_4 and RT_3U. The normal FTI value in euthyroid patients is 5.5 to 12.0.

2. The answer is C *[see II.B]*.
Biosynthesis of thyroid hormones begins with iodide binding to tyrosine, which forms MIT. MIT binds another iodide atom to form DIT. When MIT and DIT are formed, a coupling reaction occurs, which produces T_3, T_4, rT_3, and other by-products.

3. The answer is B *[see III.B.1; IV.A–B]*.
Hashimoto thyroiditis (chronic lymphocytic thyroiditis) is a cause of hypothyroidism. The incidence of Hashimoto thyroiditis is 1% to 2%, and it increases with age. It is more common in women than in men and more common in whites than in blacks. There may be a familial tendency. Patients with Hashimoto thyroiditis have elevated titers of antibodies to thyroglobulin: A titer $<$ 1:32 is seen in $>$ 85% of patients. Two variants of Hashimoto thyroiditis have been described: gland fibrosis and idiopathic thyroid atrophy, which is most likely an extension of Hashimoto thyroiditis.

4. The answer is D *[see IV.F.1–2]*.
In hyperthyroid patients, remission of thyrotoxicosis is achieved with PTU by two mechanisms: (1) interference of iodination of the tyrosyl residues, ultimately reducing production of T_4 and (2) inhibition of peripheral conversion of T_4 to T_3. Propranolol is commonly used as an adjunct to PTU for symptomatic management of hyperthyroidism.

5. The answer is E *[see II.A.1]*.
The major compounds secreted by the thyroid gland, after its stimulation by thyrotropin, are T_3 and T_4. When released from the thyroid, T_3 and T_4 are transported by plasma proteins—namely TBG and albumin.

6. The answer is E *[see III.B; IV.A.1]*.
Graves disease (diffuse toxic goiter) is the most common form of hyperthyroidism. It occurs most often in women in the third and fourth decades of life. There is a genetic and familial predisposition. The cause is linked to an autoimmune reaction between immunoglobulin G (IgG) and the thyroid.

7. The answer is A *[see III.G.3]*.
The TSH stimulation test measures thyroid tissue response to exogenous TSH. It is not commonly used to monitor thyroid replacement therapy. It may be useful in the initial diagnosis of hypothyroidism.

8. **The answer is D** *[see II.F.5.d]*.
The FTI is not an exact measure of free T_4 rather it is a mathematical interpretation between RT_3U and serum T_4 levels that estimates free T_4. The correct formula use would mean that a clinician has knowledge of TT_4, THBI, and estimated free T_4, RT_3U.

9. **The answer is A** *[see II.A.2.a]*.
An increase in the blood level of thyroid hormone (see circulating free T_4 and free T_3) signals the pituitary to stop releasing TSH. The free fraction of T_4 is available to bind at the pituitary receptors.

10. **The answer is B** *[see III.G.7.a]*.
Euthyroid patients receiving oral replacement therapy have become hypothyroid after concomitant administration of bile acid sequestrant therapy. It appears that bioavailability is reduced as a result of administering these agents at close dosing intervals. It is recommended that at least 6 hrs pass before administration of a bile acid sequestrant. It would be preferable to select another nonbile acid sequestrant when clinically possible.

11. **The answer is D** *[see II.G.1]*.
The free T_4 and the (third-generation) TSH assay should be used only for the diagnosis of patients most likely to have thyroid disease based on clinical presentation and relative risk (e.g., age, sex, family history), not for population screening. The third-generation TSH assay is also more commonly used to monitor replacement therapy, and to minimize overtreatment and the corresponding risk of accelerated bone loss.

12. **The answer is D** *[see II.G.3]*.
Cost versus benefit is critical to the decision of choosing to screen entire populations, and screening for thyroid disease has been shown to not be cost effective in the general healthy population. Screening recommendations from major medical groups has been conflicting; however, none of them recommend the routine screening of young, healthy adults.

13. **The answer is C** *[see III.F.3.c]*.
The average adult maintenance dose is 75 to 150 mcg/day, which has been shown to be 1.5 to 1.7 mcg/kg/day. The dose is usually adjusted in increments of 25 to 50 mcg/day every 4 weeks. The total daily dose used to be 100 to 200 mcg/day, which resulted in overtreatment after the introduction of the sensitive TSH assay. Elderly or chronically ill patients require an average dose of 50 to 100 mcg/day, which is 25 to 50 mcg/day less than otherwise healthy adults of the same height and weight.

14. **The answer is E** *[see III.F.3]*.
Elderly or chronically ill patients require an average dose of 50 to 100 mcg/day, which is 25 to 50 mcg/day less than otherwise healthy adults of the same height and weight. Because the average dose for replacement therapy is between 1.5 and 1.7 mcg/kg/day, weight affects the total daily dose.

15. **The answer is D** *[see II.F.1.b–f; Table 47-3]*.
The ATA has established standard nomenclature that indicates each technological improvement and the ability to detect lower levels of TSH using monoclonal antibodies. As the sensitivity of the assay improves, the lower level of detection is reported as a range in milli-International Units per liter. The most sensitive test is currently the fourth-generation IMA, with a reported lower level of detection of 0.001 to 0.002 mIU/L. In usual clinical practice the third-generation IMA is most commonly used, with sensitivity in the range of 0.01 to 0.02 mIU/L.

16. **The answer is C** *[see III.F.3.g; III.6; Figure 47-6]*.
The current third-generation TSH assay is not indicated for use in hospitalized patients who are not suspected to have thyroid disease. Studies have indicated that abnormally high or low TSH levels are detected in euthyroid hospitalized patients. Psychiatric illness may also influence TSH levels.

17. **The answer is B (IV)** *[see III.G.7; Tables 47-2 and 47-4]*.
The patient is most likely experiencing a drug interaction between raloxifene and levothyroxine. The best choice is to separate the medications by at least 12 hrs. A repeat of the TSH assay will only confirm the results, which are significantly elevated. Increasing the dose of levothyroxine may result in overtreatment.

18. **The answer is E** *[see III.G.7; Tables 47-2 and 47-4]*.
This patient is most likely experiencing a drug interaction between levothyroxine and ciprofloxacin when taken concomitantly. There is no benefit to switching to another brand of levothyroxine or increasing the dose. The best solution is to separate the doses of ciprofloxacin by 6 hrs.

19. **The answer is E (I, III, V)** *[see III.G.7; Tables 47-2 and 47-4]*.
Patients receiving oral replacement therapy who take calcium carbonate concomitantly have been shown to experience decreased free T_4 and total T_4 levels that resulted in an elevated TSH. The mechanism appears to be adsorption of levothyroxine to calcium carbonate at acid pH levels, which may reduce bioavailability. It is recommended to separate the time of ingestion of each product to reduce the chance of this interaction. Ciprofloxacin and raloxifene have also been shown to interact with levothyroxine when administered together. Separate administration times by 6 hrs for ciprofloxacin and by 12 hrs for raloxifene.

20. The answer is A *[see Tables 47-2 and 47-4]***.**
Patients receiving amiodarone therapy are at risk of developing hypothyroidism especially if there is underlying thyroid disease. Amiodarone delivers high levels of iodine to the system contributing to subclinical or clinical hypothyroidism more often. Subclinical hyperthyroidism has been observed rarely. Some patients without underlying thyroid disease may experience changes in thyroid function, while patients with underlying disease are more likely to present with hypothyroidism. Patients should be monitored closely for thyroid function when beginning amiodarone therapy.

21. The answer is C *[see II.G; III.F.3.c]***.**
The goal of levothyroxine therapy is to normalize TSH. Over replacement can result in symptoms of hyperthyroidism and lead to bone mineral density loss, osteoporosis, and palpitations. A suppressed TSH can identify excessive replacement. Serum T4 concentrations can be useful when nonadherence is suspected, but these concentrations are not routinely needed to monitor levothyroxine therapy. Dose adjustments to levothyroxine therapy should only be made in 12.5–25.0 mcg increments and the average adult dose is typically 75–150 mcg/day.

22. The answer is A *[see II.F.5.b]***.**
The thyroid hormone binding index (THBI) is a mathematical interpretation of the normalized T_3-resin uptake value (RT_3U). The THBI is calculated using the reported values from RT_3U: the patient's T_3 resin and the normal pool T_3 resin. The mean THBI is therefore by definition 1.00, with a normal range of approximately 0.83 to 1.16.

23. The answer is C *[see II.F; IV.F]***.**
Levothyroxine and desiccated thyroid are both oral thyroid hormone preparations that are indicated for primary hypothyroidism. PTU inhibits the synthesis of thyroid hormones by blocking the oxidation of iodine in the thyroid gland and is indicated in hyperthyroid disorders.

24. The answer is B *[see IV.G.2; IV.B]***.**
The most likely disease state is thyrotoxic crisis (thyroid storm). AB has many risk factors for developing a thyrotoxic crisis: Underlying Graves disease, severe emotional stress, and a sudden discontinuation of her antithyroid medication. Hashimoto thyroiditis is an autoimmune hypothyroid disorder and is unlikely as the patient already has a history of Graves hyperthyroidism. Jod-Basedow phenomenon is hyperthyroidism following ingestion of iodine or iodide, there is not anything in the patient's history to suggest iodine ingestion. Factitious hyperthyroidism is the result of an overdose of thyroid hormone, while the clinical symptoms may suggest this; her medical history rules it out. Plummer disease would be evident on physical exam.

25. The answer is C *[see IV.F.1; IV.G.2]***.**
PTU is a thioamide which inhibits the synthesis thyroid hormones which would be essential for the treatment of a hyperthyroid state like thyroid storm. β-Blockers are effective at controlling the symptoms induced by increased adrenergic tone, however, lisinopril is not a β-blocker. The addition of a synthetic thyroid hormone like levothyroxine has no place in thyroid storm; it will not induce negative feedback; on the contrary, it would contribute to the hyperthyroid state. Methimazole is a thioamide, however, only PTU prevents peripheral deiodination of T_4 to T_3. Delirium will resolve with the treatment of the underlying disease, quetiapine may actually increase TSH, and is not warranted in thyroid storm.

26. The answer is A *[see III.G.8]***.**
FDA black box warning: Do not use thyroid hormones, including levothyroxine, either alone or with other therapeutic agents, for the treatment of obesity or for weight loss. They are ineffective for weight reduction in euthyroid patients and may produce serious or even life-threatening manifestations of toxicity, particularly when given in association with sympathomimetic amines such as those used for their anorectic effects.

Study Questions

1. Severe hypotension may result in what type of acute renal failure?

(A) Prerenal
(B) Intrarenal
(C) Postrenal
(D) Intrinsic
(E) Parenchymal

2. Why might sodium polystyrene sulfonate (SPS) be utilized in ARF?

(A) It reduces calcium levels in the serum.
(B) It increases calcium levels in the serum.
(C) It increases potassium levels.
(D) It reduces potassium levels in the serum.
(E) It elevates glucose levels.

Study Questions

Directions for questions 1–14: Each of the questions, statements, or incomplete statements in this section can be correctly answered or completed by **one** of the suggested answers or phrases. Choose the **best** answer.

1. Body surface area (BSA) is used in calculating chemotherapy doses because

(A) BSA is an indicator of tumor cell mass.
(B) BSA correlates with cardiac output.
(C) BSA correlates with gastrointestinal transit time.
(D) the National Cancer Institute requires that BSA be used.
(E) the U.S. Food and Drug Administration (FDA) requires that BSA be used.

2. The rationale for combination chemotherapy includes all of the following *except*

(A) biochemical enhancement of effect.
(B) rescue of normal cells.
(C) overcoming or preventing resistance.
(D) biochemical nullification of effect.
(E) cytotoxic to both resting and dividing cells.

3. All of the following chemotherapy agents can be administered intrathecally *except*

(A) methotrexate.
(B) cytarabine.
(C) hydrocortisone.
(D) thiotepa.
(E) vincristine.

4. Hypersensitivity reactions have been commonly associated with all of the following agents *except*

(A) asparaginase.
(B) busulfan.
(C) carboplatin.
(D) etoposide.
(E) paclitaxel.

5. Which of these supportive agents may have a greater risk than benefit in patients with cancer when the goal is cure due to the potential increased risk of tumor progression?

(A) Antiemetics
(B) Colony-stimulating factors
(C) Corticosteroids
(D) Erythropoietin-stimulating agents
(E) Oprelvekin (IL-11)

6. How do antimetabolites exert their cytotoxic effect?

(A) Inhibiting DNA synthesis by sliding between DNA base pairs
(B) Inhibiting RNA synthesis by sliding between RNA base pairs
(C) Acting as false metabolites in the microtubules
(D) Acting as false substitutions in the production of nucleic acids
(E) Promoting microtubule assembly and stabilization

7. All of the following chemotherapy agents work through affecting microtubule function *except*

(A) docetaxel.
(B) vinblastine.
(C) mitoxantrone.
(D) vincristine.
(E) vinorelbine.

8. When does the neutrophil nadir associated with chemotherapy agents generally occur?

(A) During administration of the chemotherapy
(B) 1 to 2 days after therapy
(C) 10 to 14 days after therapy
(D) 1 month after therapy
(E) When the platelet count begins to rise

9. Which of the following statements describes hemorrhagic cystitis?

(A) It is caused by excretion of tumor cell breakdown products.
(B) It is associated with ifosfamide or cyclophosphamide administration.
(C) It is caused by the administration of mesna.
(D) It can be prevented or treated with acrolein.
(E) It can be treated with granulocyte colony-stimulating factor (G-CSF).

10. All of the following chemotherapy agents are vesicants *except*

(A) doxorubicin.
(B) mechlorethamine.
(C) vincristine.
(D) methotrexate.
(E) idarubicin.

Directions for questions 11–15: Each agent in this section is most closely associated with **one** of the following adverse effects. Each effect is used only **once**. Choose the **best** answer, **A–E**.

(A) Cardiotoxicity
(B) Conjunctivitis
(C) Diarrhea
(D) Pulmonary fibrosis
(E) Constipation

11. Vincristine

12. Irinotecan

13. Doxorubicin

14. Cytarabine

15. Bleomycin

Answers and Explanations

1. **The answer is B** *[see III.B]*.
BSA correlates with cardiac output, which determines renal and hepatic blood flow and thus affects drug elimination.

2. **The answer is D** *[see III.D.2]*.
Combination chemotherapy has been developed to have maximal cytotoxicity to tumor cells and minimal toxicity to normal cells. The drugs are dosed and scheduled such that maximal cell kill occurs, while sparing normal cells as much as possible. Combination regimens often contain agents with different spectrums of toxicity.

3. **The answer is E** *[see III.E.3]*.
Intrathecally administered vincristine is fatal. All syringes of vincristine must be labeled "Fatal if given intrathecally. For intravenous use only."

4. **The answer is B** *[see V.I]*.
Hypersensitivity reactions have been commonly associated with asparaginase, carboplatin, etoposide, and paclitaxel. Busulfan is not commonly associated with hypersensitivity reaction.

5. **The answer is D** *[see V.A.1.c]*.
Erythropoietin-stimulating agents (ESAs) have been found to increase the likelihood of tumor progression in certain patient populations and therefore should not be used in patients with cancer when the goal is cure.

6. **The answer is D** *[see IV.D]*.
Antimetabolites are structural analogs of naturally occurring substrates for biochemical reactions. They inhibit DNA synthesis by acting as false substitutions in the production of DNA.

7. **The answer is C** *[see IV.E]*.
Docetaxel is a taxane, which works by promoting microtubule assembly and stabilization, resulting in inhibition of cell division. Vincristine, vinblastine, and vinorelbine are vinca alkaloids, which work by preventing microtubule formation. Mitoxantrone is an antitumor antibiotic, which works by DNA intercalation.

8. **The answer is C** *[see V.A.2]*.
Bone marrow suppression, particularly of the neutrophils, usually is the most profound 10–14 days after chemotherapy.

9. **The answer is B** *[see V.K]*.
Hemorrhagic cystitis results from irritation of the lining of the bladder by acrolein, a metabolite of ifosfamide and cyclophosphamide. Mesna may be used to inactivate the acrolein, thus preventing hemorrhagic cystitis.

10. **The answer is D** *[see V.B.2]*.
Vesicant chemotherapy agents may cause local necrosis if extravasated outside the vein. Doxorubicin, idarubicin, mechlorethamine, and vincristine are all classified as vesicants.

11. **The answer is E** *[see V.C.3; V.E.–G]*.
Severe constipation and paralytic ileus is associated with the use of vincristine.

12. **The answer is C** *[see V.C.3; V.E.–G]*.
Severe diarrhea, requiring treatment with atropine and/or loperamide, is associated with irinotecan.

13. **The answer is A** *[see V.C.3; V.E.–G]*.
Cardiotoxicity is associated with cumulative doses of doxorubicin and other antitumor antibiotics.

14. **The answer is B** *[see V.C.3; V.E.–G]*.
Conjunctivitis occurs with high-dose cytarabine; patients receiving high-dose cytarabine should receive prophylaxis with steroid eye drops.

15. **The answer is D** *[see V.C.3; V.E.–G]*.
Pulmonary toxicity, including fibrosis, is associated with cumulative doses of bleomycin.

Study Questions

Directions for questions 1–7: Each of the questions, statements, or incomplete statements in this section can be correctly answered or completed by **one** of the suggested answers or phrases. Choose the **best** answer.

1. An emaciated 69-year-old man with advanced inoperable throat cancer is hospitalized for pain management. He is receiving a morphine solution (40 mg orally) every 3 hrs for pain. He complains of dysphagia and the frequency with which he must take morphine. An appropriate analgesic alternative for this patient would be

(A) changing to a controlled-release oral morphine.
(B) increasing the dose of the oral morphine solution.
(C) changing to intramuscular methadone.
(D) changing to transdermal fentanyl.
(E) decreasing the frequency of oral morphine administration.

For questions 2–3: A 52-year-old woman with a diagnosis of ovarian cancer presents with complaints of pain. Her pain was reasonably well-controlled with two capsules of oxycodone every 4 hrs until 2 weeks ago, at which point she was hospitalized for pain control. She was placed on meperidine (75 mg) every 3 hrs but still complained about pain. Her meperidine dosage was increased to 100 mg every 2 hrs.

2. At this dosage of meperidine, the patient is likely to experience

(A) excellent pain relief.
(B) respiratory depression.
(C) worsening renal function.
(D) myoclonic seizures.
(E) excessive sedation.

3. An appropriate next step in this patient's therapy would be to

(A) add an NSAID.
(B) discontinue the meperidine and convert her to a controlled-release oral morphine or oxycodone.
(C) continue the present meperidine dosage because she will eventually get relief.
(D) decrease the meperidine dose to avoid side effects.
(E) consider hypnosis or relaxation techniques.

4. A 20-year-old victim of a motor vehicle accident is 3 days postsurgery for orthopedic and internal injuries. He has been in severe pain, and was placed on a regimen of intramuscular morphine (5 to 10 mg) every 4 hrs as needed for pain. A pain consultant starts the patient with a 20-mg intravenous morphine loading dose, and then begins a continuous intravenous morphine infusion with as-needed morphine boosters. About 2 hrs after this regimen is started, the patient is asleep. The nurse is concerned and calls the physician. The physician should

(A) call for a psychiatric consult.
(B) administer naloxone.
(C) examine the patient, and reconfirm the dosage and monitoring parameters.
(D) add an injectable NSAID.
(E) add an amphetamine.

5. Potential adverse effects associated with aspirin include all of the following *except*

(A) gastrointestinal ulceration.
(B) renal dysfunction.
(C) enhanced methotrexate toxicity.
(D) cardiac arrhythmias.
(E) hypersensitivity asthma.

6. All of the following facts are true about NSAIDs *except* which one?
   (A) They are antipyretic.
   (B) There is a ceiling effect to their analgesia.
   (C) They can cause tolerance.
   (D) They do not cause dependence.
   (E) They are anti-inflammatory.

7. Which of the following narcotics has the longest duration of effect?
   (A) Methadone
   (B) Controlled-release morphine
   (C) Levorphanol
   (D) Transdermal fentanyl
   (E) Dihydromorphone

Directions for questions 8–13: The questions and incomplete statements in this section can be correctly answered or completed by **one or more** of the suggested answers. Choose the answer, **A–E**.
(A) if **I only** is correct
(B) if **III only** is correct
(C) if **I and II** are correct
(D) if **II and III** are correct
(E) if **I, II, and III** are correct

8. Agents that are safe to use in a patient with bleeding problems include
   (I) choline magnesium trisalicylate.
   (II) acetaminophen.
   (III) ketorolac.

9. Which of the following drugs bind or capture excess TNF-α?
   (I) Adalimumab
   (II) Etanercept
   (III) Leflunomide

10. Leflunomide has been associated with
    (I) diarrhea.
    (II) alopecia.
    (III) anemia.

11. Which of the following agents needs to be administered with: Dihydroergotamine (DHE 45):
    (A) Ibuprofen.
    (B) IV metoclopramide.
    (C) Sumatriptan.
    (D) Acetaminophen.
    (E) Rizatriptan.

12. Which of the following should be done when eletriptan is administered with ketoconazole:
    (A) Eletriptan should not be administered within 72 hrs of treatment with ketoconazole.
    (B) Eletriptan should be used at the same time of ketoconazole administration time.
    (C) Eletriptan should be administered within 2 hrs of ketoconazole administration time.
    (D) None of the above.

Answers and Explanations

1. **The answer is D** *[see II.B.2.c.(8)]*.
   Patients with throat cancer often cannot take oral analgesics. The patient described in the question is also having pain difficulties with an every 3-hr regimen. Transdermal fentanyl is a good alternative because, after titration, excellent analgesia can be produced without using oral or parenteral agents. Also, the frequency of analgesic use may be decreased when titration has occurred.

2. **The answer is D** *[see II.B.3.g]*.

3. **The answer is B** *[see II.B.2.c.(1); II.B.2.d.(1)]*.
   Myoclonic seizures can occur after frequent, high-dose meperidine owing to the accumulation of the metabolite, normeperidine. Both oxycodone and meperidine have short durations of effect. In the chronic pain patient, an around-the-clock regimen, using a controlled-released oral morphine, would be an appropriate alternative. With titration, the patient should have good pain relief with an every 8- to 12-hr regimen.

4. **The answer is C** *[see II.B.3.c]*.
   A patient suffering from pain cannot sleep properly. When the pain is adequately controlled, the patient may sleep initially for many hours. This usually is not oversedation owing to the narcotic. These patients should be monitored closely (e.g., respiratory rate), and other sedating drugs should be eliminated. Usually, no other intervention is needed.

5. **The answer is D** *[see II.A.4]*.
   Aspirin has several adverse effects and drug interactions. However, cardiac arrhythmias are not induced by aspirin.

6. **The answer is C** *[see II.A.2]*.
   Unlike the opiates, NSAID use is not associated with the development of tolerance.

7. **The answer is D** *[see Table 51-2]*.
   Transdermal fentanyl is a controlled-release dosage form that is effective for up to a 72-hr period. All of the other drugs listed in the question are effective for periods of 1 to 8 hrs.

8. **The answer is C (I, II)** *[see II.A.4.b].*
Unlike aspirin and NSAIDs, acetaminophen and choline magnesium trisalicylate lack antiplatelet effects. Therefore, they are safe to use for patients with bleeding problems.

9. **The answer is C (I, II)** *[see II.A.1].*
Adalimumab, etanercept, and infliximab act by binding or capturing excess TNF-α, one of the dominant cytokines or proteins that play an important role in the inflammatory response. The exact mechanism of action of leflunomide, a novel drug used to treat rheumatoid arthritis, is not completely known, but it is thought to inhibit pyrimidine synthesis.

10. **The answer is E (I, II, III)** *[see II.A.4.a; II.A.4.f.(4)].*
Leflunomide has been associated with weight loss, diarrhea, nausea, alopecia, rash, anemia, and transient elevations in liver function tests.

11. **The answer is B** *[see II.D.5]***.**
Dihydroergotamine can cause nausea and vomiting. It needs to be administered with IV antiemetic. DHE 45 should not be used as monotherapy.

12. **The answer is A** *[see II.D.1.e]***.**
Because eletriptan is metabolized by cytochrome P450 enzyme CYP3A4, it should not be used within 72 hrs of treatment with potent CYP3A4 inhibitors such as ketoconazole, itraconazole, nefazodone, troleandomycin, clarithromycin, nelfinavir, and ritonavir.

52 Nutrition and the Hospitalized Patient

ROBERT A. QUERCIA, KEVIN P. KEATING

I. NUTRITIONAL PROBLEMS IN HOSPITALIZED PATIENTS

A. Incidence. It has been estimated that 30% to 50% of patients admitted to hospitals have some degree of malnutrition. As many as 75% of patients undergo a deterioration of nutritional status while hospitalized.

B. Definitions

1. **Malnutrition** is a pathological state, resulting from a relative or absolute deficiency or excess of one or more essential nutrients.
2. **Marasmus** is a chronic disease that develops over months or years as a result of a deficiency in total caloric intake. Depletion of fat stores and skeletal protein occurs to meet metabolic needs. Marasmic patients are generally not hypermetabolic and are able to preserve their visceral protein compartment as determined by measurements of serum albumin, prealbumin, and transferrin.
   - **a.** Marasmus is a well-adapted form of malnutrition, and despite a cachectic appearance, immunocompetence, wound healing, and the ability to handle short-term stress are generally well preserved.
   - **b.** Nutritional support in these patients should be initiated cautiously because aggressive repletion can result in severe metabolic disturbances, such as hypokalemia and hypophosphatemia.
3. **Kwashiorkor** is an acute process that can develop within weeks and is associated with visceral protein depletion and impaired immune function. It is the result of poor protein intake with adequate to slightly inadequate caloric intake; thus, patients usually appear well nourished. A hypermetabolic state (e.g., trauma, infection) combined with protein deprivation can rapidly develop into a severe kwashiorkor malnutrition characterized by hypoalbuminemia, edema, and impaired cellular immune function.
   - **a.** In hospitalized patients, the development of kwashiorkor has been implicated in poor wound healing, gastrointestinal (GI) bleeding, and sepsis.
   - **b.** Aggressive nutritional support to replete protein stores and decrease morbidity and mortality is indicated when the diagnosis of kwashiorkor is made.
4. **Mixed marasmic kwashiorkor** is a severe form of protein–calorie malnutrition that usually develops when a marasmic patient is subjected to an acute hypermetabolic stress, such as trauma, surgery, or infection.
   - **a.** This condition results in depletion of fat stores, skeletal muscle protein, and visceral protein.
   - **b.** Because of the marked immune dysfunction that develops in this state, vigorous nutritional support is indicated.

II. NUTRITIONAL ASSESSMENT AND METABOLIC REQUIREMENTS

A. Nutritional assessment. The most commonly used tools for nutritional assessment are as follows:

1. **Subjective global assessment (SGA)** relies heavily on the patient's history.
   - **a.** SGA takes into account:
     - **(1)** Recent weight change
     - **(2)** Diet history

Study Questions

Directions: Each of the questions, statements, or incomplete statements in this section can be correctly answered or completed by **one** of the suggested answers or phrases. Choose the **best** answer.

1. A 32-year-old, well-nourished man involved in a motor vehicle accident was admitted to the surgical intensive care unit with multiple long bone fractures and abdominal injuries with no nutritional support for 4 days. This patient is most likely

(A) suffering from moderate-to-severe kwashiorkor malnutrition.
(B) at low risk for hospital-acquired infection and other complications.
(C) not suffering from protein or calorie malnutrition.
(D) suffering from severe marasmus malnutrition.
(E) not a candidate for aggressive nutritional support.

2. A patient in the ICU on a ventilator was placed on a glucose system PN formulation providing 2040 kcal/day and 98 g protein/day. A measured energy expenditure (MEE) of 2038 kcal and RQ of 1.1 were subsequently obtained. Which of the following is correct based on this information?

(A) The patient is receiving adequate glucose calories, and an adjustment in the program is not necessary.
(B) The daily protein intake has to be decreased to reduce the patient's RQ.
(C) The PN formulation should be switched to a lipid system formulation to reduce the carbon dioxide load.
(D) The patient is retaining oxygen from the glucose calories in the PN formulation.
(E) Lipid emulsion should be added to the current PN formulation to enhance lipogenesis.

3. Total nutrient admixture (TNA)

(A) is more complicated to administer for home parenteral nutrition patients.
(B) should be filtered with a 1.2-μ filter.
(C) consists of glucose, amino acids, electrolytes, and trace minerals mixed in one container.
(D) is the method recommended by the FDA to administer lipid system PN.
(E) can be visualized for particulate matter.

4. The calorie requirements of a moderately hypermetabolic hospitalized patient are best estimated by using the

(A) nomogram method.
(B) nitrogen balance method.
(C) (EEE) method.
(D) PNI.
(E) SGA method.

5. Lipid system PN

(A) can be administered by peripheral vein if the glucose concentration is less than 15%.
(B) requires daily serum triglyceride monitoring.
(C) is contraindicated in patients with elevated carbon dioxide levels.
(D) requires daily lipid administration to provide a portion of the patient's nonprotein calorie requirements.
(E) can be administered with a maximum lipid dosage of 4.5 g/kg/day.

6. Commercial PN formulations for hypermetabolic critically ill patients

(A) are enriched in branched-chain amino acids and contain low concentrations of aromatic amino acids.
(B) contain primarily essential amino acids.
(C) have not demonstrated a positive clinical outcome benefit in this patient population.
(D) are the preferred PN formulation used in this clinical setting.
(E) are enriched with arginine to enhance immune function.

7. Which of the following methods of parenteral nutritional support would be most appropriate in a severely protein calorie malnourished patient with acute renal failure?

(A) 2% amino acid/47% dextrose.
(B) 4.25% amino acid/25% dextrose.
(C) 4% essential amino acid/47% dextrose.
(D) 4.25% amino acid/25% dextrose with dialysis on a regular basis.
(E) 2% amino acid/47% dextrose/20% lipid emulsion.

8. Which of the following statements regarding the monitoring of nutritional support is true?
   (A) Prealbumin is not the optimal marker to follow for short-term nutritional progress.
   (B) Transferrin is falsely depressed in patients with iron deficiency.
   (C) Albumin is falsely elevated in renal failure.
   (D) A positive nitrogen balance of 3 to 6 g of nitrogen daily is optimal.
   (E) A weight gain of 1.5 to 2.0 lb/day indicates optimal lean body weight gain.

9. Patients with end-stage liver disease
   (A) generally have increased levels of branched-chain amino acids and decreased levels of aromatic amino acids.
   (B) should be placed on a low-branched chain, high-aromatic amino acid PN solution.
   (C) should not have their protein restricted in the ICU as a clinical management strategy to reduce the risk of developing hepatic encephalopathy.
   (D) require glutamine-enriched amino acid solutions.
   (E) can tolerate standard glucose system formulations 4.25% amino acid/25% dextrose with regular dialysis.

For questions 10–12: A 67-year-old white female presented to the attending physician with a 3-month history of progressive difficulty swallowing and a 10-kg weight loss. She is currently 160 cm tall and weighs 50 kg. She has just undergone a distal esophagectomy and proximal gastrectomy for distal esophageal cancer. At the time of surgery, she had a feeding jejunostomy tube inserted.

10. The dieticians who are adept at using the Harris-Benedict equation have gone home for the day, and the surgeon calls you for your best guess at what the hourly goal rate for this patient should be using isotonic enteral formula, which provides 0.85 nonprotein calories (NPCs)/mL. Your answer should be
    (A) 65 mL/hr.
    (B) 75 mL/hr.
    (C) 85 mL/hr.
    (D) 95 mL/hr.
    (E) 50 mL/hr.

11. The enteral formulation the surgeon has selected is enriched with fish oils. He is hoping this additive will
    (A) prevent diarrhea.
    (B) prevent dermatitis.
    (C) prevent hyperglycemia.
    (D) improve immune function.
    (E) improve neurological function.

12. On the 5th postoperative day, the feeding jejunostomy tube becomes clogged and unusable. The patient will be NPO an additional 5 days to ensure the integrity of her surgical anastomosis. The most appropriate course at this time is
    (A) start the patient on a lipid-based peripheral PN program.
    (B) keep the patient NPO and without PN support.
    (C) have a central venous catheter inserted, and initiate a lipid-based PN program.
    (D) start the patient on a glucose-based peripheral PN program.
    (E) have a central venous catheter inserted, and start the patient on a high branched-chain amino acid parenteral program.

For questions 13–14: RJ is a 28-year-old pregnant woman. She is in the 9th week of her pregnancy and is diagnosed with hyperemesis gravidarum. Her pregravid weight was 57 kg, and her height is 5 ft., 5 in. She has lost 7 kg (12.3%) during her pregnancy. She was placed on a central glucose PN program.

13. Which one of the following represents the best estimate of her daily caloric requirements?
    (A) 1675 kcal
    (B) 1790 kcal
    (C) 2261 kcal
    (D) 2062 kcal
    (E) 1925 kcal

14. MVI-12 is used as the parenteral vitamin preparation in the PN formulation. Which of the following vitamin(s) need to be supplemented in the daily PN formulation to meet the daily requirements during pregnancy?
    (A) Vitamin K
    (B) Thiamine (B_1)
    (C) Folic acid
    (D) A and C
    (E) Pyridoxine (B_6)

For questions 15–17: A 55-year-old male with multiple traumatic injuries and type II diabetes was admitted to the surgical ICU. He was placed on mechanical ventilation and initiated on glucose system PN. After 3 days of PN therapy his blood glucose levels have ranged from 250 to 285 mg/dL over the past 24 hrs with 80 U of insulin/L in his PN formulation. He is on no other insulin supplementation at this time.

15. The nutritional support service recommends an insulin drip with the goal of achieving a blood glucose level of
    (A) 180 to 225 mg/dL.
    (B) 200 to 215 mg/dL.
    (C) 140 to 200 mg/dL.
    (D) 65 to 100 mg/dL.
    (E) 70 to 105 mg/dL.

16. What parenteral trace mineral therapy may be an effective adjunct if the insulin drip fails to achieve the glucose level goal?

(A) 20 to 40 mg zinc/day
(B) 150 to 200 μg chromium/day
(C) 0.5 to 1.5 mg copper/day
(D) 150 to 400 mcg manganese/day
(E) 40 to 60 μg selenium/day

17. The recommended ACP guideline for management of glucose levels in this patient population has shown that:

(A) The range of optimal glucose level is definitive.
(B) Hyperglycemia results in decreased duration of PN therapy.
(C) Most patients receiving intensive insulin therapy have no reduction in mortality but have a significantly increased risk for severe hypoglycemia.
(D) Length of time on the ventilator is decreased.
(E) A & C.

For questions 18–19: A 35-year-old female with severe morbid obesity (BMI = 51 kg/m^2) of more than 12 years duration and refractory to conventional obesity treatment was entered into a bariatric surgery program. The patient underwent a Roux-en-Y procedure without any major postoperative complications.

18. The patient was readmitted to the hospital 3 months after discharge with intolerance to solid and liquid foods and persistent hyperemesis. She also presented with generalized paresthesia, ataxis, and mental confusion. Which of the following nutrients is most likely deficient in this patient?

(A) Selenium
(B) Vitamin D
(C) Calcium
(D) Thiamine
(E) Vitamin E

19. This patient should be placed on which of the following nutrient supplementations to prevent potential cardiomyopathy?

(A) Folate (1 mg/day)
(B) Vitamin B_{12} (350 to 1000 mcg/day)
(C) Selenium (40 to 80 mcg/day)
(D) Vitamin A (10,000 IU/day)
(E) Vitamin K (300 mcg/day)

For questions 20–22: A pharmacist managing the PN department of an IV home infusion company decided to review all technical aspects of PN preparation with the pharmacy staff in an effort to update procedures and educate pharmacy staff on current standards of PN admixtures.

20. There is some confusion among the staff as to where to obtain the most current document on medication standards for pharmacy prepared sterile products that provides evidence-based instructions for pharmacy design, quality assurance, washing, garbing, and personnel training and evaluation to improve compounding practice for PN admixtures. The most appropriate source to obtain this information is the

(A) ASHP 2015 Initiative.
(B) ASPEN Practice Guidelines.
(C) *USP* Chapter <797> Monograph.
(D) National IV Therapy Association.
(E) FDA Intravenous Compounding Guidelines.

21. In reviewing their procedures for storage of prepared PN admixtures, they found a beyond-use date of 14 days under refrigeration until PN is initiated in the home setting. Based upon the most current standards for pharmacy prepared sterile products, which one of the following is the correct beyond-use date for storage of PN admixtures prepared for home use?

(A) 30 hrs under refrigeration
(B) 3 days under refrigeration
(C) 14 days under refrigeration
(D) 24 hrs at room temperature
(E) 9 days under refrigeration

22. In compounding PN for home patients, there are several patients with SBS for whom physicians are prescribing the addition of the amino acid glutamine to the PN formulation. The pharmacists must use nonsterile glutamine powder to compound these PN formulations. In updating their procedure manual, what would be the risk-level for compounding these specialty PN formulations based on the most current document on medication standards for pharmacy prepared sterile products?

(A) Intermediate-risk level
(B) High-risk level
(C) Low-risk level
(D) Medium-risk level
(E) Minimum-risk level

For questions 23–24: A 28-year-old white male involved in a motor vehicle accident was admitted to the SICU with severe abdominal and head injuries. The patient is fluid restricted because of his head injury and was subsequently placed on a concentrated glucose system PN. His calcium and phosphate serum levels are quite low and because of his fluid restriction, they want to add as much calcium and phosphate to the PN formulation to correct these electrolyte deficiencies.

23. Which of the following strategies would allow for the best calcium and phosphate solubility?
    (A) Use a brand of amino acids that has the lowest pH.
    (B) Calcium should be added and diluted in the PN prior to the addition of phosphate.
    (C) The amino acid concentration should be kept as low as possible.
    (D) The temperature of the PN solution should be kept as high as tolerable.
    (E) The pH of the PN solution should be increased by the addition of 0.1N sodium hydroxide.

24. The form of calcium phosphate that is most soluble in PN solutions is
    (A) dibasic.
    (B) divalent.
    (C) monobasic.
    (D) trivalent.
    (E) tribasic.

Answers and Explanations

1. **The answer is A** *[see I.B.3]*.
   A hypermetabolic state (e.g., trauma, infection) combined with protein deprivation can rapidly develop into a severe kwashiorkor malnutrition characterized by hypoalbuminemia, edema, and impaired cellular immune function.

2. **The answer is C** *[see V.D.1]*.
   Even in the presence of appropriate amounts of NPCs administered as carbohydrate, the normal carbon dioxide load generated by glycolysis may be excessive for the patient with underlying pulmonary dysfunction. PN lipid system formulations, in which the lipid component constitutes 40% to 50% of the total NPCs, may be beneficial in reducing the ventilatory demands in respiratory failure patients because lipolysis generates less carbon dioxide than glycolysis.

3. **The answer is B** *[see III.A.6.b.(2).(b).(iii)]*.
   A particle filter (i.e., 1.2 μ) should be used with TNA administration.

4. **The answer is C** *[see II.B.1]*.
   Energy requirements are determined as nonprotein calories by indirect calorimetry, estimated energy expenditure, and the simple nomogram method. The nomogram method is the least accurate method of estimating caloric requirements.

5. **The answer is D** *[see III.A.6.b.(1)]*.
   The lipid system PN is a formulation in which lipid is administered daily to provide a substantial portion of the NPCs.

6. **The answer is C** *[see V.C.1]*.
   PN formulations enriched in branched-chain amino acids have been made available with the rationale that, being the preferred fuel source in this patient population, it would enhance protein synthesis, decrease protein catabolism, and improve the patient's clinical outcome. However, these more expensive branched-chain amino acid formulations have not been shown to favorably influence clinical outcomes in critically ill patients.

7. **The answer is D** *[see V.B.3]*.
   Standard glucose system formulations (4.25% amino acid/25% dextrose) can generally be used in renal failure patients who are being dialyzed on a regular basis. This formulation is particularly useful in severely malnourished patients because it can provide adequate protein to attain positive nitrogen balance, which is not possible with renal failure PN.

8. **The answer is D** *[see II.B.2.a.(4)]*.
   A positive nitrogen balance of 3 to 6 g is the goal.

9. **The answer is C** *[see V.C.3]*.
   Protein requirements in ICU patients should not be restricted as a clinical management strategy to reduce the risk of developing hepatic encephalopathy.

10. **The answer is B** *[see II.B.1.c]*.
    Use the nomogram of 30 kcal/kg to determine the NPCs/day, and divide that by the NPCs/mL of the enteral formula to determine the volume of formula per day, which is divided by 24 hrs to yield the hourly goal rate.

11. **The answer is D** *[see V.A.5]*.
    Omega-3 polyunsaturated fatty acids are derived from fish oils and are currently found in some enteral formulations. These fatty acids have been shown experimentally to enhance immune response.

12. The answer is A *[see III.A.3.b]*.
With the use of new catheter technology and new techniques for infusion, it is now feasible to administer peripheral PN in selected patients for short-term therapy (7 to 10 days) with a low incidence of peripheral vein thrombophlebitis. This method of PN administration avoids the potential of more serious complications associated with central venous route administration.

13. The answer is A *[see V.I]*.
The estimated basal energy expenditure is calculated using the pregravid weight in the Harris-Benedict equation. An additional 300 kcal/day is added to the basal energy expenditure to provide the required calories per day during pregnancy.

14. The answer is A *[see V.I.3]*.
An additional 65 μg of vitamin K needs to be added to the daily PN formulation when MVI-12 is used as the parenteral vitamin preparation to meet the daily requirements during pregnancy.

15. The answer is C *[see V.H.2]*.
ACP recommends a target blood glucose level of 140 to 200 mg/dL if insulin therapy is used in SICU/MICU patients

16. The answer is B *[see II.B.5.g]*.
Suggested IV requirements of chromium for deficiency and severe glucose intolerance are 150 to 200 μg/day.

17. The answer is C *[see V.H.3.c]*.
A few studies show that IIT improves mortality, whereas most have shown that patients who receive IIT have no reduction in mortality and have a significantly increased risk for severe hypoglycemia.

18. The answer is D *[see V.L.4]*.
Thiamine deficiency is not common after bariatric surgery but is seen in patients with postoperative hyperemesis syndromes.

19. The answer is C *[see V.L.6]*.
Selenium deficiency and a life-threatening cardiomyopathy have been reported in patients after malabsorptive surgery. Supplementation of selenium at 40 to 80 mcg/day is recommended in patients undergoing malabsorptive surgery.

20. The answer is C *[see VI.A]*.
The *USP* Chapter <797> provides evidence-based instructions for pharmacy design, washing, garbing, quality assurance, and personnel training and evaluation to improve compounding practices for sterile products, including PN.

21. The answer is E *[see VI.A]*.
In the home care setting, the beyond-use date can be extended to 9 days, but the PN admixture must be stored under refrigeration at 36° to 46° F until use.

22. The answer is B *[see VI.A]*.
When PN is compounded using powdered amino acids, it is classified as a "high-level" CSP because its preparation involves the use of nonsterile ingredients and carries the highest risk for contamination by microbial, chemical, or physical matter.

23. The answer is A *[see VI.B]*.
The pH of the PN solutions is determined primarily by the concentration and type (brand) of amino acids. PN solutions containing higher concentrations of amino acids have a lower pH that allows for greater solubility of calcium and phosphate. The type (brand) of amino acid solutions commercially available differ in their pH.

24. The answer is C *[see VI.B]*.
Dibasic calcium phosphate is very insoluble, whereas monobasic calcium phosphate is relatively soluble.

Study Questions

Directions: Each of the numbered items 1–6 is based on the case. The remaining questions (7–10) are based on the statement, not based on the case. Select the **one** lettered answer or completion that is **best** in each question.

Case: A 28-year-old white female patient was admitted to the hospital for a kidney transplant from a deceased donor who had died 12 hrs earlier. She had a history of type I diabetes mellitus since 8 years old. She started chronic hemodialysis 2 years ago. She was blood typed and the final cross-match was negative. She underwent a successful renal transplant.

Lab at admission: Na 130 mEq/L (135–145), K 5.1 mEq/L (3.5–5.0), Cl 99 mEq/L (98–110), CO_2 18 mEq/L (22–28), Cr 9.5 mg/dL (0.8–1.2), BUN 65 mg/dL (5–15), hemoglobin 9.5 gm/dL (13–15), and glucose 185 mg/dL (60–100).

Virus serology: CMV and EBV titer negative and donor positive for CMV and EBV, Hepatitis A, B, & C serology negative.

Vital signs: BP 150/90 mm Hg, pulse 65/min, RR 12/min, Temp. 98.6°F.

Physical exam: Pale, slightly edematous.

Allergy: no known allergy

Medications on admission: Human NPH/regular insulin, 35/10 units in the morning and 10/5 units in the evening; calcium carbonate 1250 mg t.i.d., calcitriol 0.5 mcg orally daily, enalapril 5 mg b.i.d., metoclopramide 10 mg q.i.d., and erythropoietin 10,000 units sq per week

1. The patient received Simulect® with cyclosporine, mycophenolate, and prednisone. The nurse asked about Simulect®. Which of the following is an appropriate response?

(A) Simulect® is useful, but patient's weight gain should be less than 3% from the dry weight before therapy.
(B) Simulect® is useful agent to treat rejection, but chest x-ray and monitoring of patient's fluid status are required before this therapy.
(C) Simulect® is a chimeric IgG with specificity against IL-2 receptor, and it is useful for prevention acute cellular rejection.
(D) Simulect® is a humanized IgG product against IL-2 receptor, and it is useful in preventing acute humeral rejection.
(E) Simulect® is a rabbit serum against human T cells, and it is useful for prevention and treatment of rejection.

2. On day 7, her serum creatinine was 1.4 mg/dL and BUN 28 mg/dL. Her urine output was excellent and her blood cyclosporine level was 250 ng/mL (200–300). She was discharged to her home. Several days later, she developed a worsening hypertension of 170/105 mm Hg. Which of the following medication(s) she is taking worsened her hypertension?

I. Cyclosporine
II. Prednisone
III. Mycophenolate

(A) **I** only
(B) **III** only
(C) **I** and **II**
(D) **II** and **III**
(E) **I**, **II**, and **III**

3. Due to her worsening hypertension, her local physician wants to start Cardizem® CD 240 mg daily. What is your advice for this hypertension therapy?

(A) Cardizem® CD will decrease cyclosporine metabolism, so please reduce the cyclosporine dose by 25% and check cyclosporine level twice a week.
(B) Cardizem® CD will decrease cyclosporine metabolism, so please increase cyclosporine dose by 25% and check cyclosporine level twice a week.
(C) Cardizem® CD will increase cyclosporine metabolism, so please switch cyclosporine to tacrolimus.
(D) Cardizem® CD will decrease cyclosporine metabolism, so please switch cyclosporine to tacrolimus.
(E) Cardizem® CD will increase cyclosporine metabolism, so please switch cyclosporine to azathioprine.

4. Which of the following is most appropriate regarding prophylactic regimen for her infections?

I. Co-trimoxazole s.s. daily for PCP prophylaxis
II. Nystatin for prophylaxis of fungal infection
III. Valcyte® for CMV disease

(A) **I** only
(B) **III** only
(C) **I** and **II**
(D) **II** and **III**
(E) **I**, **II**, **and III**

5. Which of the following is correct regarding Myfortic®?

I. It is an enteric-coated formulation of mycophenolic acid.
II. Its major side effect is leukopenia.
III. It causes severe hyperlipidemia.

(A) **I** only
(B) **III** only
(C) **I** and **II**
(D) **II** and **III**
(E) **I**, **II**, and **III**

6. The patient's urine output decreased, her creatinine rose to 2.2 mg/dL (baseline: 1.4 mg/dL) and her feet had +2 edema. Her cyclosporine dose was 150 mg twice daily and her trough level was 450 ng/mL (200 to 300). She felt shaky and subsequent physical exam revealed a mild hand tremor. Acute rejection was ruled out by kidney biopsy. Which of the following is the appropriate adjustment of her immunosuppression?

(A) Increase cyclosporine dose to 175 mg b.i.d. and prednisone 10 mg q.d.
(B) Reduce cyclosporine dose to 125 mg b.i.d. and monitor cyclosporine trough level.
(C) Increase prednisone from 10 mg to 20 mg daily.
(D) Switch cyclosporine to tacrolimus.
(E) Stop cyclosporine and start thymoglobulin.

End of the case

7. A 38-year-old woman came to your clinic and complained of hair loss and did not want to take an immunosuppressant anymore. Which of the following is an appropriate advice for her problem?

(A) Switch mycophenolate mofetil to sirolimus
(B) Stop her prednisone and add methylprednisolone
(C) Switch her tacrolimus to cyclosporine
(D) Switch her mycophenolate mofetil to Myfortic
(E) Add azathioprine to her regimen

8. Which of the following is *not* a side effect of corticosteroid therapy?

(A) Osteoporosis
(B) Leukopenia
(C) Moon faces
(D) Poor wound healing
(E) Hypercalcemia

9. Which of the following is likely to decrease tacrolimus blood concentration when it is used concomitantly?

(A) Grapefruit juice
(B) Erythromycin
(C) St. John's wort
(D) Voriconazole
(E) Verapamil

Answers and Explanations

1. The answer is C *[see III.E.2]*.
Simulect® (basiliximab) is a chimeric monoclonal antibody against the Interleukin-2 receptor. This drug can be used as prevention of an acute cellular rejection. The dose for rejection treatment is 20 mg on day 0 and day 4. It occasionally causes mild fever, but it does not cause any serious side effects. (A) Orthoclone (OK3) requires < 3% weight gain. (B) Simulect® does not require for monitoring fluid status by x-ray. (D) Simulect® does not prevent acute humeral rejection. (E) Simulect® is used only for prevention of rejection, not for the treatment of rejection.

2. **The answer is C** *[see III.A.1; III.F]***.**
Cyclosporine and prednisone increase the blood pressure. Cyclosporine (Neoral®) promotes the vasoconstriction and causes renal dysfunction, which contributes to hypertension. Prednisone (Deltasone®) increases fluid and sodium retention, which contributes to hypertension. Mycophenolate mofetil (CellCept®) is an antimetabolite inhibiting DNA synthesis and cell proliferation. Its side effects include leukopenia and thrombocytopenia, and it does not cause hypertension.

3. **The answer is C** *[see Table 53-2]***.**
Cardizem® CD (diltiazem) CD is a cytochrome P450 enzyme inhibitor that decreases cyclosporine metabolism. When cyclosporine is used concurrently with diltiazem, it is necessary to decrease cyclosporine dose by 25% in order to prevent the toxicity. Frequent monitoring of cyclosporine blood levels and the cyclosporine dose adjustment should be made based on the blood levels.

4. **The answer is E** *[see IV.A]***.**
All of these drugs are required for posttransplant infection prophylaxis. Co-trimoxazole (Bactrim) single strength (s.s.) once daily for pneumonitis jirovecci, nystatin 5 mL swish and swallow four times daily for fungal infection, and valganciclovir (Valcyte) 450 to 900 mg daily for CMV are important prophylactic regimen.

5. **The answer is C** *[see III.B.2.a]***.**
Myfortic® is an enteric-coated formulation of mycophenolate sodium that inhibits inosine monophosphate dehydrogenase. Its major side effects include gastrointestinal side effects (e.g., nausea, vomiting, or diarrhea) and leukopenia. It does not cause hyperlipidemia, but sirolimus does.

6. **The answer is B** *[see III.A.1]***.**
This is a typical symptom of cyclosporine toxicity, which is confirmed by her high blood level (therapeutic level, 200 to 300 ng/mL) with tremor, acute renal dysfunction (serum creatinine 2.2 mg/dL from baseline 1.4 mg/dL), and +2 edema. The dose of cyclosporine should be reduced by 25 mg (There are 25 mg and 100 mg capsules), and the blood levels as well as signs and symptoms should be closely monitored.

7. **The answer is C** *[see III.A.2]***.**
Tacrolimus causes alopecia (hair loss) and cyclosporine causes hirsutism.

8. **The answer is E** *[see III.F]***.**
All of the above are side effects of corticosteroid therapy except hypercalcemia. The corticosteroid use causes calcium loss by kidney resulting in hypocalcemia.

9. **The answer is C** *[see Table 53-2]***.**
All of the above except St. John's wort are CYP3A inhibitors, which increase tacrolimus blood concentrations. St. John's wort is a CYP3A inducer, which decreases tacrolimus levels.

Study Questions

Directions: Each of the questions, statements, or incomplete statements in this section can be correctly answered or completed by **one** of the suggested answers or phrases. Choose the **best** answer.

1. The underlying assumption of cost-minimization analysis (CMA) is

(A) calculation of cost minimization ratio.
(B) consequences or outcomes are equivalent.
(C) costs are equivalent.
(D) patient satisfaction is equivalent
(E) no more than two comparators in any analysis.

2. Which one of these statements is *not* true for the differences between economic studies and randomized clinical trials (RCTs)?

(A) Generalizability and applicability of the results differ between economic studies and RCTs.
(B) Clinical end point and economic end point are identical.
(C) RCTs tend to have inflated benefits and additional protocol-driven costs.
(D) Sample size of the economic study is normally larger than in the RCT.
(E) Clinical efficacy assessment through the RCTs as compared to clinical effectiveness through the economic study.

3. In choosing an instrument to measure the health-related quality of life (HRQOL), which of the following is *not* a key component of the assessment?

(A) Reliability as a sign of consistency for the instrument.
(B) Validity of the instrument in order to assure its accuracy.
(C) Incorporate similar questionnaires into a single instrument after calibration.
(D) Sensitivity and specificity of the instrument.
(E) Length of the instrument.

4. In choosing a study perspective, the current pharmacoeconomic guidelines have suggested which one of the following perspectives to be included?

(A) Society
(B) Payers
(C) Patients
(D) Providers
(E) Practitioners

Directions for questions: The questions and incomplete statements for questions 5–6 in this section can be correctly answered or completed by **one or more** of the suggested answers. Choose the answer, **A–E.**

(A) if **I only** is correct
(B) if **III only** is correct
(C) if **I and II** are correct
(D) if **II and III** are correct
(E) if **I**, **II**, **and III** are correct

5. When interpreting outcomes research amongst multiple countries, what issues needs special attention?

(I) Cost computations
(II) Health care funding and cost-allocating mechanisms
(III) Patients' variations and beliefs

6. Which one of these pharmacoeconomic techniques does not address both cost and consequences?

(I) Cost-benefit analysis
(II) Cost-effectiveness analysis
(III) Cost of illness

7. Which of the following is an example of a clinical outcome indicator?

(A) Dollars spent treating acute myocardial infarction
(B) Resources used in diagnosing the presence of medical errors
(C) Duration of hospitalization and mortality versus discharge rate for ventricular fibrillation patients treated with amiodarone
(D) Functional capacity of patients treated with ramipril in the presence of cardiovascular risk factors
(E) Patient satisfaction survey upon discharge

Answers and Explanations

1. The answer is B *[see IV.C]***.**
CMA assumes all consequences compared are equivalent. Patient satisfaction would represent a humanistic outcome and is not considered in a CMA. For this reason, only the cost of each alternative is compared with the least expensive alternative being chosen.

2. The answer is B *[see IX.A]***.**
Clinical and economic end points are generally not equal. In the sequence of the study events, efficacy should come before effectiveness and is routinely a key outcome associated with the RCTs as compared to effectiveness being associated with the economic or outcomes study.

3. The answer is C *[see VI.D.1–3]***.**
A key process involved in each instrument used to assess quality of life is the need to "calibrate" and "recalibrate" the psychometric properties in order to make sure it is adequately assessing the instrument's intention. This would be of paramount concern when one incorporates items from one satisfactory instrument to that of another similar instrument. Both instruments on their own might meet all necessary purposes. However, when combining them, the process of recalibration is again necessary to adequately assure the reconfigured instrument's value.

4. The answer is A *[see III.B]***.**
The societal perspective must be included. It is critical in the health care environment to identify the perspective from which a decision is being made because that perspective directly affects the final decision. The decision to add a high-cost, moderately effective therapy for the treatment of hospitalized patient might be different if viewed from a hospital formulary committee (in-house budgetary concerns) than from the local community, national government (saving lives at whatever expense).

5. The answer is E *[see IX.B.1–3]***.**
All of the issues stated need special attention and play a major role in developing multinational economic evaluations to avoid carrying out a study that when completed cannot be generalized to the broad patient population.

6. The answer is B *[see IV.A]***.**
The cost of illness methodology is carried out as an assessment of the necessary resources that will be used to treat a designated illness. Resources are measured in terms of dollars, and there are no comparator groups in the evaluation.

7. The answer is C *[see I.A.3]***.**
Clinical outcomes include the following: length of hospital stay, adverse drug reactions, hospital readmission, and death. These are definable measures of a patient's response to a given treatment, such as amiodarone used for the treatment of ventricular fibrillation.

Study Questions

Directions: Each statement in this section can be correctly completed by **one or more** of the suggested phrases. Choose the **correct** answer, **A–E**:

A if **I** only is correct
B if **III** only is correct
C if **I** and **II** are correct
D if **II** and **III** are correct
E if **I**, **II**, and **III** are correct

1. Healthy human volunteers are used in drug development for

I. phase I testing after the submission of an investigational new drug (IND) application.
II. generic drug development for an abbreviated new drug application (ANDA) submission.
III. phase III testing just before the submission of a new drug application (NDA).

2. The required information contained in a NDA that is *not* included in the ANDA consists of

I. preclinical animal toxicity studies.
II. clinical efficacy studies.
III. human safety and tolerance studies.

3. A product line extension contains the NDA-approved drug in a new

I. dosage form.
II. dosage strength.
III. therapeutic indication.

Directions: Each statement in this section can be correctly completed by **one** of the suggested phrases. Choose the **best** answer.

4. The regulations developed by the U.S. Food and Drug Administration (FDA) for the pharmaceutical industry for meeting the minimum requirements in the manufacturing, processing, packing, or holding of human and veterinary drugs are known as

(A) good manufacturing practices (GMPs).
(B) quality assurance (QA).
(C) quality control (QC).
(D) pre-approval inspection (PAI).
(E) scale-up and post-approval changes (SUPACs).

5. The unit within the pharmaceutical manufacturer that ensures that the finished dosage form has met all the specifications for its intended use is the

(A) analytical methods unit.
(B) marketing and sales unit.
(C) PAI unit.
(D) QA unit.
(E) QC unit.

6. Manufacturers may make a change in the formulation after market approval. If the change in the formulation is considered a minor change, the manufacturer needs to report the change to the FDA only in the

(A) annual report.
(B) preapproval supplement.
(C) IND submission.
(D) changes being effected supplement, 30 days (CBE-30).
(E) no report is required for a minor change.

Answers and Explanations

1. The answer is C (I, II) *[see I.C.2.b; I.F.2]***.**
Phase I testing is the first set of human studies performed during new drug development. Phase I studies establish the tolerance and toxicity of the drug in humans. Bioequivalence studies for generic drug development are most often performed in healthy human volunteers. These studies establish the bioequivalence of the generic drug product against the brand drug product. Phase III testing entails large-scale, multicenter clinical studies performed in patients with the disease or condition to be treated. Phase III studies determine the safety and efficacy of the drug in a large patient population.

2. The answer is E (I, II, and III) *[see I.C.5; I.F.6]***.**
The development of a new drug requires extensive toxicity and efficacy testing in animals and humans. The NDA documents all studies performed on the drug. The ANDA is used for generic drug product submissions. The generic drug product is similar to the original brand drug product that has already been marketed. Because the efficacy, safety, and toxicity of this drug product have been studied and documented, further studies of this nature are unnecessary.

3. The answer is C (I, II) *[see I.D]***.**
Product line extensions are developed after further studies with the original NDA-approved drug product. From these studies, the manufacturer may develop a new dosage form (e.g., controlled-release product) or a new dosage strength. A new therapeutic indication requires an NDA.

4. The answer is A *[see V]***.**
Quality control and quality assurance follow GMP regulations to ensure that the finished product meets all applicable specifications for quality. The FDA may inspect a manufacturing site (PAI) before the drug application is approved. In addition, the FDA must be notified about any proposed changes to an approved drug product.

5. The answer is E *[see V.D]***.**
The QC unit performs the appropriate tests on the dosage form. PAI is performed by FDA compliance inspectors, who examine the pharmaceutical manufacturer and review the procedures and records for manufacturing the finished dosage form before the administration grants market approval. The analytical development unit develops the analytical methods used in testing the drug product.

6. The answer is A *[see IV.C.1]***.**
All changes in the formulation must be reported to the FDA. A minor change is a change that has minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they may relate to the product's safety or effectiveness. Changes that are unlikely to have any detectable effect on formulation quality and performance can be instituted without approval by the FDA and need only to be reported in the annual report.

Study Questions

Directions: Each question, statement, or item in this section can be correctly answered or completed by **one** of the suggested answers or phrases. Choose the **best** answer.

1. Which of the following is responsible for the acid-fast staining characteristic of mycobacteria?

(A) The peptidoglycan
(B) The polysaccharide capsule
(C) The cytoplasmic membrane
(D) The cell wall mycolic acid
(E) The cell wall lipoteichoic acid

2. Of the following features, which is unique to gram-positive bacteria?

(A) Cytoplasmic membrane
(B) Endotoxin
(C) Outer membrane
(D) Peptidoglycan
(E) Spore formation

3. Which structure is characteristic of a prokaryotic organism?

(A) Nuclear membrane
(B) 80S ribosome
(C) Peptidoglycan
(D) Electron transport chain
(E) Segmented genome

4. Which of the following is an advantage for the bacterium that is attributable to the bacterial capsule?

(A) It is antiphagocytic.
(B) It is a source of nutrition.
(C) It provides protection from dry, harsh environments.
(D) It allows for the exchange of DNA between different bacteria.
(E) It inactivates antimicrobials.

5. Which of the following is a protozoan infection that can lead to lesions in the eye if it is acquired congenitally (in utero)?
   (A) Malaria
   (B) Giardiasis
   (C) Cryptosporidiosis
   (D) Toxoplasmosis
   (E) Amebiasis

6. The envelope of an enveloped virus is derived from which of the following sources?
   (A) The viral capsomeres
   (B) The host cell membrane
   (C) The viral matrix proteins
   (D) The 80S ribosome
   (E) The retroviral reverse transcriptase

Answers and Explanations

1. **The answer is D** *[see III.A.3.c; III.B.4.b].*
   The acid-fast stain uses a procedure to stain cells that have an outer layer of a waxy lipid, which is composed of mycolic acid and glycolipids (acid-fast, stained red). This waxy layer prevents removal of the stain by an acid rinse. The stain is removed from cells that lack that layer; these cells are then counterstained blue (non–acid-fast). The peptidoglycan (and its thickness) has a greater effect on the staining properties of the gram stain. The polysaccharide capsule stain is a colloidal stain that is excluded from the area occupied by the capsule. Lipoteichoic acid is a feature of the gram-positive cell wall.

2. **The answer is E** *[see III.B.4.a; III.B.6].*
   Endospores or bacterial spores are dehydrated multishelled structures formed by some gram-positive organisms (*Clostridium* and *Bacillus*) in response to adverse conditions. All bacteria have a cytoplasmic membrane, and nearly all have peptidoglycan cell walls (except mycoplasma). The outer membrane and endotoxin are unique to gram-negative organisms.

3. **The answer is C** *[see III.B.1].*
   Eukaryotic organisms have membrane-bound organelles (nucleus and the associated nuclear membrane, Golgi apparatus, mitochondria, lysosome, etc.). The bacterial ribosome is 70S, whereas the eukaryotic ribosome is 80S. Aerobic and facultative anaerobic bacteria use the electron transport chain, although it is contained in the bacterial cytoplasmic membrane rather than in the membrane of the mitochondria, as it is in the eukaryotic cell. Peptidoglycan is a structure of most bacteria, but not found in eukaryotic cells. Some RNA viruses have a segmented genome.

4. **The answer is A** *[see III.B.5.a].*
   The capsule is antiphagocytic, provides some adherence properties, and is somewhat of a barrier to hydrophobic molecules. The sex pilus mediates the exchange of DNA. An endospore protects the bacterium from harsh environments. Specific enzymes (e.g., β-lactamase) inactivate antimicrobials.

5. **The answer is D** *[see II.B.4.b.(2)].*
   Toxoplasmosis, the infection caused by *Toxoplasma gondii*, is usually mild, although, when acquired during pregnancy, can be transmitted to the fetus resulting in abortion, stillbirth, or neonatal disease (chorioretinitis, blindness, encephalitis, and hepatosplenomegaly).
   Malaria, associated with *Plasmodia* species, leads to a number of issues for the mother and infant when the infection is acquired during pregnancy, but after birth, the issues tend to be more related to the susceptibility to future infections with *Plasmodia* species Amebiasis is caused by *Entamoeba histolytica*. *Giardia lamblia* is responsible for giardiasis, which is a watery diarrhea. *Cryptosporidium* species infections usually result in a mild, self-limiting diarrhea.

6. **The answer is B** *[see IV.C.4].*
   Enveloped viruses assemble at a host cell membrane, usually the cytoplasmic membrane, and then exit the host cell by budding through the membrane, which creates the associated membrane envelope. Additional viral proteins and glycoproteins are added to the membrane to assist with the attachment of the virion particle to the next cell.

Study Questions

Directions: Each question, statement, or item in this section can be correctly answered or completed by **one** of the suggested answers or phrases. Choose the **best** answer.

1. A man was ill 10 days ago with a viral illness. Laboratory analysis of the patient's blood reveals that the patient's antiviral antibodies have a high ratio of IgM/IgG. What does this tell you?

(A) It is unlikely that the patient had encountered this virus before his recent illness.
(B) The patient is predisposed to IgE responses to this virus.
(C) This information is unrelated to the recent viral illness.
(D) This patient's response is due to a memory response.
(E) It is likely that this patient is developing an autoimmune disorder.

2. Which class of antibody has the longest serum half-life and opsonizes antigens for phagocytosis through two different pathways?

(A) Immunoglobulin A (IgA)
(B) Immunoglobulin D (IgD)
(C) Immunoglobulin E (IgE)
(D) Immunoglobulin G (IgG)
(E) Immunoglobulin M (IgM)

3. Urticaria that appears rapidly after the ingestion of food usually indicates which type of hypersensitivity reaction?

(A) Type I
(B) Type II
(C) Type III
(D) Type IV

4. The mechanism of pathogenesis for which of the following autoimmune disorders is due to widely distributed immune complexes?

(A) Systemic lupus erythematosus (SLE)
(B) Insulin-dependent diabetes mellitus (IDDM)
(C) Graves disease
(D) Hashimoto thyroiditis
(E) Multiple sclerosis

5. A patient receives long-term, high-dose therapy with penicillin. After approximately 2 weeks of therapy, the patient has a low-grade fever, rash, and muscle and joint pain. Which type of hypersensitivity accounts for these symptoms?

(A) Type I
(B) Type II
(C) Type III
(D) Type IV
(E) This is unlikely to be due to a hypersensitivity

6. The treatment of multiple sclerosis (MS) might include which of the following agents?

(A) Neostigmine
(B) Cyanocobalamin
(C) Omalizumab
(D) Propylthiouracil
(E) IFN-β-1b

7. The therapeutic role of muromonab-CD3 in acute renal graft rejection is probably based on

(A) activation of T-cell function and increased secretion of cytokines.
(B) destruction of T cells by complement.
(C) opsonization of T cells for phagocytosis.
(D) apoptosis of activated T cells.
(E) activation of T_{REG} cells.

8. Which is a current clinical application of intravenous human immunoglobulin (IVIG)?

(A) Prophylaxis after hepatitis B virus (HBV) exposure
(B) Treatment of humoral immunodeficiency
(C) Prophylactic infant immunization for respiratory syncytial virus (RSV)
(D) Prophylaxis for Rh disease by infant immunization
(E) Treatment for snake bites

For questions 9 and 10: An 18-year-old college student has a deep puncture wound. The student is unsure of his history of vaccination.

9. If no other information is available, what should the physician recommend?

(A) No vaccination
(B) Tetanus immunoglobulin (TIG)
(C) Tetanus toxoid (Td)
(D) Both TIG and Td at separate sites
(E) Administer IVIG and Tdap

10. If the student had received a full series of diphtheria, pertussis, tetanus (DTaP) vaccinations as a child, and received the Tdap prior to entry into college last year, what should the physician recommend?

(A) No vaccination
(B) Tetanus immunoglobulin (TIG)
(C) Tetanus toxoid (Td)
(D) Both TIG and Td at separate sites
(E) Administer IVIG and Tdap

11. $CD4^+$ T cells specifically recognize antigens in which form?

(A) Bound to major histocompatibility complex (MHC) class I molecules on the surface of any nucleated cell
(B) In free, soluble form in extracellular fluids
(C) Bound to MHC class II molecules on the surface of special antigen-presenting cells (APCs)
(D) Bound to complement receptors on professional antigen-presenting cells (APCs)
(E) Associated with class II MHC on the surface of T_C cells

12. The normal consequence of complement activation by either the lectin or alternative pathway includes all of the following EXCEPT?

(A) Acute inflammation
(B) Immune complex clearance
(C) Cytolytic action
(D) Recruitment of leukocytes
(E) Opsonization of microbes

13. In antiviral immunity, what directly recognizes and kills viral-infected cells?

(A) Complement
(B) Antiviral antibodies
(C) Interferons
(D) Eosinophils
(E) Cytotoxic T cells (CTLs)

14. A patient was skin tested with purified protein derivative (PPD), which was administered to determine previous exposure to *Mycobacterium tuberculosis*. The patient developed redness and induration at the skin test site 48 hrs after inoculation. Histologically, the reaction at this site would most probably show

(A) plasma cell infiltration.
(B) eosinophils.
(C) neutrophils.
(D) acid-fast bacilli.
(E) T cells and macrophages.

15. Graft versus host disease (GVHD) is associated primarily with which type of transplantation?

(A) Kidney
(B) Heart
(C) Bone marrow
(D) Cornea
(E) Autografts

16. The prophylactic use of cyclosporine in graft rejection is probably based on its ability to

(A) competitively inhibit the IL-2 at the IL-2 receptor.
(B) inhibit synthesis of antibodies, thereby preventing hyperacute rejection.
(C) inhibit activation of B cells, thereby preventing acute rejection.
(D) block transcription of the IL-2 gene and synthesis/secretion of IL-2.
(E) induce apoptosis in activated T cells.

17. Which statement about pneumococcal and meningococcal vaccines is true?

(A) They are both available as a purified polysaccharides or conjugated polysaccharide.
(B) They are both recommended for children < 2 years of age.
(C) Each vaccine formulation contains all serotypes of disease-causing organisms.
(D) They are live attenuated, requiring only a single dose to be effective.
(E) They should not be administered during pregnancy.

18. A patient currently taking methyldopa develops hemolytic anemia, which resolves shortly after the drug is withdrawn. The most probable explanation is that the patient was experiencing

(A) an atopic hypersensitivity.
(B) a type II hypersensitivity.
(C) immune complex hypersensitivity.
(D) cell-mediated hypersensitivity.
(E) a type IV hypersensitivity.

19. Infliximab (Remicade) is a chimeric monoclonal antibody that binds directly to TNF-α. Patients taking this medication should be advised that they are

(A) more susceptible to infections because TNF-α is important for synthesizing IgM.
(B) more susceptible to infections because they will generate more lymphocytes in the absence of TNF-α.
(C) less susceptible to infections because T_H1 responses will predominate in the absence of TNF-α.
(D) more susceptible to infections because the initiation of inflammation will be less efficient without TNF-α.
(E) less susceptible to infections because they will not initiate an acute-phase response without TNF-α.

20. What would be the typical time frame for the appearance of a type IV hypersensitivity reaction in a person already sensitized to the antigen?

(A) Within a few minutes
(B) Within a few hours
(C) Within a few days
(D) Within a few weeks
(E) Within a few months

21. For a patient who was experiencing a type I hypersensitivity, including difficulty breathing and loss of consciousness, which of the following would be the most appropriate medical intervention?

(A) injection of epinephrine
(B) injection of nonsteroidal anti-inflammatory drugs
(C) injection of antihistamines
(D) injection of corticosteroids
(E) administer an oral H_2-receptor inhibitor

Answers and Explanations

1. The answer is A *[see IV.B]***.**
The primary immune response to an infection is characterized by the initial production of IgM beginning 4 to 6 days and peaking 9 to 14 days after introduction of the antigen. Under the influence of T_H cells, activated B cells will undergo isotype switching to produce antibodies that might be more effective (e.g., IgG, longer lasting, opsonic, distributed well in tissues; IgA, high concentrations in mucous; IgE, parasitic infections and mast cell activation). Memory responses maintain the isotype effective from the previous immune response.

2. The answer is D *[see IV.F.2.c]***.**
IgG has the longest lasting serum half-life (21 days for most subclasses) and is the most plentiful antibody in the serum. Antigen bound by IgG is opsonized for phagocytosis by neutrophils and macrophages via phagocyte Fc receptors; however, IgG is also able to activate complement, which will lead to the addition of covalently bound C3b to the microbe surface. C3b is also an opsonin for which phagocytes have receptors that will assist with phagocytosis.

3. The answer is A *[see VI.B.4.c]***.**
Food allergies are usually type I reactions. In a patient with mast cells already associated with IgE specific to a food allergen, the allergic response usually occurs shortly after ingestion. Mast cell activation and degranulation in the gastrointestinal tract leads to smooth muscle contraction (vomiting) and increased mucous and acid secretion. Allergen absorbed into the circulation may lead to mast cell degranulation in the skin (e.g., urticaria) or anaphylaxis.

4. The answer is A *[see VII.C.3]***.**
In SLE, persistent circulating immune complexes (typically containing nuclear antigens, such as nucleoproteins and nucleic acids) are responsible for much of the pathology. In Graves disease, an antibody acting as a TSH agonist hyperstimulates the thyroid. In IDDM, T-cell cytotoxicity, and potentially antibody production, leads to the destruction of the beta islet cells in the pancreas. In Hashimoto thyroiditis, antibodies and CTLs (and macrophages) infiltrate the thyroid. With multiple sclerosis, T_H1 cells and the resulting inflammatory responses are thought to be responsible for the demyelination.

5. The answer is C *[see VI.D.2]***.**
One of the most common causes of a type III hypersensitivity reaction is the response to drugs, often when they are used long term at a high dose and delivered intravenously. The treatment is to discontinue the drug.

6. The answer is E *[see VII.B.8]***.**
Treatment with IFN-β-1b reduces the frequency of MS flare-ups. The precise mechanism of action is currently unknown but may involve the activation of suppressor T cells and reduced production of proinflammatory cytokines. Neostigmine is used as an anticholinergic agent in myasthenia gravis. Cyanocobalamin is administered in autoimmune pernicious anemia to replace nonabsorbed vitamin B_{12}. Propylthiouracil is used as an antithyroid medication in Graves disease. Omalizumab is a monoclonal antibody that targets IgE.

7. The answer is C *[see X.B.2.d]***.**
Muromonab-CD3 is a mouse anti-CD3 monoclonal antibody that binds to all T cells because CD3 is a constant part of the antigen receptor of each T cell. The binding of muromonab-CD3 opsonizes the T cells for phagocytosis, chiefly in the liver, and the overall effect is a reduction in the total number of T cells. A later secondary phase of activity seems to involve antigenic modulation of the T cells such that the CD3 is removed from the surface, rendering those T cells incapable of signaling antigen binding. Mouse antibodies are inefficient at activating human complement. Some T-cell activation with cytokine secretion occurs, but it is an undesirable side effect of muromonab-CD3 administration.

8. **The answer is B** *[see X.B.1.b; Table 57-2]*.
IVIGs are used to replace antibodies in immunodeficient individuals. Each of the other choices is a formulation of passive transfer of antibodies; however, they are either enriched for specific antibodies or monoclonal antibodies (in the case of the RSV prophylaxis). Hepatitis B immunoglobulin (HBIG) is administered intramuscularly. Anti-Rh antibody is also administered intramuscularly to the mother immediately postpartum (sometimes during pregnancy) but not to the infant. Snake bite antivenin is derived from sera produced in horses.

9. **The answer is D** *[see X.D.2.a]*.
A patient with an uncertain history of vaccination and a tetanus-prone wound requires both active and passive vaccination. TIG provides immediate protection if the individual does not have memory. Td begins the series that leads to the establishment of memory. A tetanus-prone wound in an individual with a full series of active vaccinations requires no treatment if the last vaccination in the series was administered less than 5 years earlier. These recommendations are general guidelines.

10. **The answer is A** *[see X.D.2.a.(1)]*.
Even if the wound is a tetanus-prone wound, booster vaccination within 5 years obviates the need for additional tetanus vaccination.

11. **The answer is C** *[see I.B.6.b.(1).(b)]*.
$CD4^+$ (helper) T cells have TCRs that recognize fragments (epitopes) of immunizing antigens (immunogens) only when the peptide fragments are bound to MHC class II molecule on the surface of APCs (B cells, macrophages, or dendritic cells). $CD8^+$ T cells recognize peptide fragments bound to MHC class I molecules. As a result, T cells cannot be activated inappropriately by soluble antigens.

12. **The answer is B** *[see II.D.2.d]*.
The four functions of complement are inflammation, opsonization, cell lysis, and immune complex clearance. The classical pathway of complement activation is responsible for immune complex clearance because the antibody associated with the complexes initiates the classical pathway. When complement is activated, regardless of the pathway of activation, the complement components have functions that lead to all three of the other actions. Acute inflammation allows greater movement of plasma proteins and phagocytes from blood to tissue. Opsonization of immune complexes enhances their phagocytosis. Cytolysis of microorganisms by the membrane attack complex often results in their killing.

13. **The answer is E** *[see III.B.2.b]*.
Antiviral antibodies are important in extracellular immunity to viruses by neutralizing them for infection of additional cells and targeting the viruses for opsonization by complement. Interferons are secreted from viral-infected and other cells (e.g., macrophages, T cells) and, after binding to receptors, induce the appearance of antiviral proteins in other cells. CTLs recognize viral-infected cells and cause direct cytotoxicity.

14. **The answer is E** *[see VI.E.1]*.
Type IV hypersensitivity reactions are delayed after the introduction of antigen because antigen-specific T cells become activated and attract other cells, such as macrophages, to the site of antigen introduction (e.g., the epidermis of the skin in contact sensitivity, the lungs in tuberculosis). Inflammation is primarily caused by tissue damage and secretion of proinflammatory cytokines by the infiltrating cells. Although histamine release from local mast cells can also occur, H_1-antagonists of histamine usually do not have significant effects because T cell and macrophage activation, migration, and secretion are not greatly affected by these drugs.

15. **The answer is C** *[see IX.D]*.
In bone marrow transplantation, marrow containing mature lymphocytes is transplanted to a generally immunosuppressed host. The greatest problem is an immune response by the graft lymphocytes against HLA and other tissue antigens of the host. In renal and cardiac transplantation, the greatest problem is rejection of the foreign organ by the immune system of the host. Corneal transplants do not elicit rejection nor do autograft transplants (transplants from one part of the body to another on the same individual).

16. **The answer is D** *[see III.A]*.
Cell-mediated immune mechanisms are central in acute graft rejection, and the inhibition of T-cell activation appears to be the key element in immunosuppression. Responding T cells require signaling from IL-2 to reach full activation and progress to cell division. IL-2 is produced by activated T cells and can act in an autocrine manner. Cyclosporine blocks the cascade of signals that occur when T cells encounter specific antigen. The T-cell signaling is important for the transcription of the IL-2 gene. Inhibiting those signals inhibits the synthesis of IL-2 and prevents full T-cell activation and division. Its effects are limited to activated T cells. Because it has no direct effect on antibody synthesis, it is not useful in the hyperacute rejection phenomena, which is based on antibody-mediated mechanisms. Hyperacute rejection is essentially untreatable because it depends on the presence of antibodies in the graft recipient.

17. The answer is A *[see X.C.2.b; Table 57-3]***.**
The pneumococcal and meningococcal vaccines are multivalent and contain purified polysaccharide (PPSV23 and MPSV4, respectively) from a number of different serotypes (indicated by the number associated with each vaccine designation above). However, these vaccines do not contain polysaccharide from all of the relevant infectious agents. The pneumococcal and meningococcal vaccines are also formulated as a conjugate vaccine (MCV4 and PCV13, respectively). The pneumococcal vaccine is recommended for infants and children, beginning at 2 months. The minimum age for administration of the meningococcal vaccine is 2 years, although the recommended age dosing is 11 to 12 years.

18. The answer is B *[see VI.C.1]***.**
This patient was experiencing a type II hypersensitivity reaction, which is characterized by antibody-mediated lysis of host cells (in this case, erythrocytes) due to the presence of exogenous antigen (methyldopa). An atopic hypersensitivity (type I, IgE mediated) would have exhibited atopic symptoms, such as urticaria. Immune complex hypersensitivity symptoms would include a skin rash, fever, and joint pain.

19. The answer is D *[see Table 57-1]***.**
TNF-α is involved in inflammation and T_H1 responses. Inflammation is particularly important for responses to bacterial infections. Infliximab is prescribed for a number of autoimmune disorders that involve inflammatory mechanisms.

20. The answer is C *[see VI.E]***.**
Type IV hypersensitivity reactions are mediated by T cells (T_H1, T_H2, and CTL) and the inflammation associated with the T-cell activity. As such, the recruitment of the T cells typically takes 48 to 72 hrs after the introduction of the antigen. The classic example of a type IV hypersensitivity reaction is the tuberculin skin test.

21. The correct answer is A *[see VI.B.6.e]***.**
Many of the interventions will act on the allergic responses associated with a type I hypersensitivity reaction; however, this patient is experiencing a severe reaction. Epinephrine more immediately reverses the airway constriction.

Study Questions

Directions: Each of the questions, statements, or incomplete statements in this section can be correctly answered or completed by **one** of the suggested answers or phrases. Choose the **best** answer.

1. All of the following are examples of specific receptors for drug action **except**

(A) stomach acid.
(B) membrane proteins.
(C) cytoplasmic proteins.
(D) nuclear proteins.
(E) DNA.

2. A 40-year-old teacher was prescribed lovastatin for the treatment of hypercholesterolemia. She wanted to know the mechanism of the drug before taking it. Her pharmacist explained to her that lovastatin acts by blocking the substrate-binding site of the enzyme β-hydroxy-β-methylglutaryl-coenzyme A (HMG-CoA) reductase, which catalyzes the rate-limiting step in cholesterol biosynthesis. Such drug effect is known as

(A) addition.
(B) synergism.
(C) noncompetitive antagonism.
(D) potentiation.
(E) competitive antagonism.

3. A 70-year-old man had prolonged bleeding during an elective knee surgery. Subsequently, the patient admitted to the surgeon that he had been self-administering 81 mg aspirin daily. The consultant pharmacist explained to the patient that, although aspirin has a short plasma half-life, it can irreversibly inhibit platelet function by acetylating the nonsubstrate-binding site of the platelet cyclooxygenase, resulting in prolonged effect on platelet aggregation. This drug effect is known as

(A) potentiation.
(B) competitive antagonism.
(C) synergism.
(D) addition.
(E) noncompetitive antagonism.

4. A 65-year-old woman with intractable pain secondary to bony metastasis of breast cancer had been receiving escalating doses of morphine sulfate intravenously. At 10 A.M., she was found to be unresponsive, her respiratory rate was 4 breaths per minute, and her pupils were pinpointed. Naloxone (Narcan), a competitive antagonist of the opiate receptor, was given intravenously and repeated once. She gradually became conscious and began to complain of pain unrelieved by morphine given at the previous dose. This is most likely because

(A) naloxone directly aggravates the pain caused by the bony metastasis.
(B) naloxone reduces the E_{max} for morphine.
(C) naloxone reduces the ED_{50} for morphine.
(D) naloxone increases the E_{max} for morphine.
(E) naloxone increases the ED_{50} for morphine.

5. Which of the following statements regarding signal transduction is **incorrect**?

(A) Thyroxine-bound receptors act on DNA and regulate specific transcription of genes.
(B) Cyclic adenosine monophosphate can act as a second messenger.
(C) The level of drug receptors at the cell surface increases with chronic stimulation by receptor agonists.
(D) Binding of ligand to cell surface receptors can lead to synthesis of proteins.
(E) Antacids act by interacting with small ions normally found in the gastrointestinal tract.

6. A pharmacist is consulted about selecting a drug that is relatively safe and effective for treating the patient. He searches the literature and obtains the following data that may help guide his decision. The $TD_{0.1}$ and $ED_{99.9}$ for drug A are 20 mg and 0.4 mg, respectively; whereas the $TD_{0.1}$ and $ED_{99.9}$ for drug B are 15 mg and 0.2 mg, respectively. Which of the following statements is true?

(A) Drug A has a higher $TD_{0.1}$ and thus should be the drug of choice.
(B) Both drugs have the same margin of safety, so more information is needed.
(C) Drug B has a higher margin of safety and thus is preferred to drug A.
(D) Drug A is preferred because it has a greater margin of safety than drug B.
(E) The information obtained is irrelevant.

7. Which of the following statements concerning a drug receptor is true?

(A) It is only found on the plasma membranes of cells.
(B) Its expression is induced only by exogenously added drugs.
(C) It can bind endogenous ligand to produce physiological activity.
(D) It is mostly composed of sugars (polysaccharides).
(E) Receptor desensitization or downregulation have no impact on the therapeutic effect of the drug.

8. Which of the following statements concerning morphine and hydromorphone (Dilaudid) is true?

(A) Hydromorphone is a more effective analgesic because it has a smaller ED_{50} than morphine.
(B) Morphine and hydromorphone are equally potent because they have the same E_{max}.
(C) Morphine has a greater ED_{50} and is thus a less effective analgesic than hydromorphone.
(D) Hydromorphone is a more potent analgesic because it has a greater E_{max} than morphine.
(E) Hydromorphone has a smaller ED_{50} and thus is a more potent analgesic than morphine.

9. A 72-year-old man with hypertension has been taking high-dose propranolol (Inderal) for 20 years. He left home for a week and forgot to bring his medication with him. One day, he was found collapsed on the floor and was brought to the emergency room. His blood pressure was 300/180, heart rate was 180 beats per minute, and retinal hemorrhage was observed. Which of the following best explains this situation?

(A) The β-adrenergic receptors in the cardiac muscles underwent spontaneous mutation and became hyperactive.
(B) Reduction in the chronic antagonism of the β-adrenergic receptor led to downregulation of the β-adrenergic receptor.
(C) The propranolol that he had previously ingested remained in his body and acted as a receptor agonist.
(D) Long-term administration of propranolol results in desensitization of cardiac muscles to endogenous β-adrenergic stimulation.
(E) Reduction in the chronic level of receptor blockade results in supersensitivity to stimulation with endogenous catecholamines.

10. A 42-year-old man with non-small cell lung carcinoma tells his pharmacist that his doctor had prescribed erlotinib (Tarceva) for treating his cancer. The patient asked what erlotinib is and how it works. His pharmacist explains to him that it is a drug that

(A) prevents the binding of growth factors to their receptors.
(B) prevents growth factors from activating their receptors.
(C) boosts the functions of growth factor receptors.
(D) neutralizes a receptor on cancer cells by an antibody mechanism.

11. A 65-year-old woman experienced anginal pain with ST-segment elevation on electrocardiogram (ECG). She was treated with IV heparin, nitroglycerin, and atenolol (Tenormin) for acute myocardial infarction. Then 2 hrs later, when her nurse replaced her Foley bag, she noticed frank blood draining out of the Foley catheter. The physician checked the patient's partial thrombin time, which was > 150 secs. The patient was then administered protamine, which acts by

(A) promoting thrombosis.
(B) reacting with and neutralizing the effect of heparin.
(C) directly inhibiting bleeding.
(D) enhancing secretion of procoagulants.

12. Inverse agonist is a relatively new designation for drug action that a physician asks you about. Your explanation would include the fact that

(A) these agents may have biological function by altering the interaction between the receptor and G protein.
(B) there is no known drug with this type of effect.
(C) these agents can desensitize receptors to agonist stimulation.
(D) the inverse form of these drugs can stimulate physiological response.

13. A 55-year-old man with a history of heart disease was being treated with 20 mg of atorvastatin (Lipitor) but this was not adequate to bring his LDL cholesterol down to acceptable levels. So his physician increased the dose to 40 mg, which resulted in a 30% lowering in LDL. This would be an example of a

(A) quantal dose–response relationship.
(B) population dose–response relationship.
(C) cumulative dose–response relationship.
(D) graded dose–response relationship.

14. All of the following are examples of non–receptor-mediated drug effects **except**

(A) magnesium sulfate for treatment of constipation.
(B) calcium carbonate for relief of heartburn.
(C) halothane for inducing anesthesia.
(D) isopropyl alcohol used for its topical antibacterial activity.
(E) amphotericin B for fungal infections.

15. Which of the following salts will most likely yield an aqueous solution with a pH < 7?

(A) Sodium salicylate
(B) Potassium chloride
(C) Magnesium sulfate
(D) Potassium penicillin
(E) Atropine sulfate

16. All of the following functional groups are weak bases **except**

(A) aromatic amines.
(B) sulfonamide.
(C) tertiary amines.
(D) imines.

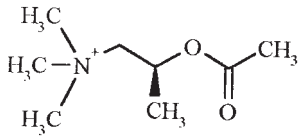
17. The dissociation constant of a drug at its receptor is most closely related to

(A) the maximal response produced by the drug.
(B) the number of spare receptors available.
(C) the affinity of the drug for the receptor.
(D) the total number of receptors available to the drug.
(E) allosterism.

18. All of the following statements about a structurally specific agonist are true **except**:

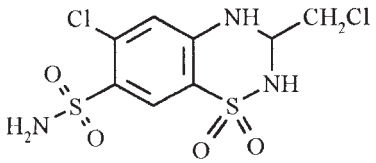
(A) Activity is determined more by its chemical structure than by its physical properties.
(B) The entire molecule is involved in binding to a specific endogenous receptor.
(C) The drug cannot act unless it is first bound to a receptor.
(D) A minor structural change in a pharmacophore can produce a loss in activity.
(E) The higher the affinity between the drug and its receptor, the greater the biological response.

19. The dextro (d) form of β-methacholine (structure shown) is approximately 500 times more active than the levo (l) enantiomer. The observed difference in pharmacological activity between the two isomers is most likely the result of differences in



(A) receptor selectivity.
(B) dissolution.
(C) distribution.
(D) interatomic distance between pharmacophore groups.
(E) solubility.

20. The compound shown in the figure can be classified as a(n)

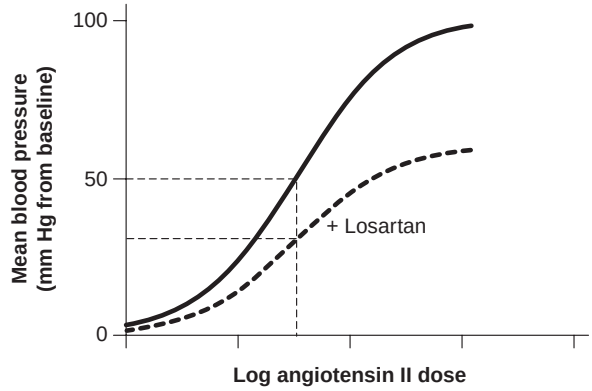


(A) acid.
(B) base.
(C) organic salt.
(D) organic base.
(E) inorganic salt.

21. Which of the following acids has the highest degree of ionization in an aqueous solution?

(A) Aspirin; $pK_a = 3.5$
(B) Indomethacin; $pK_a = 4.5$
(C) Warfarin; $pK_a = 5.1$
(D) Ibuprofen; $pK_a = 5.2$
(E) Phenobarbital; $pK_a = 7.4$

22. The *solid line* on the graph in the following figure shows the change in mean blood pressure (from baseline of 90 mm Hg) with increasing bolus doses of angiotensin II in an experimental animal model. The *dashed line* is the response to the same doses of angiotensin II in the animal 2 hrs after an intravenous administration of 10 mg/kg of losartan, an antagonist of the angiotensin receptor. Based on the responses before and after the angiotensin antagonist, which of the following statements would most likely be true?

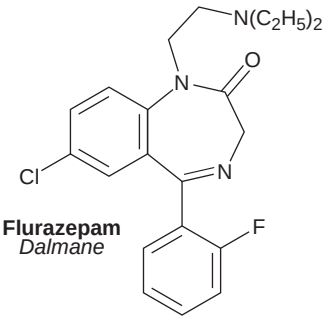


(A) Angiotensin II is a partial agonist.
(B) Losartan may interact irreversibly with the angiotensin receptor.
(C) Losartan is a partial agonist.
(D) Angiotensin II may be an inverse agonist.
(E) Angiotensin and losartan are probably working at different sites in the animal.

23. The structure–activity relationship of a drug can be altered by all of the following parameters **except**

(A) stereochemistry.
(B) specific functional groups.
(C) bioisosteric substitution.
(D) *cis–trans* conformation.
(E) the salt form of the drug.

24. Flurazepam has pK_a of 8.2. What percentage of flurazepam will be ionized at a urine pH of 5.2?



Flurazepam
Dalmane

(A) 0.1%
(B) 1%
(C) 50%
(D) 99%
(E) 99.9%

25. Which of the following isomers can only be distinguished in a chiral environment or by measuring the direction of rotation of plane-polarized light in a polarimeter?

(A) geometric isomers
(B) enantiomers
(C) diastereomers
(D) bioisosteres

26. The organic functional groups responsible for a particular pharmacological activity are called a(n)

(A) bioisostere.
(B) eutomer.
(C) epimer.
(D) pharmacophore.
(E) stereochemistry.

27. All of the following are basic functional groups **except**

(A) guanidine.
(B) primary amine.
(C) amide.
(D) amidine.
(E) tertiary amine.

28. The partition coefficient (P) of a drug is best described as

(A) the water solubility of a drug at a specific pH.
(B) the presence of nonionizable functional groups that make a drug lipid soluble.
(C) the ratio of drug solubility in a lipophilic solvent to solubility in an aqueous solvent.
(D) the presence of ionizable functional groups that make a drug water soluble.
(E) the characterization of a drug as an acid or a base.

29. An inorganic salt of imide containing drug can be made by the addition of which of the following?

(A) NaOH
(B) H_2SO_4
(C) HCl
(D) HNO_3
(E) HBr

Directions for questions 30–34: The questions and incomplete statements in this section can be correctly answered or completed by **one or more** of the suggested answers. Choose the answer, A–E.

A if **I only** is correct
B if **III only** is correct
C if **I and II** are correct
D if **II and III** are correct
E if **I, II, and III** are correct

30. Which of the following statements may be true of drugs that are enzyme inhibitors?

I. They may be destroyed by the enzyme/receptor.
II. They can bind to a site different from that of the substrate.
III. They can form covalent bonds with their receptors.

31. Examples of strong electrolytes (i.e., completely dissociated in an aqueous solution) include

I. acetic acid.
II. pentobarbital sodium.
III. diphenhydramine hydrochloride.

32. Precipitation may occur when mixing aqueous solutions of meperidine hydrochloride with which of the following solutions?

I. Sodium bicarbonate injection
II. Atropine sulfate injection
III. Sodium chloride injection

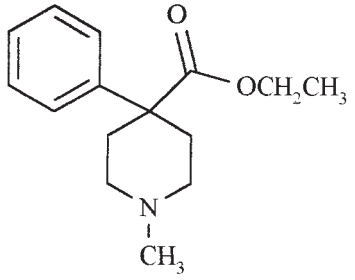
33. Drugs classified as synthetic include which of the following?

I. epinephrine
II. morphine
III. fondaparinux

34. The excretion of a weakly acidic drug is generally more rapid in alkaline urine than in acidic urine. This process occurs because

I. a weak acid in alkaline media will exist primarily in its ionized form, which cannot be reabsorbed easily.
II. a weak acid in alkaline media will exist in its lipophilic form, which cannot be reabsorbed easily.
III. all drugs are excreted more rapidly in an alkaline urine.

Questions 35–37: Refer to the drug meperidine (Demerol; structure shown).



35. Functional groups present in the molecule shown include

I. an ester.
II. a tertiary amine.
III. a carboxylic acid.

36. Meperidine is classified as a

I. weak acid.
II. salt.
III. weak base.

37. Assuming that meperidine is absorbed after oral administration and that a large percentage of the dose is excreted unchanged, the effect of alkalinization of the urine will increase its

I. duration of action.
II. rate of excretion.
III. ionization in the glomerular filtrate.

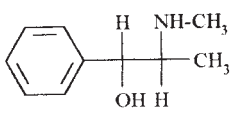
38. Which of the following statements regarding digoxin (Lanoxin) would be true?

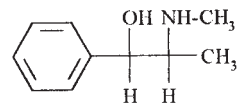
I. It is a glycoside.
II. It is a naturally occurring compound.
III. It mimics the actions of an endogenous hormone.

Directions for questions 39–43: The relationship of each pair of structures shown in this section is most closely associated with **one** of the following terms. The terms may be used more than once or not at all.
Choose the **best** answer, **A–E**.

(A) Geometric isomers
(B) Enantiomers
(C) Diastereomers
(D) Bioisosteres
(E) Conformational isomers

39.





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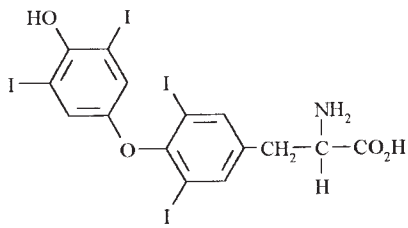

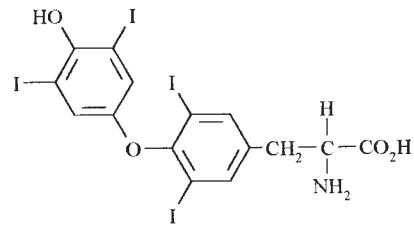

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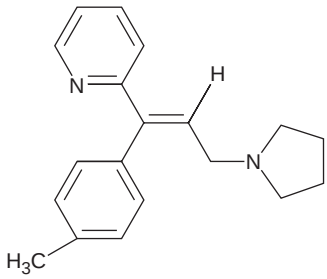

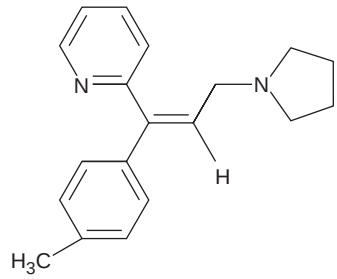

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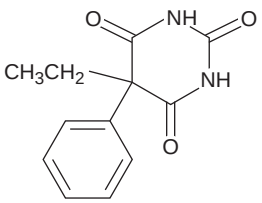

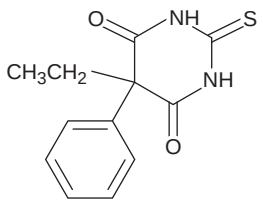

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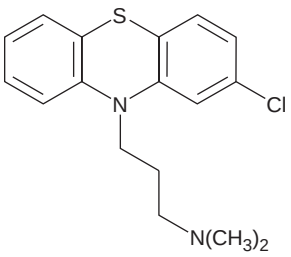

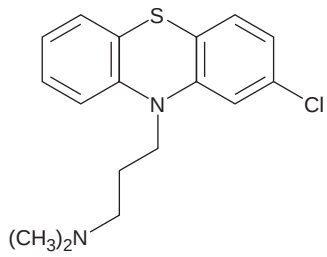

Answers and Explanations

1. **The answer is A** *[see VII.D.1]*.
The receptor would be a specific entity of the cell that drugs interact with to modify cell behavior. Although stomach acid is neutralized by antacids, it is not considered a specific receptor.

2. **The answer is E** *[see III.D.1]*.
Lovastatin reversibly binds to the substrate-binding site of the enzyme HMG-CoA reductase, which catalyzes the rate-limiting step in the synthesis of cholesterol, thus lowering the cholesterol level. Therefore, lovastatin inhibits the enzyme by competitive antagonism.

3. **The answer is E** *[see III.D.2]*.
Aspirin can covalently modify the platelet cyclooxygenase through acetylation of the enzyme other than the substrate-binding site, causing irreversible inhibition of platelet aggregation. Therefore, aspirin inhibits platelet function by noncompetitive antagonism of cyclooxygenase.

4. **The answer is E** *[see III.C.1]*.
Naloxone is a competitive antagonist of opiate receptor. If one compares the log dose–response curve of both morphine and naloxone to that of morphine alone, the morphine–naloxone curve is shifted to the right. As a result, the ED_{50} for morphine is increased. This means that a larger than previous dose of morphine is required for achieving the same analgesic effect.

5. **The answer is C** *[see III.E.2]*.
The level of drug receptors at the cell surface usually decreases when the target cells are chronically stimulated by receptor agonists. Downregulation of receptors may be a protective mechanism that can prevent the target cells from being overstimulated.

6. **The answer is C** *[see IV.C]*.
The margin of safety of the two drugs can be helpful in guiding selection of a drug. Margin of safety is the ratio of $TD_{0.1}$ to $ED_{99.9}$. Thus, the margin of safety for drug A is 20 mg ÷ 0.4 mg, or 50, whereas the margin of safety for drug B is 15 mg ÷ 0.2 mg, or 75. Because drug B has a greater margin of safety than drug A, drug B is relatively safe at the dosage given to produce the desired effect.

7. **The answer is C** *[see II.A; III.C; III.E.1–2]*.
A drug receptor, such as muscarinic cholinergic receptor that can bind atropine, normally binds endogenous acetylcholine to produce the physiological responses controlled by the parasympathetic autonomic nervous system. Receptors may be found on plasma membranes, cytoplasm, or nuclei of cells and are primarily proteinaceous in nature, although they can have sugar or lipid modifications. Receptor downregulation may lead to the phenomenon of tachyphylaxis.

8. **The answer is E** *[see III.B.1]*.
The efficacy of a drug is determined by its E_{max}, whereas its potency is measured by the ED_{50}. Hydromorphone has a smaller ED_{50} and thus is a more potent analgesic than morphine. Hydromorphone and morphine are both agonists for opiate receptors, and they have the same analgesic efficacy (i.e., they have the same E_{max}) if sufficient amounts of both drugs are used.

9. **The answer is E** *[see III.E.3]*.
A chronic level of blocking the β-adrenergic receptors by propranolol results in upregulation of the receptor level. When the patient ceased taking the drug, the cardiac muscles became supersensitive to stimulation with endogenous catecholamines. This resulted in the hypertensive crisis that caused cerebral hemorrhage and loss of consciousness.

10. **The answer is B** *[see III.C.4]*.
Erlotinib is a small molecule that inhibits the tyrosine kinase domain of the epidermal growth factor (EGF) receptor on cancer cells.

11. **The answer is B** *[see VII.D.1]*.
Protamine is a chemical antagonist of heparin that acts via an acid–base interaction.

12. **The answer is A** *[see III.C]*.
Inverse agonists stabilize the form of the receptor that is not bound to G proteins and are not agonists in the classical sense. This uncoupling of receptor and G protein may reduce basal cellular signaling even in the absence of agonists. β-Receptor antagonists are thought to have this type of activity apart from preventing the actions of catecholamines.

13. **The answer is D** *[see IV.B]*.
Increasing doses of a drug usually produces greater responses and this is described as a graded response. This would be true in an individual or a population of patients.

14. **The answer is C** *[see VII]*.
All the choices have a nonreceptor mechanism for producing their effects except for halothane that activates inhibitory receptors on neurons.

15. **The answer is E** *[see VI.B.6]*.
The solution must contain an acidic substance to have a pH $<$ 7. Atropine sulfate is a salt of a weak base and a strong acid; therefore, its aqueous solution is acidic. Sodium salicylate and potassium penicillin are both salts of strong bases and weak acids; therefore, their aqueous solutions are alkaline. Magnesium sulfate and potassium chloride are salts of strong bases and strong acids; therefore, their aqueous solutions are neutral.

16. **The answer is B** *[see VI.B.3–4; Table 58-2; Table 58-3]*.
All these groups would accept a proton under physiological conditions except the sulfonamide, which would donate a proton instead.

17. **The answer is C** *[see III.A]*.
The dissociation constant of a drug is the concentration at which half the available receptors are bound and the inverse of this value is the affinity of the drug–receptor interaction.

18. **The answer is B** *[see V; VI]*.
The binding of a drug to its receptor usually involves only specific functional groups. These groups make up what is known as the pharmacophore of the drug molecule. Although the entire drug molecule is present at the receptor site, only a portion of it, the pharmacophore, is required for a biological response. The affinity of drug–receptor interaction does not predict whether the drug behaves as an agonist (having biological activity) or an antagonist; in fact, antagonists often have higher affinities for the receptor than agonists.

19. **The answer is A** *[see V.E.1]*.
The term *enantiomer and the d* and *l* indicate that the β-methacholine has a chiral center and exhibits optical isomerism. Because the optical isomers have different orientations in space, one orientation will give a better fit than the other and will most likely have greater biological activity than the other. Dissolution, distribution, interatomic distances, and solubility are all related to the physical and chemical properties of the two compounds, which are identical because the compounds are enantiomers.

20. **The answer is A** *[see VI.B.3; Table 58-2]*.
The aryl sulfonamide donates a proton to behave as an acid due to the electron-withdrawing action of the aromatic ring.

21. **The answer is A** *[see VI.B.2]*.
The pK_a (the negative log of the acid ionization constant) indicates the relative strength of an acidic drug. The lower the pK_a of an acidic drug, the stronger it is as an acid. A strong acid is defined as one that is completely ionized or dissociated in an aqueous solution; therefore, the stronger the acid, the greater the ionization.

22. **The answer is B** *[see III.C.2]*.
The decrease in the maximal angiotensin II effect (E_{max}) after treatment with losartan would indicate that the number of receptors available to produce drug effect has been reduced. This occurs when antagonist interacts in an irreversible manner with the receptor and leaves only a limited number of receptors through which the agonist can only produce a less than maximal response.

23. The answer is E *[see V.A–E]*.
All of the choices except the salt form of the drug would influence the interaction of the drug with its receptor.

24. The answer is E *[see VI.B.5]*.
Flurazepam (take note of the suffix, which helps classify the compound) is a benzodiazepine and thus a basic compound. Because the pH is less than the pK_a, flurazepam is in an acidic environment and therefore exists primarily in the ionized form. The percentage ionized can be easily calculated by using the rule of nines. The $|pH - pK_a|$ is 3, so the ratio is 99.9%:0.01% in favor of the ionized form.

25. The answer is B *[see V.E.1.a & d]*.
Enantiomers are nonsuperimposable mirror images of each other that have identical physical and chemical properties except for the rotation of plane-polarized light. Enantiomers are distinguishable in a chiral environment. Geometric isomers, diastereomers, and bioisosteres each have unique physical and chemical properties.

26. The answer is D *[see V.B; V.D; V.E.1.c; V.E.2.b]*.
The pharmacophore describes the critical organic functional groups and their spatial relationship within a drug molecule required for a specific pharmacological activity. A bioisostere is a compound containing an atom or group of atoms that is spatially and electronically similar to another molecule that produces a similar biological activity. A eutomer is one of a pair of enantiomers that has the desired pharmacological activity. The other isomer is the distomer that may not have pharmacological activity or may cause adverse effects. Epimers are a pair of compounds that have exactly the same stereochemistry in all positions except one.

27. The answer is C *[see VI.B.4; Table 58-1; Table 58-3]*.
Primary and tertiary amines are basic because they have a free pair of electrons that can accept a proton. The quaternary amines are neutral because there are no free electrons available to accept a proton. Guanidines and amidines also have free electrons to accept a proton and therefore they are basic functional groups. Amides are neutral compounds although they appear to have a free pair of electrons like the amines, but the difference is that the electrons on the amide nitrogen are in resonance with the double bond on the carbonyl, making them unavailable to accept a proton.

28. The answer is C *[see VI.A.1]*.
The partition coefficient is defined as the ratio of the solubility of an agent in an organic lipophilic solvent (i.e., *n*-octanol) to its solubility in an aqueous buffer. The functional groups present, either ionizable or nonionizable, influence the partition coefficient.

29. The answer is A *[see Table 58-2; VI.B.3.a, 4.a, & 6.a]*.
The imide is a weak acid, so adding a strong base like sodium hydroxide (NaOH) or potassium hydroxide (KOH) will produce an inorganic salt. All the other choices (i.e., sulfuric acid, hydrochloric acid, nitric acid, and hydrobromic acid) are strong acids and would not produce a salt upon addition to the weak acid imide.

30. The answer is E (I, II, and III) *[see III.D]*.
Suicide inhibitors are drugs that are metabolized or destroyed in the process of inhibiting enzymatic activity, whereas allosteric inhibitors target a site distinct from that for the substrate. Some drugs interact irreversibly with their enzyme target due to covalent bonding.

31. The answer is D (II, III) *[see VI.B.6]*.
Almost all salts (with very few exceptions) are strong electrolytes, and the terminology *pentobarbital sodium* and *diphenhydramine hydrochloride* indicates that each compound is salt. Acetic acid is a weak acid; therefore, it is a weak electrolyte.

32. The answer is A (I) *[see VI.B]*.
When meperidine hydrochloride solution is mixed with the alkaline solution of sodium bicarbonate, a neutralization reaction occurs with the possible precipitation of the water-insoluble free base meperidine. A neutralization reaction occurs when acidic solutions are mixed with basic solutions, or conversely. No reaction, in terms of acid–base, occurs when solutions are mixed with other acidic or neutral solutions or when basic solutions are mixed with other basic or neutral solutions. There should be no reaction, then, when the meperidine hydrochloride solution, which is acidic, is mixed with the acidic solution of atropine sulfate or the neutral solution of sodium chloride.

33. The answer is B (III) *[see VIII.B.3]*.
Both epinephrine and morphine are naturally occurring, whereas fondaparinux is a synthetic derivative of heparin.

34. The answer is A (I) *[see VI.B]*.
A weakly acidic drug will be more ionized in an alkaline urine; therefore, it will be more polar and thus more soluble in the aqueous urine. It would also be less liposoluble, less likely to undergo tubular reabsorption, and thus more likely to be excreted.

35. The answer is C (I, II) *[see VI.B; Table 58-1]*.
The molecule contains a basic nitrogen, which is bonded to three carbon atoms (i.e., a tertiary amine), and an ethyl carboxylate, which is an ester group. An ester is the product of the reaction of an alcohol with a carboxylic acid that forms an alkyl carboxylate. There is no free carboxylic acid present. However, if this molecule is subjected to hydrolysis, it forms a carboxylic acid and ethyl alcohol.

36. The answer is B (III) *[see VI.B; Table 58-3]***.**
Because meperidine contains a tertiary amine, it is classified as a base; because it is an organic base, it is considered weak. The nitrogen is not protonated. It is not ionic and therefore is not a salt.

37. The answer is A (I) *[see VI.B]***.**
Alkalinization of the urine decreases the ionization of meperidine, making it more liposoluble and thus more likely to undergo reabsorption in the kidney tubule. This results in a decreased rate of excretion and an increased duration of action. The six-member, nonaromatic ring is a piperidine ring that is substituted at the 4-position (nitrogen is position 1) with a phenyl ring. The compound does not contain a piperazine ring or a propyl group.

38. The answer is C (I, II) *[see VIII.A]***.**
The cardiac glycoside digoxin occurs naturally in foxglove and strophanthus plants but it does not substitute or mimic the actions of endogenous hormones.

39. The answer is C *[see V.E.2]***.**
These molecules are isomers that have two asymmetric carbon atoms. They are not superimposable and are not mirror images; therefore, they are known as diastereomers.

40. The answer is B *[see V.E.1]***.**
These molecules are isomers that have one asymmetric carbon atom. They are nonsuperimposable mirror images; therefore, they are enantiomers.

41. The answer is A *[see V.E.2.c]***.**
These molecules have different spatial arrangements; however, these molecules do not have an asymmetric center. The presence of the double bond, which restricts the rotation of the groups on each carbon atom involved in the double bond, characterizes this type of isomerism as geometric.

42. The answer is D *[see V.D]***.**
These molecules are neither isomers nor the same compound because one contains three oxygens, whereas the other contains two oxygens and a sulfur. Because oxygen and sulfur are in the same periodic family, they are isosteric and are known as bioisosteres.

43. The answer is E *[see V.E.3]***.**
These structures are actually two views of the same compound. Rotation around the side chain single bonds connecting the ring nitrogen to the tertiary nitrogen produces these two different conformations. Thus, these are conformational isomers.

Study Questions

Directions for questions 1–7: Each of the questions, statements, or incomplete statements in this section can be correctly answered or completed by one of the suggested answers or phrases. Choose the best answer.

1. Which of the following emissions from the decay of radionuclides is most commonly used in nuclear medicine diagnostic imaging?

(A) x-ray
(B) β
(C) α
(D) γ
(E) positron

2. Which of the following radionuclides is most commonly used in nuclear pharmacy practice?

(A) gallium-67 (^{67}Ga)
(B) thallium-201 (^{201}Tl)
(C) technetium-99m (^{99m}Tc)
(D) iodine-123 (^{123}I)
(E) xenon-133 (^{133}Xe)

3. Which of the following radionuclides is produced using a generator?

(A) technetium-99m (^{99m}Tc)
(B) thallium-201 (^{201}Tl)
(C) gallium-67 (^{67}Ga)
(D) xenon-133 (^{133}Xe)
(E) iodine-123 (^{123}I)

4. Which of the following radiopharmaceuticals can be used in skeletal imaging?

(A) ^{99m}Tc albumin aggregated
(B) ^{99m}Tc medronate disodium
(C) xenon-133 gas *USP*
(D) thallous chloride (^{201}Tl) *USP*
(E) ^{99m}Tc disofenin

5. Which of the following radiopharmaceuticals is used in the diagnosis of acute cholecystitis?

(A) ^{99m}Tc sulfur colloid
(B) ^{99m}Tc medronate disodium
(C) ^{99m}Tc albumin
(D) ^{99m}Tc exametazime
(E) ^{99m}Tc disofenin

6. Which of the following cyclotron-produced radiopharmaceuticals is used for assessing regional myocardial perfusion as part of an exercise stress test?

(A) thallous chloride ^{201}Tl *USP*
(B) sodium iodide ^{123}I
(C) gallium citrate ^{67}Ga *USP*
(D) ^{111}In pentetate
(E) ^{57}Co cyanocobalamin

7. Glomerular filtration and the urinary collection system can best be evaluated using which of the following agents?

(A) ^{99m}Tc sulfur colloid
(B) ^{99m}Tc albumin
(C) ^{99m}Tc sestamibi
(D) ^{99m}Tc disofenin
(E) ^{99m}Tc pentetate

Directions for questions 8–11: The questions and incomplete statements in this section can be correctly answered or completed by one or more of the suggested answers. Choose the answer, **A–E**.

A if **I only** is correct
B if **III only** is correct
C if **I** and **II** are correct
D if **II** and **III** are correct
E if **I**, **II**, and **III** are correct

8. The definition of the optimal radiopharmaceutical includes which of the following attributes?

I. short half-life
II. photon with a 100–300 keV energy
III. rapid localization in target tissue and quick clearance from nontarget tissue

9. Which of the following statements are true for sodium pertechnetate technetium-99m (^{99m}Tc) *USP*?

I. It is used to radiolabel all other ^{99m}Tc radiopharmaceuticals.
II. The molybdenum-99 (^{99}Mo) breakthrough limit is < 0.15 μCi ^{99}Mo/mCi ^{99m}Tc (< 0.15 kBq/MBq).
III. It has a physical half-life of 16 hrs.

10. Which of the following organs can be imaged with technetium-99m (^{99m}Tc) sulfur colloid?

I. liver
II. spleen
III. bone marrow

11. Which of the following radiopharmaceuticals may be used to image the thyroid gland?

I. sodium iodide ^{131}I
II. sodium pertechnetate ^{99m}Tc *USP*
III. sodium iodide ^{123}I

Directions for questions 12–16: Each of the following mechanisms of localization is most closely related to one of the following radiopharmaceuticals. The mechanisms may be used more than once or not at all. Choose the best answer, **A–E**.

A metabolic trapping
B phagocytosis
C capillary blockade
D active transport
E passive diffusion

12. thallous chloride ^{201}Tl *USP*

13. ^{99m}Tc albumin aggregated *USP*

14. ^{99m}Tc sulfur colloid

15. ^{99m}Tc exametazime

16. ^{18}F fludeoxyglucose

Answers and Explanations

1. The answer is D *[see I.B.3.b]*.
Current camera technology most efficiently detects γ radiation. α and β emissions are not useful in nuclear medicine imaging because of their harmful particulate emissions and low tissue penetration. Although x-ray emissions can be used as in the case of the mercury daughter of the thallous chloride ^{201}Tl parent, they are not efficiently detected. Annihilation radiation associated with positron decay can be imaged, but this technology is currently limited to a few specialized centers.

2. The answer is C *[see II.A.1]*.
^{99m}Tc has become the radionuclide of choice in current nuclear pharmacy practice since its introduction in the mid-1960s. ^{99m}Tc fulfills all of the requirements of the optimal radiopharmaceutical, with its physical half-life of 6 hrs, 140 keV γ energy emission, ready availability, cost, and ability to be radiolabeled to various biologically active compounds.

3. The answer is A *[see II.A.1.a]*.
^{99m}Tc is obtained via commercially supplied, sterile, pyrogen-free generator systems. A generator is a device used to separate a short half-life radionuclide from the longer lived parent nuclide, while retaining the parent to produce more of the daughter nuclide. In this way, short–half-life nuclides can be made available on a continuous basis at great distances from the sites of generator production.

4. The answer is B *[see IV.A.2]*.
The ^{99m}Tc-diphosphonate compounds are the most popular bone-imaging agents currently used in nuclear medicine imaging. They are rapidly taken up by skeletal bone; 50% of the administered dose is adsorbed onto bone hydroxyapatite and the remainder is excreted by the kidneys. The imaging advantages of the ^{99m}Tc, coupled with the sensitivity of bone agent localization in skeletal bone hydroxyapatite, allow for detection of bone pathology before evidence of pathology can be shown by conventional x-ray.

5. The answer is E *[see VI.C.1–2]*.
^{99m}Tc-disofenin is an iminodiacetic acid derivative, which is useful for hepatobiliary imaging due to its ability to be selectively cleared by a carrier-mediated hepatocyte pathway. Lack of gallbladder visualization is an abnormal finding suggestive of acute cholecystitis.

6. The answer is A *[see III.A.1]*.
Regional uptake of thallous chloride ^{201}Tl *USP* is proportional to myocardial blood supply. The injection of ^{201}Tl in concert with a treadmill exercise stress test determines myocardial perfusion at maximum cardiac output when cardiac demand outstrips supply and the distribution of ^{201}Tl is less after affected by collateral blood supply within the myocardium. Regions that do not take up ^{201}Tl are interpreted as areas of infarct or ischemia. If these focal areas of decreased uptake subsequently fill in with redistributed ^{201}Tl, they are interpreted to be areas of ischemia, in contrast with areas of infarct, which remain as diminished areas of activity.

7. **The answer is E** *[see VII.B.1]*.
^{99m}Tc-pentetate is cleared through glomerular filtration in the same manner as inulin and can be used to determine the GFR as well as in the evaluation of obstruction of vascular supply and renal morphology.

8. **The answer is E (I, II, III)** *[see I.C]*.
The optimal radiopharmaceutical has a half-life short enough to minimize radiation exposure to the patient yet long enough to allow for collection of imaging information. It should incorporate a γ-emitting radionuclide, which decays with the emission of a photon energy between 100 and 300 keV, which is efficiently detected with current instrumentation. The radiopharmaceutical should localize rapidly in the organ system of interest and be metabolized, excreted, or both from the nontarget tissues to maximize contrast and minimize radiation-absorbed dose.

9. **The answer is C (I, II)** *[see II.A–B]*.
Sodium pertechnetate ^{99m}Tc *USP* decays by isomeric transition and has a physical half-life of 6 hrs. The emission of a γ photon has the energy of 140 keV.

10. **The answer is E (I, II, III)** *[see VI.B.1]*.
^{99m}Tc-sulfur colloid localizes within the reticuloendothelial system, 80% to 90% of the dose is phagocytized by the Kupffer cells of the liver, 5% to 10% by the spleen, and the balance by the bone marrow.

11. **The answer is E (I, II, III)** *[see VIII.B]*.
Although all of the listed agents accumulate in the thyroid gland, only sodium iodide ^{123}I possesses ideal imaging characteristics and organification into thyroid hormone. Although the imaging properties of sodium pertechnetate ^{99m}Tc *USP* are good, the pertechnetate ion is trapped only by the thyroid and not organified, thus limiting the information provided by the image.

12. **The answer is D** *[see III.A.1]*.
Thallous chloride ^{201}Tl *USP* is a monovalent cation with distribution analogous to potassium ion (K^+). Myocardial uptake is by active transport via the Na^+/K^+-ATPase pump.

13. **The answer is C** *[see V.A.1]*.
After IV administration of ^{99m}Tc-albumin aggregated *USP*, 80% of the radiolabeled albumin particles become trapped by capillary blockade in the pulmonary circulation.

14. **The answer is B** *[see VI.B.1]*.
After the administration of ^{99m}Tc-sulfur colloid, 80% to 90% of the dose is phagocytized by the Kupffer cells of the liver, 5% to 10% by the spleen, and the balance by the bone marrow.

15. **The answer is E** *[see IX.A.1]*.
^{99m}Tc-exametazime is used for evaluating brain perfusion. It possesses a lipophilic partition coefficient that is sufficient to diffuse passively across the BBB almost completely within one pass of the cerebral circulation, and that is sufficiently retained to permit data collection.

16. **The answer is A** *[see IX.B.1]*.
^{18}F-fludeoxyglucose is used in evaluating cerebral function by mapping the distribution of cerebral glucose metabolism. As an analog of glucose, ^{18}F-fludeoxyglucose is transported into the brain by carrier-mediated transport mechanisms responsible for transporting glucose across the BBB. Because the presence of the fluorine atom in the position 2 prevents metabolism beyond the phosphorylation step, ^{18}F-fludeoxyglucose becomes metabolically trapped within the brain.

Study Questions

Choose the best answer for questions 1-5.

1. In the provision and billing of MTM services for a Medicare Part D patient, the pharmacist must complete:

I. a comprehensive medication review.
II. a personal medication record.
III. a medication action plan.

(A) **I** only
(B) **III** only
(C) **I** and **II** only
(D) **II** and **III** only
(E) **I**, **II**, and **III**

2. Mrs. Smith has recently been diagnosed with hypertension and hypercholesterolemia. She presents to your pharmacy today with new prescriptions for hydrochlorothiazide and simvastatin. When she picks up her medications, she asks to speak with the pharmacist. She asks several questions about her new regimen and inquires about how she can check her own blood pressure. According to the transtheoretical model for behavioral change, what stage is Mrs. Smith?

(A) Precontemplation
(B) Contemplation
(C) Preparation
(D) Action
(E) Maintenance

3. Which of the following are forms of active listening interview techniques?

I. Restoration
II. Facilitation
III. Silence

(A) **I** only
(B) **I** and **II** only
(C) **I** and **III** only
(D) **II** and **III** only
(E) **I**, **II**, and **III**

4. The documentation of your recommendation for the patient to have a follow-up A1c obtained in 3 months should be noted in which section of a SOAP note?

(A) Subjective
(B) Objective
(C) Observations
(D) Assessment
(E) Plan

5. Pharmacists who bill Medicare for MTM services must have a:

I. pharmacist license.
II. national provider identifier number.
III. medication appropriateness index number.

(A) **I** only
(B) **I** and **II** only
(C) **I** and **III** only
(D) **II** and **III** only
(E) **I**, **II**, and **III** only

Answers and Explanations

1. The answer is E *[see III.G; Table 60-5]***.**
The provision of MTM for Medicare Part D must include the five core components of MTM. A comprehensive medication review, personal medication record for the patient, and a patient-centric medication action plan represent three of the five core components. The remaining two are intervention and referral and documentation and follow-up.

2. The answer is C *[see III.A.4; Table 60-1]***.**
The patient is preparing to take action toward changing her personal care of her hypertension and hypercholesterolemia by seeking medical attention, picking up her new prescriptions, asking for information from the pharmacist, and showing interest in wanting to learn to self-monitor. This is the stage preparation instead of action because the patient has not yet implemented the changes in her personal care.

3. **The answer is D** *[see III.B.2.k; Table 60-2]*.
Facilitation and silence are well-recognized methods of utilizing active listening within a patient interview. Restoration is not one of the active listening skills. The remaining active listening skills are interpretation, reflection, clarification, empathy, and confrontation.

4. **The answer is E** *[see III.D.4; Table 60-3]*.
When using a SOAP format for documentation, all recommendations, including follow-up lab work, should be noted in the plan (P) section of the SOAP note. The sections of a SOAP note are subjective, objective, assessment, and plan. Observation is not a section.

5. **The answer is B** *[see III.F.2]*.
Since 2006 under the Medicare Modernization Act of 2003, licensed pharmacists can bill for MTMS provided to patients. Pharmacists need a national provider identifier number (NPI#).

Study Questions

Directions: Each of the questions, statements, or incomplete statements can be correctly answered or completed by **one** of the suggested answers or phrases. Choose the **best** answer.

1. The phrase "one which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function," describes

(A) a side effect.
(B) an adverse drug reaction.
(C) an adverse drug event.
(D) a medication error.
(E) prescribing error.

2. Type A reactions are characterized by which of the following?

(A) Idiosyncratic reactions
(B) A function of patient susceptibility
(C) Caused by drug–drug interactions
(D) Permanent medical complication
(E) Death

3. The MedWatch form is *not* the appropriate form to report which of the following events?

(A) A vaccine event described in the Vaccine Adverse Event Reporting System (VAERS) "Reportable Events Table"
(B) A suspected counterfeit drug
(C) A malfunctioning ventilator
(D) A drug that is contained in a package with unclear labeling
(E) An adverse reaction resulting in patient death

4. Type B adverse drug reactions are

(A) generally serious and can be life threatening.
(B) a result of the known pharmacology of the drug.
(C) usually predictable.
(D) responsible for the majority of ADRs.
(E) usually dose dependent.

5. HIPPA rules require the following before reports are submitted to the FDA.
   (A) Written permission of the patient
   (B) Written permission of the patient's attending physician
   (C) Written permission of the patient and the patient's attending physician
   (D) Written permission from the medical records department
   (E) Reports can be submitted without authorization of the patient or health care providers

6. Reasons for close scrutiny of previously unreported ADRs in newly marketed drugs are based on all of the following concerns except:
   (A) Premarketing clinical trials may have a small number of subjects.
   (B) Groups based on age, race, and ethnicity may not be represented in the same proportion in study groups as in the general population.
   (C) ADRs that have been reported in premarketing trials are not included as part of the FDA surveillance of events in the voluntary reporting system.
   (D) Trials are relatively short in duration.
   (E) Trials may not effectively test medications that will be chronically administered agents.

Answers and Explanations

1. **The answer is B** *[see II.C]***.**
   This is the definition from the WHO.

2. **The answer is C** *[see III.A.2]***.**
   Type A reactions can be caused by drug–drug interactions. Idiosyncratic reactions and reactions caused by patient susceptibility are generally in the classification of type B reactions.

3. **The answer is A** *[see VI.A.1]***.**
   All the others are reportable on the MedWatch form. The National Childhood Vaccine Injury Act requires the use of a VAERS form to report vaccine-related injuries.

4. **The answer is A** *[see III.A; III.B]***.**
   The other answers describe type A reactions.

5. **The answer is E** *[see VI.B.3]***.**
   The Health Insurance Portability and Accountability Act (HIPAA) Rule permits covered entities to disclose protected health information without authorization for specified public health purposes.

6. **The correct answer is C** *[see VI.B.c.1]***.**

E. The Sorry Works Coalition (http://www.sorryworks.net) is an organization of various individuals (health care professionals, lawyers, insurance executives, concerned citizens, etc.) who promote the necessity of **disclosure and apology** following error. The coalition provides training and education programs.

F. The Institute for Safe Medication Practices (http://www.ismp.org) focuses its efforts on **medication error prevention and patient safety**. The ISMP publishes four different safety newsletters, provides consulting services, and presents numerous educational programs, services, safety recommendations, and activities.

G. The National Patient Safety Foundation (http://www.npsf.org) represents **stakeholders from a broad array of disciplines**, including patients and families. The NPSF mission is focused on **improving patient safety**. It provides numerous resources, publications, and activities directed at improving the care of patients.

H. The Institute for Healthcare Improvement (IHI) has created the IHI "Open School" at http://www.ihi.org/offerings/IHIOpenSchool/Pages/default.aspx. Online modules regarding patient safety and quality assurance are available. Additional resources and material are provided. Student chapters of the Open School exist and information is provided on how to initiate these chapters.

Study Questions

Directions: Each of the questions, statements, or incomplete statements can be correctly answered or completed by **one** of the suggested answers or phrases. Choose the **best** answer.

1. A major result in the 2000 Institute of Medicine (IOM) report is that

(A) pharmacists are not blamed for most medical errors.
(B) surgeons make more mistakes than any other health professional.
(C) pharmacists make more mistakes than any other health professional.
(D) there is now more emphasis on error prevention.

2. A pharmacist is presented a prescription for 250 mcg of levothyroxine. Which of the following dosages would be equivalent to that amount?

(A) 2.5 mg
(B) 0.25 g
(C) 0.25 mg
(D) 25 g

3. A prescription is written for warfarin 1.0 mg. The community pharmacist accidentally dispenses 10 mg. The patient develops severe bleeding within 3 days and nearly dies. Which of the following is the most accurate assessment of this prescription?

(A) A trailing zero is present in this prescription and could have contributed to the pharmacist's error.
(B) This is an example of a leading zero, which contributed to the error and the patient tragedy.
(C) Sound-alike medications contributed to this error.
(D) This does not qualify as an error based on the National Coordinating Council for Medication Error Reporting and Prevention (NCCMERP) definition.

4. A hospital pharmacy begins stocking new intravenous mini-bags of a neuromuscular-blocking agent. The packaging is similar to a commonly used intravenous antibiotic. The addition of the new mini-bags was not widely communicated to all personnel. One weekend, several doses of this new product were accidentally dispensed in place of the intended doses of antibiotic. Several patients suffered respiratory arrest and one of the patients eventually died. What would a root cause analysis of this error find?

(A) The only cause of this error was a pharmacist who was not paying attention. The pharmacist should be dismissed.
(B) Poor communication practices is a latent defect in this pharmacy system and significantly contributed to the error.
(C) The pharmacy technicians are to blame for this error, not the pharmacist, because the technicians obtained the mini-bags from stock and placed the labels on the bags. The pharmacist checked only the technician's work. The technician should be dismissed.
(D) This is an example of an extra dose error.

5. What do the following abbreviations MS, MSO_4, and $MgSO_4$ have in common?
   (A) Common abbreviations for morphine sulfate
   (B) Common abbreviations for magnesium sulfate
   (C) Should not be used in the Joint Commission–accredited institutions
   (D) Approved abbreviations in most hospitals

6. A major error in a hospital pharmacy resulted in a total parenteral nutrition solution being mistaken for a cardioplegic solution for coronary bypass surgery. Which of the following is true regarding the root cause analysis that was done at the hospital after the error?
   (A) The primary objective is to find out which pharmacist made the mistake that allowed this to take place.
   (B) The result of the analysis would be the admission that an error had taken place.
   (C) All factors that could have contributed to this error would be identified and analyzed.
   (D) A root cause analysis would be inappropriate in this case.

Answers and Explanations

1. **The correct answer is D** *[see I.A.2]***.**
   The IOM report revealed alarming data on deaths related to medical errors. The report contributed to increased efforts to improve patient safety.

2. **The correct answer is C** *[see III.D]***.**
   Although this may seem to be an elementary question and answer, a wrong dose error such as this could easily lead to a serious injury or death to a patient.

3. **The correct answer is A** *[see IV.A.4]***.**
   Warfarin 1.0 mg is an example of a trailing zero. The Joint Commission has included this in its "do not use" list of abbreviations. However, in the community setting, it is a practice that can still be frequently seen on prescriptions. When a trailing zero is observed, much caution should be exercised in interpreting the prescription.

4. **The correct answer is B** *[see VI.A.2]***.**
   Poor communication was a major contributing factor to this tragic series of errors. The drug was a high-risk drug and had similar packaging as another commonly used drug. These are two major ingredients for the serious error that took place. This does not absolve the technician and pharmacist totally from any blame but emphasizes the significant role that failure of communication played within this pharmacy system. The system was as much or more to blame than any individuals. Firing the individuals does not repair the problem of poor communication in the system but only sets the stage for a similar mistake to occur again.

5. **The correct answer is C** *[see IV.A.6]***.**
   These abbreviations are included in the Joint Commission's "do not use" list. Errors resulting in serious harm have occurred after mix-ups with morphine and magnesium.

6. **The correct answer is C** *[see VI.A.2]***.**
   A root cause analysis is not intended to focus on blame but on all factors that could have been related to this error. Factors might have included training of pharmacist and technicians, the actual drug order, and the label. The contribution of such factors might not be discovered if the focus is on only identifying which pharmacist, technician, or other professional is to blame.

Study Questions

Directions: Each of the numbered items or incomplete statements in this section is followed by answers or by completions of the statement. Select the **one** lettered answer or completion that is **best** in each case.

1. You have been dispensing narcotics to a patient for several months for "back" pain. You are reasonably convinced that the drug is supporting an addiction. You call the physician and she tells you that she is using the narcotic for "back" pain. Select the best answer:

(A) Refuse to refill the narcotic since it is not a "legitimate" medical purpose.
(B) Fill the refill because pain is a "legitimate" medical purpose.
(C) Call the medical board and report the physician.
(D) Suggest OTC ibuprofen.
(E) Give the patient part of the prescription.

2. Which of the following narcotic drugs has been approved by the FDA for use in the treatment of narcotic addiction?

(A) Morphine
(B) Codeine
(C) Methadone
(D) Hydrocodone
(E) None of the above

3. For the U.S. government to place a drug into Schedule III, which of the following findings must be made concerning the drug?

(A) The drug or other substance has a high potential for abuse.
(B) Abuse of the drug or other substance may lead to limited physical dependence or psychological dependence relative to the drugs or other substances in Schedule IV.
(C) The drug or other substance has no currently accepted medical use in treatment in the United States.
(D) Abuse of the drug or other substance may lead to moderate or low physical dependence or high psychological dependence.
(E) There is a lack of accepted safety for use of the drug or other substance under medical supervision.

4. Under the Federal Controlled Substances Act, all of the following items must appear on a controlled substance prescription label *except* the

(A) name, address, and DEA number of the pharmacy.
(B) name of the patient.
(C) name of the prescribing practitioner.
(D) serial number assigned to the prescription.
(E) date of the initial filling of the prescription.

5. Under the Federal Controlled Substances Act, all of the following entities must register with the DEA *except*

(A) prescribers of controlled substances.
(B) pharmacists who dispense controlled substances.
(C) distributors of controlled substances.
(D) importers of controlled substances.
(E) universities conducting instructional activities with controlled substances listed in Schedules II to V.

6. Under the Federal Controlled Substances Act, which of the following statements concerning the emergency dispensing of a Schedule II controlled substance is true?

(A) The practitioner who authorizes the oral prescription must, within 7 days, deliver a written prescription to the dispensing pharmacist.
(B) The quantity prescribed and dispensed must be limited to the amount necessary to adequately treat the patient during the emergency period.
(C) It is not reasonably possible for the practitioner to provide a written prescription to be presented to the person dispensing the controlled substance before the dispensing.
(D) No appropriate alternative treatment is available, including administration of a controlled substance that is not in Schedule II.
(E) All of the above statements are true.

7. Under the Federal Controlled Substances Act, the crime transfer warning, "Caution: Federal law prohibits the transfer of this drug to any person other than the patient for whom it was prescribed," must appear on the prescription container label of all controlled substances *except*

(A) Schedule II controlled substances.
(B) Schedule III controlled substances.
(C) Schedule IV controlled substances.
(D) Schedule V controlled substances.

8. Which of the following statements concerning drug recall classification is true?
   (A) A Class I recall is a situation in which the use of, or exposure to, a violative product is not likely to cause adverse health consequences.
   (B) A Class I recall is a situation in which the use of, or exposure to, a violative product may cause temporary or medically reversible adverse health consequences or in which the probability of serious health consequences is remote.
   (C) A Class I recall is a situation in which there is a reasonable probability that the use of, or exposure to, a violative product will cause serious adverse health consequences or death.
   (D) A Class II recall is a situation in which the use of, or exposure to, a violative product is not likely to cause adverse health consequences.
   (E) A Class III recall is a situation in which there is a reasonable probability that the use of, or exposure to, a violative product will cause serious adverse health consequences or death.

9. Under the Federal Food, Drug, and Cosmetic Act, all of the following statements are considered a misbranding of a drug *except* if
   (A) the labeling is false or misleading in any particular.
   (B) an oral contraceptive is dispensed without the required patient package insert.
   (C) the drug is an imitation of another drug, or if it is offered for sale under the name of another drug.
   (D) the drug consists in whole or in part of any filthy, putrid, or decomposed substance.

10. All of the following oral medications are exempt from child-resistant packaging *except*
   (A) Anhydrous cholestyramine in powder form
   (B) Nitroglycerin preparations in sustained-release form
   (C) cyclically administered oral contraceptives in manufacturers' mnemonic (memory-aid) dispenser packages that rely solely on the activity of one or more progestogen or estrogen substances
   (D) pancrelipase preparations in tablet, capsule, or powder form that contain no other prescription medication

Answers and Explanations

1. **The answer is B** *[see I.I.2]*.
   "Back Pain" is a "legitimate medical purpose" making the prescription valid and the best answer is to fill the order.

2. **The answer is C** *[see VIII; VIII.A; I.I.2.c.(2)]*.
   Methadone is approved by the FDA for use in the treatment of narcotic addiction. Only a properly registered narcotic treatment program may dispense methadone for maintenance or detoxification treatment. Pharmacies that are not registered may only dispense methadone for severe pain.

3. **The answer is D** *[see I.A.3]*.
   To place a drug into Schedule III, the U.S. government must make the following findings concerning the drug: (1) it has a potential for abuse less than the drugs or other substances in Schedules I and II; (2) it has a currently accepted medical use in treatment in the United States; and (3) abuse of the drug may lead to moderate or low physical dependence or high psychological dependence.

4. **The answer is A** *[see I.I.8.c.(1)–(7)]*.
   A pharmacy's DEA number is not required to appear on the medication container label dispensed to the patient.

5. **The answer is B** *[see I.B.2.a–k; I.B.9.d]*.
   Agents and employees of DEA registrants, such as pharmacists, are exempt from registering with the DEA. Pharmacies, not the individual pharmacists, must register with the DEA.

6. **The answer is E** *[see I.I.4.a–b]*.
   Emergency dispensing of an oral Schedule II controlled substance prescription must be done in strict compliance with the law. Before dispensing such a prescription, the pharmacist must make the threshold determination that ALL three factors that define an emergency situation (see I.I.4.a) are present. If any one of the three factors is absent, the prescription is not for an emergency situation, and a written prescription must be presented to the pharmacist.

7. **The answer is D** *[see I.I.8.c.(7)]*.
The federal crime transfer warning label is not required to appear on the prescription container label of Schedule V controlled substances.

8. **The answer is C** *[see II.H.2.a–c]*.
A Class I recall is a situation in which there is a reasonable probability that the use of, or exposure to, a violative product will cause serious adverse health consequences or death.

9. **The answer is D** *[see II.I.1, 2]*.
The Federal Food, Drug, and Cosmetic Act states that a drug is considered adulterated if it consists in whole or in part of any filthy, putrid, or decomposed substance. The terms misbranding and adulteration are often referred to in literature and case law as being the same or similar violations under the law. However, the Act sets forth specific instances of adulteration and specific instances of misbranding.

10. **The answer is B** *[see III.A.1]*.
Only sublingual dosage forms of nitroglycerin are exempt from child-resistant packaging.

2. **Potential adverse effects.** The pharmacist should ensure that patients are aware of the possible adverse effects associated with a medication. Patients should understand the following:
   a. The **frequency** of an adverse effect. This will help patients recognize common adverse effects and not be overly concerned with those that are rare.
   b. The **severity** of an adverse effect. This will help patients focus on those adverse effects that are severe and not those that are inconsequential.
   c. What action should be taken to **manage** or **minimize** the adverse effect. This will help patients deal with possible adverse effects in the appropriate manner.
3. **Proper storage.** The pharmacist should counsel patients on how to store medications properly to ensure stability and potency.
4. **Over-the-counter (OTC) products.** The pharmacist should instruct patients about the use of OTC products that may not be appropriate when taking a prescribed product.

B. Counseling health professionals. Health professionals (i.e., in an institutional setting) may administer medications to patients. In these cases, the pharmacist should ensure that the health professional has sufficient knowledge to administer the product. Information that health professionals would need include the following:

1. The choice of a particular product
2. The proper dosage, dosage regimen, and route of administration
3. The availability of commercially made products
4. Potential adverse effects
5. Drug interactions
6. Physical incompatibilities
7. Safe handling and disposal procedures
8. Nutritional interactions or requirements
9. Drug interference with laboratory tests

V. PATIENT MONITORING.

The provision of pharmaceutical care requires a **pharmaceutical care plan**. Monitoring a patient's need for medication and the effect of the medication on the patient maximizes the effectiveness. Undesired outcomes associated with drug therapy are frequently called **drug therapy problems**.

A. Pharmaceutical care plan. To increase the frequency and benefits of desired outcomes, a pharmaceutical care plan should include the following:

1. **Assessment.** A review of the medical conditions and symptoms to determine the need for medication
2. **Plan.** A decision of an appropriate drug therapy based on the assessment of the patient
3. **Monitoring.** A review of the outcomes of drug therapy (i.e., goals and end points) to determine whether the patient is obtaining the desired outcomes

B. Drug therapy problems are evidence of less-than-optimal drug therapy. Detection requires an assessment of the need for a change in drug therapy. Possible problems include:

1. **Unnecessary drug therapy.** The medication cannot be associated with a medical condition or the presence of a condition in which nondrug therapy is more appropriate.
2. **Wrong drug.** The drug is not indicated for the condition or is not delivering the desired outcomes, or a more effective drug is available.
3. **Dose too low.** Incorrect dose, frequency, administration, or duration of therapy results in an insufficient dose of drug to the patient.
4. **Adverse drug reaction.** An allergic reaction, drug interaction, or an undesirable effect occurs from a medication.
5. **Dose too high.** Incorrect dose, frequency, or duration results in more medication than is required.
6. **Inappropriate adherence.** The patient is not taking the optimal amount of medication owing to cost, administration difficulties, alternative health beliefs, or a lack of understanding of the need for the medication.
7. **Need additional drug therapy.** Owing to an undertreated condition, synergism with concurrent drug therapy or prophylactic therapy is required.

Study Questions

Directions: Each of the questions, statements, or incomplete statements can be correctly answered or completed by **one** of the suggested answers or phrases. Choose the **best** answer.

1. Medication orders differ from prescriptions in which of the following ways? They
   (A) are intended for ambulatory use.
   (B) contain only the generic name of the medication.
   (C) are intended for institutional use.
   (D) may be transmitted electronically.
   (E) contain the quantity of medication to be dispensed.

2. If a therapeutic intervention is necessary, all of the following information should be communicated to the prescriber *except*
   (A) a declaration that "a mistake was made."
   (B) a brief description of the problem.
   (C) a reference source that documents the problem.
   (D) an alternative or suggestion to resolve the problem.
   (E) a description of the clinical significance of the problem.

3. The following information should be recorded on a prescription *except* the
   (A) prescription number.
   (B) date of filling.
   (C) expiration date.
   (D) product and quantity dispensed.
   (E) pharmacist's initials.

4. A prescription label usually contains all of the following *except* the
   (A) quantity dispensed.
   (B) lot number.
   (C) patient's diagnosis.
   (D) expiration date.
   (E) prescriber's name.

5. Auxiliary and cautionary labels should be used for all of the following purposes *except* to
   (A) substitute for verbal consultation.
   (B) ensure proper usage.
   (C) inform of storage requirements.
   (D) comply with regulatory requirements.
   (E) warn against the concomitant use of certain drugs or foods.

6. The following items are essential for a patient profile system *except*
   (A) the patient's name.
   (B) the prescriber's Drug Enforcement Administration (DEA) registration number.
   (C) the patient's allergies.
   (D) the patient's birth date.
   (E) instructions for medication use.

7. The following are drug therapy problems *except*
   (A) an adverse effect from a medication.
   (B) symptoms caused by undertreatment.
   (C) a drug–drug interaction.
   (D) an undiagnosed condition.
   (E) an allergic reaction to a medication.

Answers and Explanations

1. **The answer is C** *[see I.B]***.**
   Medication orders are written for the care of inpatients. Both medication orders and prescriptions may contain the brand or generic name of the drug and may be transmitted electronically. Only prescriptions contain the quantity of medication to be dispensed.

2. **The answer is A** *[see II.C.1]***.**
   Information provided to the prescriber during a therapeutic intervention should include a description of the problem, reference source, description of the clinical significance, and an alternative. Informing the prescriber that a mistake was made does not encourage cooperation and resolution of the problem.

3. **The answer is C** *[see III.A]***.**
   The prescription number, date of filling, product and quantity dispensed, and pharmacist's initials should be recorded on the prescription. The expiration date of the product is not required.

4. **The answer is C** *[see III.E.1]***.**
   The quantity of medication dispensed, lot number, expiration date of the product, and prescriber's name are usually included on the label. The patient's diagnosis, although listed in the patient's profile, is not included on the prescription label.